

Developing a screening tool for
the cognitive deficits experienced by patients
with high-grade glioma after the completion of
radiotherapy.



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Thesis Summary

Gliomas are associated with an array of debilitating symptoms. Whilst overall prognosis can vary, it is generally poor for those diagnosed with a high-grade glioma (HGG). Treatment is available to extend survival and manage symptoms, however, median survival is just 15 months. As curative treatment is not available, quality of life (QoL) is a key priority for patients. Cognitive decline is a common symptom and is recognised as a potential side effect of radiotherapy. The term cognition describes the mental processes involved in how we perceive, understand, and formulate responses to stimuli. Therefore, impairment to this could impact how patients conduct themselves on a daily basis and impede QoL.

Although the National Institute for Health and Care Excellence (NICE) state that patients with deficits may benefit from specialist cognitive support, such as neurorehabilitation, there is currently no standardised referral criteria for patients to access this. As most patients are followed up outside of a specialist setting, this PhD worked towards developing a simple screening tool, that is applicable in a primary care setting, to identify patients who may benefit from cognitive specialist assessment and support.

Four study stages were conducted. Firstly, a systematic review was undertaken to determine which cognitive deficits have been reported in patients with brain tumours after radiotherapy. This informed a public survey, to explore which deficits highlighted in the review were relevant for patients with HGG. Following this, a focus group aimed to better understand how patients and their families describe cognitive deficits and their impact of QoL. Using this cumulative data, two easily administered screening tools consisting of four questions were drafted for patients and their families, to screen for cognitive deficits which might benefit from cognitive support. The final stage was the face validation of these proposed questions. This was done using cognitive interviews, to ensure questions were easy to understand, relevant and suitable to potential users.

This research provides a new insight into the nature of cognitive decline in patients with HGG. The screening tool presented is the first to be designed for ease of administration in non-specialist settings while prioritising the subjective experiences of patients.

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Lay Summary

High-grade glioma (HGG) is a particularly aggressive form of brain cancer, with approximately 30% of patients surviving beyond 1 year and 18% beyond 5. There is currently no available cure for HGG, but treatment is available to increase survival and manage symptoms. However, treatments such as radiotherapy may cause patients to experience negative side-effects. This along with the tumour symptoms can prove to be challenging for the patient to maintain a good quality of life (QoL).

Cognitive issues are common in patients with HGG after completing radiotherapy. Cognition is term used to describe a person's ability to take in, process and act on information. Therefore, any issues with this may make it difficult for patients to carry out daily activities, which could then impact their QoL. Once treatment is complete, patients usually rely on primary care services to identify if they may benefit from extra support for their symptoms, however, there is currently no standardised method of determining if patients require cognitive support. Therefore, many patients are left to navigate cognitive issues alone. The purpose of this PhD is to work towards developing a simple screening tool, which can be used in a primary care setting, for patients who may benefit from cognitive support.

In order to do this, four study stages were conducted. This included a systematic review, and survey which aimed to gain a better understanding of the types of cognitive issues that are experienced by patients with HGG. Then a focus group was completed. This worked to highlight the impact these symptoms have on QoL and how they are identified by patients and their families. Once this was done, two sets of questions were drafted as a proposed screening tool. The final stage of this PhD was the evaluation of these questions. This was done to make sure that the questions were both easy to understand, relevant and suitable for patients and their families.

This research is the first to provide such an in depth look into how cognitive issues are experienced by patients with HGG and how it effects and is identified by those around them. This has led to the drafting of a screening tool, aimed to address the gap in patient care. Although more work is needed before its benefits can be seen, the research presented in this thesis provides the foundation for this.

1: Chapter 1: Introduction

In this chapter, I describe the clinical context in which this research has been conducted, presenting an overview of brain tumours and the common diagnostic and treatment pathways that high-grade glioma (HGG) patients often follow, which will highlight the gaps in screening and access to care which this work seeks to address. In addition, I aim to demonstrate the complexity around our current understanding of cognition and the challenges associated with providing a standard definition. I will then present the aims of this PhD.

1.1 Brain tumours

According to Cancer Research UK, an average of 12,288 primary brain tumours were diagnosed each year between 2016 and 2018 [1]. Of these, approximately half were deemed to be malignant [2]. Worldwide, an estimated 18.1 million cases of cancer were diagnosed in 2020. Of these only 1.7% were located in the brain and central nervous system (CNS), meaning that whilst this affects many people each year, brain cancers are still regarded as rare in comparison to others, such as breast cancer that accounts for 12.5% of all cancers [3]. Rare cancers are often under researched due to their low prevalence, meaning that these cancers are often incurable and have less streamlined treatment pathways [4].

Whilst primary brain tumours are considered rare, metastatic brain tumours are more prevalent. Metastatic brain cancers are diagnosed in between 10 and 26% of patients who die from cancer [5], and are therefore the most common type of brain tumour. Whilst these tumours originate from other areas of the body, primary brain tumours very rarely spread to other organs [6]. However, depending on their grading, they can grow rapidly and spread to other areas in the brain and spine.

The term primary brain tumour refers to any tumour that arises from the cells within the central nervous system (CNS). The most commonly of which are gliomas, which originate from glial cells. Gliomas account for approximately 75% of primary brain tumours diagnosed in adults [7]. Glial cells (or 'neuroglia') are non-neuronal cells located in the CNS and peripheral nervous system (PNS). These cells, when first identified by Rudolf Virchow in the 19th century, were suggested to act as so-called "Nervenkitt" (this is often translated as 'nerve-glue')[8], as he believed that they formed a type of connective tissue in the brain. Virchow describes "this connective substance forms in the brain, in the spinal cord, and in the higher sensory nerves a sort of putty' (neuroglia), in which the nervous elements are embedded"[9]. This initial description

led to them being named 'glial cells' as derived from the Greek word 'glia' meaning glue [10].

Since this original observation, the true nature of these cells has been further revealed. It is now understood that although glial cells do not directly participate in synaptic interactions and electrical signaling, they play more of a supportive roll[11]. They provide both physical and metabolic support to neurons by maintaining homeostasis, providing neuronal insulation through formation of myelin sheaths and maintenance of synaptic function[12]. There are several types of glial cell including astrocytes, oligodendrocytes and ependymal cells which are found in the CNS [13]. Each of these cells can give rise to a different type of tumour.

1.2 Glioma classification and grading

Tumours are often considered to be either malignant (cancerous) or benign (noncancerous). A tumour is defined malignant or benign upon the consideration of several factors. This includes the growth rate. The growth rate of malignant tumours tends to be higher than that of benign. However, this is not always the case. It is easier to differentiate between the two on the basis of their ability to spread. Malignant tumours are able to spread beyond their tissue of origin. This is due to their ability to travel through the basal membrane of healthy tissue (figure 1). This allows the tumour to invade locally and have the potential to travel to other areas of the body via the bloodstream or lymphatic system. This may result in the formation of a secondary cancer site known as a metastasis. Whilst benign tumours may be able to grow fairly substantially, they lack this ability and therefore only grow within the tissue of origin [14].

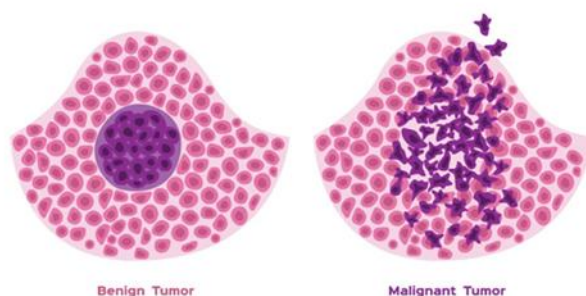


Figure 1: Visualisation of tumour interaction with the basal membrane [6]

The differences in the ways tumours progress has led to the development of tumour grading systems. Tumours found all over the body are graded according to several factors including histopathology and specialist observation [15]. Grading allows for a more accurate prediction of the way the tumour is more likely to behave. For the purpose of this thesis, grading will follow the system presented by the World Health Organisation (WHO), as this is the most widely accepted grading system for central nervous system (CNS) tumours. This can then serve as a guide for the best course of treatment and provide a more accurate understanding of patient prognosis. Grading in brain tumours often ranges from one to four, with one being the least aggressive and four being the most. However, as gliomas are intraparenchymal tumours, they do not fit into the afore mentioned categories of 'malignant' or 'benign'. Whilst other types of brain tumour may be enclosed to a specific tumour site, gliomas can infiltrate throughout the parenchyma [16]. Therefore, whilst gliomas rarely metastasise, and some may be relatively slow to spread, as they are not confined within a basement membrane their grading cannot be interpreted with the same outlook as many other cancers. As a result of this, the WHO classification for glioma works to grade the rate in the glioma is likely to spread. Whilst different forms of glioma exhibit different properties, which influence their rate of infiltration, gliomas are often seen to transform from less to more aggressively spreading forms [17].

Ependymoma is the least common form of glioma. Originating from ependymal cells, this form of glioma ranges from WHO grade one to three. Surgical resection is often the first treatment option. Providing full resection is possible, grade one and two tumours may not require further treatment. For grade three tumours however, post-operative radiotherapy is carried out to reduce the risk of recurrence [18]. Oligodendroglioma is a type of tumour that stems from oligodendrocytes and accounts for 5-18% of gliomas [19]. Tumours made up of purely oligodendrocytes are uncommon, however, they are often found as a major component of 'unspecified' or 'mixed' gliomas. These are tumours consisting of cells of varying origin [20].

Astrocytomas, formed from astrocytes, are the most common form of primary glioma. WHO grade one astrocytoma is known as 'pilocytic astrocytoma'. This subtype of astrocytoma is often observed in children and young adults. It is defined by its characteristic elongated and hair-like appearance, as well as a fairly slow clinical course [21]. The nature of such tumours means that recurrence is unlikely following complete resection. Of the astrocytoma subtypes, WHO grade two is the most common [22]. Known as 'diffuse astrocytoma', it is distinguishable as being diffusely infiltrating leading to a tumour shape with undefined edges. Whilst diffuse

astrocytomas are slow growing, they have been reported to have a tendency to develop into grade three astrocytoma [23].

WHO grade three astrocytoma, 'anaplastic astrocytoma', is a fairly aggressive form of glioma. It is classified as such due to the presence of an abundance of pleomorphic astrocytes accompanied with clear evidence of mitosis. This causes them to divide rapidly and lack the resemblance and function of normal cells. Whilst fast spreading, anaplastic astrocytomas have a more favourable prognosis than glioblastoma (grade 4 astrocytoma). Recurrence is common with anaplastic astrocytoma, however, a better response to treatment can increase survival dramatically [24]. Glioblastoma is the name given to the highest grade of glioma. This form of tumour is histologically distinguishable from other grades. Its unique features include the presence of necrosis as well as abnormal growth of surrounding blood vessels [25]. Tumours graded one or two are referred to as 'low-grade', whereas grade three or four tumours are 'high-grade'.

As previously stated, the WHO classification of CNS tumours is the most widely accepted for the classification of CNS tumours. This has recently been revised in its 5th Edition in order to keep up to date with the rapid developments in molecular diagnostics. This was published in 2021, and presents tumour classification with a much more nuanced approach with a higher emphasis on the molecular features of tumours [26]. Whilst most research published to date references a system that is more focussed on the histological characteristics as explained above, I recognise that the new classification has worked to refine the nomenclature in order to develop a more nuanced approach to the classification of brain tumours. In this I acknowledge that there is a spectrum which ranges from tumours with a variable but slower-progressing course, such as oligodendroglioma or astrocytoma, to fast-growing tumours such as glioblastoma, a particularly aggressive subtype. It is the latter which is particularly alluded to in the context of 'high grade glioma' as described in this thesis.

1.3 Diagnosis

Early symptoms of brain tumours often include the presence of a headache. This can often manifest as a dull pain of moderate intensity and not specifically localised [27]. Such headaches can be attributed to many other conditions. Due to the regularity of headaches, they can be misdiagnosed as anything from stress, to being resultant of a poor working environment. Other possible early symptoms, such as seizures or sensorial dysfunction, are more alarming and therefore tend to trigger a more immediate referral for further tests [28]. Symptoms of HGG are very similar to those

exhibited by individuals with other forms of brain tumour. The most common initial symptoms experienced by patients include headaches, seizures and cognitive symptoms [29].

Following the initial referral, patients will be sent for a computed tomography (CT) with contrast or a magnetic resonance imaging (MRI) scan [30]. CT scans work by using multiple x-rays to acquire a rapid, high-resolution three-dimensional image of the patient's brain. MRI works to achieve a similar result, however, unlike the CT scan, MRIs do not use ionising radiation. MRI machines work by measuring the interaction between the nuclei of cells and a strong magnetic field. Whilst this removes the necessity of x-ray exposure, it is more time consuming and complicated. Care must be taken when dealing with strong magnetic fields to minimize visual artefacts and ensure the safety of the patient [31]. If an abnormality is detected at the imaging stage, the patient will then be sent for a biopsy. Once a sample of the tumour has been extracted, histopathological examination will be conducted to determine the nature of the growth.

Although HGG may present with the same symptoms as other tumour types, varying grades of glioma each have a different general prognosis. For low-grade gliomas (LGG) a 'watch and wait' policy can sometimes be adopted dependent on the severity of the patients' symptoms [32]. Lesions of this nature can cause very few symptoms for a number of years. In cases such as this, it is vital that the patient is continually monitored to keep track of growth and the possibility of progression to high-grade status [33]. The diagnosis of a HGG however, comes with a sense of urgency. The aggressive nature of HGG causes it to spread rapidly. Without treatment, survival is only around three months [34]. The determination of HGG prognosis in patients who have had treatment is complex. Prognosis can vary widely dependent on specific prognosis, with molecular status and age impacting on survival as this may determine how the patient reacts to treatment. The possible use of surgical resection, radiation and chemotherapy, has increased the median survival rate of Glioblastoma to 14.6 months [35]. However, patients with grade 3 tumours have a better prognosis, with patients with anaplastic astrocytoma having a median survival of 2 to 3 years [36]. Therefore, whilst the diagnosis of HGG comes with a sense of urgency, the use of treatment means that many patients are living with the detrimental effects of their tumour and subsequent treatment for an extended period of time.

1.4 Standard Treatment for high-grade glioma

Once a diagnosis has been established and, if appropriate, the first step of treatment is traditionally surgical resection to remove as much of the tumour as possible. Whilst this is not always possible, due to location of the tumour or the patient being unfit for surgery, it is often deemed a key prognostic factor [37]. Once maximum resection has been achieved, the next standard step of treatment is radiotherapy. As with surgery, each patient is fully assessed to determine if radiotherapy will be beneficial to them. Once this has been determined by a multidisciplinary team radiotherapy can begin. Brain imaging is a vital component of the process of radiotherapy. It not only enables target location and highlights areas of avoidance prior to delivery, but it also verifies the location of the target during delivery and assesses the location of the deposited dose [38].

Fractionated radiation treatments are typically delivered on a daily basis over the course of several weeks. Each session delivers a dose of approximately 1.8 to 2.0 Gy [39]. This results in a total dose in the range of 45-54 Gy. Radiation is often delivered to the target site with a one to two cm margin on the defined gross tumour volume (GTV) [38]. Chemotherapy is often used in conjunction to radiotherapy. The most commonly used anti-cancer drug for glioma is temozolomide (TMZ) [40]. Chemotherapy works by destroying infiltrative tumour cells that may have spread to areas outside of the radiation site [41].

With such a poor prognosis, treatment for high-grade glioma is not used as a curative measure. It is instead used to manage the tumour which in turn, extends life expectancy and alleviates symptom burden [42]. This is important in terms of QoL as HGG is accompanied by a range of debilitating symptoms. These vary dependent on the patient but can range from physical, psychological and cognitive deficits such as memory and processing issues[43].

1.5 Radiotherapy

Radiotherapy is a technique that uses high energy ionizing radiation to destroy cancer cells. There are several processes that take place when radiation interacts with matter. Whilst these processes may vary dependent on the properties of the substance it interacts with, I will just be focusing on what causes radiotherapy to be lethal for both normal and abnormal tissue.

The detrimental effect of radiotherapy can be attributed to both the direct and indirect actions it can inflict on cells. Direct action is a term used to describe when radiation directly alters the DNA of a cell. During the mitosis stage of the cell cycle, the cell is

in the process of dividing. As this takes place, the DNA strands of the cell are exposed. When ionising radiation interacts with this, it causes one or both of the DNA strands to break, often leading to cell death [44].

Indirect action is when the water in cells is ionized by radiation. When water molecules are ionized, it causes the hydrogen and oxygen molecules to split into H₂ and O. As these molecules attempt to restabilise, many will convert back into H₂O, however, some may turn into H₂O₂ (hydrogen peroxide). Hydrogen peroxide is toxic to cells and its presence results in cell death [45]. As previously stated, the standard radiotherapy protocol followed for the treatment of HGG is targeted to the tumour site. However, the margin around the tumour is affected, meaning that it is generally expected that healthy tissue will be destroyed as a result of radiotherapy.

The exposure of healthy brain tissue to radiation can lead to debilitating side-effects. These may be experienced as acute or delayed side-effects [46]. Acute side-effects are often experienced as headaches, nausea and hypersomnia and are often linked to an increase in intracranial pressure experienced as early as the first dose of radiotherapy. Delayed effects, whilst some early-delayed or 'subacute' effects may be reversible, often lead to long-term irreversible changes in the patient's functioning. This is due to the impact that the damage caused to healthy brain tissues disrupts the plasticity and repair processes in the brain [47]. Cognitive decline is a commonly experienced symptom by patients which is often believed to be exacerbated by radiotherapy. However, there is still a lot of uncertainty surrounding exactly how cognition is affected [48].

When considering patients with HGG, it is challenging to identify the exact cause of symptoms. The generally poor survival associated with HGG and its relative rarity, means that there is a distinct lack of longitudinal studies of patients who have not experienced tumour progression. This along with the potential damage caused by resection, radiotherapy and chemotherapy, and the complexity of both the brain and cognitive processes, mean that it is currently not possible to definitively attribute the cause of cognitive decline. However, patients who undergo radiotherapy have an extended survival and are therefore more likely to experience the burden of these treatments side effects.

1.6 What is Cognition?

Although the term cognition is frequently used when describing the symptoms experienced by patients with HGG, there is ambiguity in its use. The word cognition is defined in the Oxford dictionary as "the mental action or process of acquiring

knowledge and understanding through thought, experience, and the senses.” [49]. However, this definition does little to describe the complexity of the topic and the philosophical theories that underpin our current understanding. The concept of cognition dates back to the works of Aristotle. In particular, the Aristotelian understanding that the acquisition of knowledge begins through the senses [50].

Other philosophers have presented theories that question the certainty of the senses. For example, Plato’s argument in the *Theaetetus*, in which he rejects the proposal that knowledge is defined by perception on the grounds that what we perceive is not a true reality, but instead a fragile interpretation [51]. Such positions have since been rejected by scientists and observational and empirical methods have taken precedence. By the 19th century, when figures such as Wilhelm Wundt, Edward Titchener, Hermann von Ebbinghaus and William James were building the foundation of modern cognitive psychology, it was broadly accepted that scientific findings need to be concluded by objective procedures and empirical observations [52].

The acceptance of this way of thinking opened up an array of questions into how exactly we process and understand the world around us. There are several key approaches to further understanding human cognition. These include: experimental cognitive psychology, which involves the use of behavioral evidence to understand cognition; cognitive neuroscience, which uses both behavioral evidence and biological evidence; cognitive neuropsychology, which involves the investigation of brain-damaged individuals to understand the ways in which a healthy brain functions; and computational cognitive science, which involves the development of computational models to aid in understanding human cognition [53]. Through advances in cognitive neuroscience and cognitive neuropsychology, it is now generally accepted that different parts of the brain are responsible for different cognitive functions and behaviors [54].

Cognition is often used as an umbrella term for multiple processes. This includes all the processes that contribute to how we perceive, understand and respond to stimuli. They are often separated into categories. These categories include memory (both episodic and semantic, and long and short-term), executive functioning, language and motor dexterity. However, the separation of these domains is certainly open for interpretation. Therefore, the definition of key domains of cognition is challenging. This could be due to the many overlaps in processes. A key example would be the categorisation of working memory.

Working memory is described as the ability to retain information in order to formulate a response [55]. As previously stated, one widely accepted cognitive domain is executive functioning. Gilbert and Burgess (2008) describe executive functions as “the high-level cognitive processes that facilitate new ways of behaving, and optimise one’s approach to unfamiliar circumstances.” [56]. Therefore, by this definition, working memory would be considered an executive function. However, taking into account theories of memory systems, this becomes less clear as working memory is often described as a sub-category of short-term memory [57].

The complexity of human cognition is also highlighted by the sheer number of different methods available to test cognitive functioning. Neurocognitive assessments range from extensive batteries of tests - which claim to assess a large proportion of cognitive processes - to process-specific tasks. There are a number of reasons for the number of assessments available. For example, many assessments are designed with a specific population in mind. This could be to ensure that participants can understand the test or to help adjust scores for any additional variables [58].

In addition to this, assessments are presented as either a series of questions or tasks which are then scored. These questions or tasks often attempt to assess cognitive processes in an objective and quantifiable way. As such, due to the variation in how processes are categorised, researchers may attribute different processes to different tasks.

1.7 How does cognitive decline affect QoL

Whilst there is still ambiguity surrounding the classification of cognitive domains, it is important to recognise the integral role cognitive functioning plays in our day-to-day lives and how a decline in any cognitive processes could compromise QoL. The impact of cognitive decline on QoL is a common popular area of research. Chaves et al (2017) found that cognitive decline in elderly populations directly affected QoL by reducing the ability to perform activities of daily living. It was also found that this was heightened if accompanied by emotional disturbances or a painful medical condition [59].

It has also been seen in dementia studies, that even in instances where objective cognitive performance is seen to be within normal limits, as assessed by validated measures, individuals with self-reported or subjective cognitive impairment (SCI) report a reduction in health related quality of life (HRQoL) [60]. The effect that cognitive decline has on the QoL of individuals, even without the presence of the additional burdens associated with HGG, is clear. Whilst there are many studies into

HRQoL of patients with HGG, these studies tend to have objective measurements of cognition included as a part of a broader set of outcomes. In addition to this, there are even fewer studies looking at how cognitive decline is experienced in long-term survivors.

1.8 Current care for patients after treatment

It can be seen that patients with HGG may face an array of debilitating symptoms following treatment. Although all symptoms experienced are problematic, neurocognitive deficits can be especially disruptive to daily living and in turn be distressing to both the patient and carers [61]. Once initial treatment is complete, follow-up appointments become less frequent. Therefore, in between their quarterly scans to monitor progression, patients must rely on primary care services to deal with any progressing issues they may have. Primary care services are able to provide assessment and management of physical symptoms and straightforward depression and anxiety, as well as recognise indications for specialist referral [62].

Unlike physical symptoms, cognitive impairment is not as easily diagnosable. Issues with cognition are usually confirmed using batteries of tests that are very specific and require professionals with specialist neuropsychology skillsets to administer. For example, to test a patient ability to form memories from auditory stimuli, the California Verbal Learning Test (CVLT) would be appropriate. Whilst the test aims to provide a more detailed understanding of a patient's verbal memory, this test alone takes approximately one hour to complete [63]. This test would also require administration by a specially trained clinical (neuro) psychologist.

Therefore, a full cognitive evaluation is not appropriate for a primary care setting. In addition to this, there are currently no standardised screening methods to identify which patients may require a more in-depth evaluation of their cognitive capabilities, which therefore limits healthcare professionals (HCP's) ability to recognise when patients may need a referral. As previously mentioned, cognitive decline can contribute to a decline in QoL. Therefore, not addressing cognitive functioning in patients with HGG may lead to unmet needs [64]

A patients overall QoL is impacted by many different factors such as social, economic and health status [65]. This is particularly important with regard to patients with HGG. As treatment is not conducted with curative intent, its purpose is to extend survival while also relieving symptoms to improve QoL. This is often referred to as palliative treatment [66].

The importance of addressing changes to cognitive function is becoming increasingly acknowledged by health care professionals. In 2018 the National Institute for health and care excellence (NICE) published a set of quality standards for the diagnosis, monitoring and management for primary and metastatic brain tumours in adults [67]. In this, it is highlighted that health and social care professionals involved in caring for patients with brain tumours should be addressing the changes to cognitive functioning both during treatment and throughout follow-up. In addition to this, it is suggested that patients should be continuously considered for neurological rehabilitation and be given information on how to get a neurological rehabilitation assessment.

Neurorehabilitation is a multidisciplinary technique that is utilised to address cognitive deficits in many neurological diseases [68], the principles of which are based on neural plasticity [69]. The use of cognitive rehabilitation in adult brain tumours has become a key area of research, and with this there is emerging evidence of the value this may have for the preservation of cognitive function [70, 71]. With this being said, the complexity of cognitive symptoms and the lack of standardised referral processes and neurorehabilitation providers still remain prominent barriers for patients with brain tumours.

In addition to the possibility of patients accessing interventions to address their cognitive symptoms, identifying deficits could also be used to access more specialised day to day support. In a guide published by the National Institute of Aging [72], it is suggested that a support plan be developed in order to ensure those with cognitive impairment and their caregivers are supported as best as possible. Whilst this guide has been specifically designed for older individuals with dementia, it highlights the value of ensuring patients and caregivers have access to support in establishing aids for daily functioning. This may be of value for those with HGG considering the reliance on coping mechanisms highlighted throughout this thesis. It is also suggested that the patients and caregivers be referred to national and community resources such as support groups and respite care.

However, as there are currently no standards on how this should be conducted, it is subject to the discretion of individual HCP's. Therefore, there should be a standardised method of addressing these issues.

1.9 Aim of this PhD

In order to ensure the best quality of palliative treatments, research must be conducted to identify the unmet needs of patients and determine what could be done to fulfill them. This includes identifying gaps in services in order to develop methods

of bridging these gaps [73]. Due to tumour itself and the damage to tissue as a result of radiotherapy, patients often face detrimental changes to their cognitive abilities. This PhD is focused on those who have received radiotherapy, as by definition, they are likely to have a more favorable prognosis as they have been considered well enough to receive active anti-cancer treatment. They would therefore be more likely to live with cognitive deficits for an extended period of time, and would therefore benefit from specialist cognitive support

The overarching aim of this PhD is to systematically develop a standardised method of screening HGG patients for cognitive deficits after the completion of radiotherapy. Specifically, the tool should be quick and easy to administer in a non-specialist environment to allow detection of patients who could benefit from specialist neurocognitive assessment and specialised support.

The research presented will work towards this by addressing the following questions:

1. Which domains of cognition are seen to decline in patients with HGG after receiving radiotherapy?
2. How does cognitive decline impact the QoL of patients and those around them?
3. How can decline be best detected in patients without the use of extensive neurocognitive assessments?

In this thesis I will be presenting an iterative study design comprising four stages that have been conducted to address these questions. Firstly, I will be presenting a systematic review conducted to establish the areas of cognition reported to decline in brain tumour patients. This is followed by a publicly accessed mixed-method survey that looked into cognitive decline in patients with HGG specifically. Using the results from this, a focus group with patients with HGG and family members of patients was conducted to look further into the survey findings in order to better understand the impacts of decline on QoL and the ways in which patients and their families describe them. The findings of both the survey and focus group were then used to guide the drafting of a screening tool. The tool was face validated with patients and family members using cognitive interviews. Finally, as each stage of this PhD was guided and conducted with public and patient involvement (PPI), I will be presenting an evaluation of this with the UK National Standards.

Chapter 2: Cognitive deficits observed in adults with brain cancer receiving radiotherapy or combined chemo-radiotherapy: A systematic review and narrative synthesis

2.1 Introduction

In order to conduct this study within the context of how cognition is currently understood to be affected in patients with HGG who have had radiotherapy, this chapter provides an in-depth look at the current literature. Due to the expected limited number of studies of cognition specific to patients with HGG, this stage of the project sought to summarise the current understanding of how cognition is reported to decline in patients with a range of brain tumours (including low-grade and metastatic) after the completion of radiotherapy. The addition of radiotherapy was specified given the impact this treatment has on healthy tissue, as highlighted in the previous chapter, in order to establish a more rounded understanding of the experiences of patients following on from treatment. In synthesising the available literature, this chapter determines which areas of cognition are observed to decline, and how these are observed via the variation of neurocognitive assessments in current use.

Systematic reviews are used to facilitate evidence-based healthcare, allowing practices to be conducted in a way that is representative of clinical expertise. This in turn, can aid in reducing variation in how healthcare is delivered and ensures best practice [74]. In addition to guiding evidence-based healthcare, systematic reviews are often used as the starting point in research aimed at developing new procedures or practice guidelines. This is because evidence synthesis serves to expose gaps in knowledge and therefore highlights the need for further research [75]. The aim of any systematic review is to methodically synthesise multiple studies in order to make accessing evidence more efficient [76]. They work by summarising existing literature using explicit and reproducible methods. These methods include the systematic search, critical appraisal and synthesis of research surrounding a particular issue in a way that provides an impartial review of the available data [77].

A key limitation with systematic reviews is that their value is dependent on the research that has been conducted. Though critical appraisal is a key step in any systematic review, the way in which quality is reported may vary. This may be dependent on the type of review and the topic area. This is also exacerbated by publication bias, by which studies with results that support their proposed hypothesis tend to be generally more readily available [78]. Additionally, dependent on the topic

area, it is likely that included studies will be heterogeneous. Including studies that have differing designs and outcome measures makes it challenging to make comparisons between studies.

This is a key point of consideration for the review question addressed in this chapter. The ambiguity and complexity of the networks of the brain and how cognitive functioning and domains of cognition are defined, leave room for interpretation. Therefore, prior to conducting this review, it was presumed that heterogeneity would be expected in the included studies. As a result, it was determined that a narrative synthesis would be the most appropriate way of conducting this review.

A narrative synthesis is an approach that works to synthesise the results of included studies in a way that primarily relies on text to summarise findings. This is often the method of choice in cases where the review question requires the inclusion of a broad range of research designs and outcomes [79]. This method is focused on the exploration of relationships within and between studies. When considering a topic area where studies are expected to be heterogeneous, as it allows the influence of heterogeneity to be explored. This is important as it helps to present the literature in a way that not only summarises findings, but also provides an understanding of how the methodology of studies influences these findings [79]. This is particularly important for this research based on the complexity of cognition.

2.1.2 Aim of the review

This systematic review was conducted to establish the range and nature of cognitive deficits reported in studies of patients with brain tumours after the completion of radiotherapy.

Objectives

1. To review the available literature of studies that report cognition after radiotherapy as an outcome
2. To explore the range of methods used to assess cognition in patients with brain tumours after receiving radiotherapy
3. To identify the areas of cognition that have been reported to decline in patients with brain tumours after receiving radiotherapy.

2.2 Methods

The review protocol was submitted and published to Prospero (CRD42019123999) on the 18th of February 2019. All edits to the protocol and research updates were subsequently recorded.

2.2.1 Formulating the question

The question constructed for this systematic review was designed to be as broad as possible, whilst still capturing relevant information. This thesis focuses on HGG, however, the symptoms of HGG are similar to other types of brain tumour and given the complexity surrounding our current understanding of cognition and the relative rarity of HGG, it was decided that it may be beneficial to begin this research by looking at brain tumours as a whole. Therefore, the scope of this review was extended to other brain tumour types and grades.

The question was formulated using the PICO (Patient, Intervention, Comparison and Outcome) format [80]. For this review, the patient population were adults with brain tumours. The intervention was radiotherapy or combined chemoradiotherapy. As this was conducted as a way of collating reported cognitive outcomes, no comparison was specified. The outcome of interest was the impact on patient cognition. This was characterised as the reporting of assessments designed to assess domains of cognition or patient reported disturbances in mental processes related to learning, thinking, reasoning and judgment.

The final question was 'What are the cognitive deficits observed in adults with brain tumours after receiving radiotherapy or combined chemo-radiotherapy?'

2.2.2 Criteria of studies

Studies of any design were included if they reported post-radiation cognitive function. Patient inclusion and exclusion criteria is specified in table 1. The exclusion of paediatric patients was due to the fact that juvenile HGG is rare and the rate in which the brain is growing may impact the effect of radiotherapy on cognitive decline [81]. Pituitary gland tumours were excluded due to the specific way in which these tumours affect hormone production, which could in turn be an additional unnecessary variable in determining how cognitive deficits are reported in brain tumour patients after radiotherapy [82]. This review did not exclude studies based on their design.

Included:	Excluded:
-Adults (>18)	-Paediatric patients (<18)
-Histologically confirmed brain tumour diagnosis.	-Patients with other conditions (i.e., lymphoma) who have also received cranial radiotherapy
-Patients in remission/ successfully treated brain tumour	-Patients with pituitary gland tumours
-Any study design	-Patients still undergoing treatment
-Any radiotherapy protocol	-Studies not reported in English

Table 1: Inclusion and Exclusion criteria for studies in the systematic review

As the intervention of interest was radiotherapy, studies reporting on radiotherapy of any protocol and dose were included. This also included proton beam radiotherapy and brachytherapy. Studies focusing on chemotherapy were also included if participants also underwent radiotherapy. Although the aim of this review was not to determine which cognitive deficits are caused by radiotherapy, as stated in chapter 1, patients who undergo radiotherapy have an improved prognosis, and will therefore be living with the both the effects of their tumour and detrimental side effects of treatment. Therefore, it was necessary to capture the cognitive decline reported in patients with the combined impact of tumour and effects of radiotherapy.

Cognitive alteration as an outcome was defined as any effect which changes the degree of functioning of a pre-existing mental process. These processes include attention, memory, language, visual and audio perception, and executive functions. Studies were included if the cognitive state of patients was reported using neuropsychological tests or through patient/ carer reports. Patient/carer reports were included if they were reported in isolation or as part of a larger QoL investigation.

2.2.3 Search Strategy

The following electronic databases were searched: MEDLINE, CINAHL, EMBase, PsychInfo, Web of Science and CENTRAL. ClinicalTrials.gov and the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) were searched for any relevant on-going trials. Brain: A Journal of Neurology, British Journal of Psychology and the Journal of Clinical Oncology were also manually searched for relevant articles.

The search strategy was developed to cover all aspects of the research question. The initial search was run on the 27th of February 2019 and was re-run on the 3rd of May 2021. Figure 2 shows the search strategy used for MEDLINE. This was then adapted for other electronic databases. All sources were searched from 1970, or the date of inception if this is later than 1970. This was applied following the claim of Greene-Schloesser & Robbins (2012) [83], that prior to 1970, the brain was believed to be radio resistant. The search was limited to studies reported in English only, but

included studies where participants were assessed in another language if they were fluent in that language. Reference lists of each included study were also checked for any additional studies of interest.

```

1.exp Brain Neoplasms/ (142310)
2.("Brain Tumor" or Glioblastoma* or Glioma or "Brain Cancer*" or Astrocytoma or oligodendroglioma or
ependymoma or meningioma or haemangioblastoma or cranipharyngioma).tw. (96113)
3.1 or 2 (192408)
4.exp RADIOTHERAPY/ (172352)
5.(Radiotherap* or Chemoradiotherap* or "Radiation injur*" or "Cranial irradiation" or Radiation or "Brain Irradiation"
or "intensity modulated radiation therapy" or "stereotactic radiosurgery" or "three dimensional conformal radiation
therapy").tw. (445343)
6.exp Radiation Injuries/ (66235)
7.4 or 5 or 6 (531092)
8.("Cognition disorder*" or Cogniti* or Neurocogniti* or "Neurocognitive disorder*" or "Acquired cognitive deficit*" or
"Memory disorder*" or "Cognitive disorder*" or "Cognitive decline" or "Cognitive dysfunction*" or "Cognitive
function*" or "Executive function*" or "Mental disorder*" or "Executive disorder*" or "Mental recall" or "Mental
competency" or "Mental process*" or Mental or "Concept formation*" or "Pattern recognition").tw. (630754)
9.exp COGNITION DISORDERS/ or exp COGNITION/ (218095)
10.exp Cognitive Dysfunction/ (10325)
11.exp Neuropsychological Tests/ (166390)
12.8 or 9 or 10 or 11 (808036)
13.3 and 7 and 12 (1662)
14.limit 13 to (english language and humans and yr="1970 -Current" and "all adult (19 plus years)") (733)

```

Figure 2: Search strategy used to identify relevant studies for 'Ovid' via Medline. Date of search 03.05.2021

2.2.4 Study selection

The results of the search were imported to EndNote X9™. Studies were searched for any duplicates, which were subsequently removed. Once the duplicates were removed, all titles were screened. Any titles that obviously reported on any of the exclusion criteria were removed. All studies that remained were screened by their abstracts. Remaining papers were reviewed in full.

All screening steps for all papers were carried out by one author (FM). Ten percent of the titles, abstracts and full papers were also independently screened by a second author (AN, AB, SS, KB or JP). Had discrepancies between the judgments of the two review authors occurred, this would have been discussed with the aim of coming to an agreement. No discrepancies occurred.

2.2.5 Data extraction

A bespoke data extraction tool (Supplementary Appendix A) was adapted from the Cochrane data collection form for intervention reviews for RCTs and non-RCTs template [84]. This was used to consistently extract key data from each included paper. Identification features of each study as well as the study characteristics, population characteristics, intervention and setting and the outcome data/results were documented. In the case that studies did not detail information of interest, authors of original studies were contacted in an effort to retrieve this information. This review was developed with the input of two public and patient involvement (PPI) research partners (RPs). By suggestion of one of the RPs, the reporting of PPI in included studies was added to the extraction tool.

2.2.6 Quality assessment

The full papers were systematically reviewed to determine fit with the review question. Each paper was assessed on its clarity in terms of the data (i.e., do the authors attempt to contextualise non-significant data and draw conclusions from them?) and the way in which any possible bias is limited.

The Specialist Unit for Review Evidence (SURE) Critical Appraisal Checklists provide various checklists for papers dependent on the style of the study [85]. Each of the full texts were assessed using the correct checklist. These checklists work by scrutinising the methodology of a study. They address whether a paper has been successful in demonstrating what they claim with the use of questions around 'risk of bias' (i.e., Are the setting, locations and relevant dates provided?) and external validity (i.e. Are the measures of exposures and outcomes appropriate?).

2.2.7 Data Synthesis

Due to the nature of the review question, and its potential inclusion of qualitative and quantitative results, a narrative analysis was used. The included studies demonstrated a wide range of primary outcome measures, measurement tools and methods, therefore outcomes could not be aggregated, so a meta-analysis was not undertaken. Consequently, a narrative synthesis was more appropriate to fully describe the reported outcomes.

As a narrative synthesis was undertaken, it was not necessary to code the data variables for analysis. The synthesis of the data was undertaken following the guidelines of the Centre for Reviews and Dissemination (CRD) for undertaking reviews in health care [86]. Synthesis of results started with tabulation of the included studies as a preliminary synthesis. The determination of the cognitive domains

addressed in the included studies was done following the steps shown in figure 3. This enabled for the results reported in each study to be considered in terms of the sensitivity and specificity of the reported assessments. Following the tabulation of results, results were structured into groups dependent on the cognitive outcomes observed and summarised narratively.

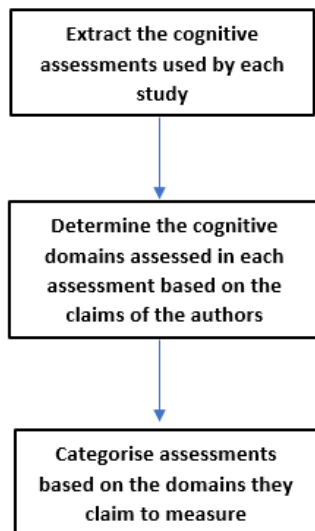


Figure 3: Steps followed in determining the areas of cognition reported in included studies

2.3 Results

2.3.1 Search results and study screening

The search generated a total of 4027 citations. 742 from Medline; 1980 from EMBase; 16 from PsychInfo; 776 from Web of Science; 222 from CINAHL; 207 from CENTRAL; 81 from the Journal of Clinical Oncology; and 3 from Brain: A Journal of Neurology. After the removal of duplicates, 3052 citations were remaining. Title and abstract screening led to the exclusion of 2971 studies. The remaining 81 studies underwent full text screening.

Of the 81 full texts screened, twenty-nine were excluded with reason. Fourteen papers were excluded due to excluded conditions or participant characteristics. Ten studies lacked participant or treatment information that would determine if the study met the inclusion criteria. Five did not report on cognition as an outcome. The completion of screening resulted in 52 studies being included in the review. The 52 studies include data from a total of 5472 participants. Figure 4 shows the PRISMA 2020 [87] flow diagram of studies.

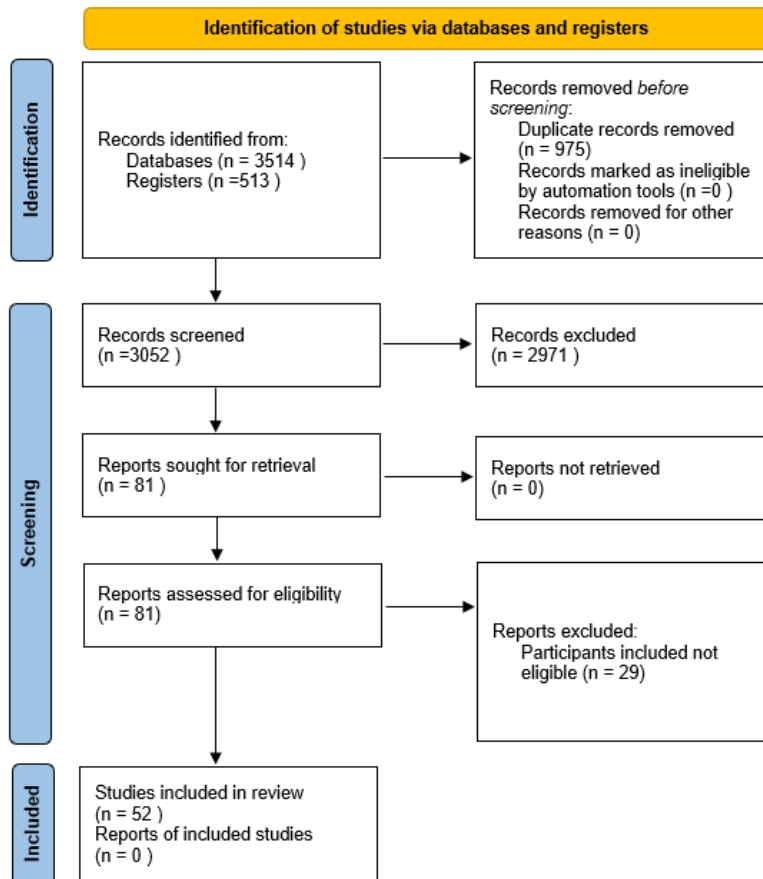


Figure 4: PRISMA 2020 flow diagram of studies [87]

2.3.2 Study Characteristics

Of the papers included, 29 included data from patients diagnosed with primary brain tumours. Seventeen of which include patients deemed to have high-grade tumours [78, 88-105] and twelve include low-grade patients [78, 89, 100, 105-116]. Twenty-one of the studies focussed on patients with metastatic brain tumours [117-139]. The majority of studies included were cohort studies which accounted for 33 of the studies. Ten studies were cross-sectional and the remaining eight were randomised controlled trials (RCTs). This is summarised in Table 2. Karnofsky Performance Status (KPS) was reported in 37 of the included studies. The lowest reported KPS score was 40 and was observed in patients with high grade tumours. However, several studies reported patients with high grade tumours to have KPS scores as high 100, which is the maximum score.

The study design of each, determined which of the SURE critical appraisal checklists were used to assess the quality of each. It was determined through the use of these checklists that twenty-one studies were deemed to be of high quality [78, 89, 93, 95,

96, 98, 102, 103, 108-111, 113, 119-121, 123, 125, 130, 131, 133, 139]. Of the remaining studies, thirty were determined to be of medium quality [90-92, 94, 97, 99-101, 104-107, 112, 114-118, 122, 124, 126-129, 132, 134-138] and one was of low quality [88]. Low and medium quality studies scored lower based aspects such as a lack of clarity on participant recruitment, lack of acknowledgment of recall or selection bias and not reporting whether or not there were any conflicts of interest. However, all included studies reported on validated cognitive assessments, and have therefore been kept in the synthesis. None of the included studies reported on the use of PPI in the design or development of their study.

The radiation protocols undergone by patients varied among the studies. Stereotactic Radiotherapy (STR) protocols, including stereotactic radiosurgery, were the most commonly reported. STR alone was reported in twenty-seven of the studies. STR was utilised alongside whole brain radiotherapy (WBRT) in four of the included studies. WBRT was the primary form of treatment in thirteen studies. Other administered protocols include hypofractionated radiotherapy, hyperfractionated radiotherapy, and brachytherapy. Table 3 details the range of protocols reported in included studies. All included studies reported on a total dose of between 15 and 60Gy.

	<i>Number of studies</i>
Total Included	52
Tumour grade and type	
High grade primary	17
Low grade primary	14
Metastatic	23
Study design	
Cohort	34
Cross-sectional	10
Randomized controlled trial	8

Table 2: Tumour characteristics and study designs of included studies¹

¹ Two studies reported on more than one tumour type.

Radiation Protocol	Number of Studies		
	High grade	Low grade	Metastasis
STR alone	10	7	10
WBRT alone	2	2	11
WBRT with STR	0	0	3
Partial RT	2	2	0
Hypofractionated	1	0	0
Hyperfractionated	1	0	0
Accelerated hyperfractionated	0	0	1
Accelerated fractionated	0	0	1
Brachytherapy	0	0	1
Proton Beam	0	1	0
Not detailed	2	3	0

Table 3: Radiotherapy protocols reported in included studies²

Twenty-eight studies included patients that had undergone surgery to some extent. This ranged from tumour biopsy to total tumour resection. The majority of these studies included patients with high-grade tumours. The remaining 24 studies did not detail if patients had undergone surgery, with the majority being studies focused on brain metastases.

Chemotherapy was reported to be utilized alongside radiotherapy in some proportion of patients in twenty-three of the included studies. Eight studies stated explicitly that chemotherapy was not used, and the remaining studies failed to report the inclusion or exclusion of participants who had undergone chemotherapy. Treatment details for individual studies are included in table 3.

A wide variety of cognitive tests were employed across the included studies. The results as shown in table 4 show that a total of 45 different cognitive assessments were utilized throughout the included studies. The most frequently used was the Mini Mental State Examination (MMSE) which was reported in 27 of the included studies.

² Multiple studies used reported the use of more than one radiation protocol.

Cognitive Assessment	Abbreviation	Number of studies	Domains Assessed	Ref
Attentive matrices test	AMT	1	Attention	[140]
Auditory consonant trigrams 9 and 18	ACT9&18	1	Memory and Executive Functioning [141]	[141]
Auditory naming test	ANT	1	Language	[142]
Biber figure learning test	BFL	1	Memory	[143]
Boston naming test	BNT	2	Language	[144]
Brief test of attention	BTA	2	Attention	[145]
Brief visual special memory test - revised	BVMT-R	5	Memory and motor dexterity	[146]
Continuous performance test	CPT	1	Attention	[147]
Controlled Oral Word Association Test	COWAT	8	Language	[148]
D2-test	D2	1	Attention and Executive Functioning	[149]
Design Fluency	DF	2	Executive Functioning, motor dexterity	[150]
Digit Span	DSpan	6	Memory	[151]
Digit Symbol	DSym	8	Executive Functioning	[151]
Dutch adult reading test	DART	1	Language and Executive Functioning	[152]
Facial recognition test	FRT	2	Executive Functioning	[153]
Grooved Pegboard tests	GPT	7	Motor dexterity	[154]
Hopkins verbal learning test-Revised	HVLT-R	13	Memory, Language and Executive functioning.	[155]
Ideomotor apraxia	IAT	1	Memory and Motor Dexterity	[156]
Judgment of line orientation test	JLO	3	Executive Functioning	[153]
Kohs Blocks	KB	1	Executive functioning	[153]
Line bisection test	LBT	1	Executive functioning and motor dexterity	[153]
Mattis Dementia Rating Scale	MDRS	1	Memory, Executive functioning and Attention	[157]
Memory comparison test	MCT	3	Memory	[110]
Mini mental state exam	MMSE	27	Memory, Executive functioning, Language, Attention and motor dexterity	[158]

Montreal Cognitive Assessment	MoCA	1	Memory, Executive functioning, Language, Attention and Motor Dexterity	[159]
Monroe-Sherman reading comprehension	MSRC	1	Executive Functioning	[160]
Multiple-choice test of vocabulary knowledge	MWT	1	Language	[137]
NeuroCog FX	NCFX	2	Memory, Executive functioning, Attention and Language	[161]
NeuroTrax programme	NeuroTrax	1	Memory, Executive functioning, Language, Motor dexterity and Attention	[162]
Picture Naming	PN	1	Memory and Language	[163]
Raven Progressive Matrices	RPM	2	Executive functioning	[164]
Repeatable battery of assessment of neuropsychological status	RBANS	1	Memory, Language, Executive functioning and Attention	[165]
Rey Auditory Verbal Learning Test	AVLT	6	Memory	[153]
Rey-Osterrieth complex figure	ROCF	3	Executive functioning and motor dexterity	[166]
Spatial recall test	SRT	2	Memory	[115]
Stroop colour word test	Stroop	7	Executive functioning	[167]
Test for attentional performance	TAP	1	Attention	[168]
Token test	TT	1	Motor dexterity and Executive functioning	[169]
Trail making tests a and b	TMT a&b	14	Executive functioning, Attention and Motor dexterity	[170]
Verbal Fluency test	VF	8	Language	[171]
Visual verbal learning test	VVL	3	Memory	[110]
Wechsler Adult Intelligence Scale-Revised	WAIS-r	7	Memory, Language and Executive functioning	[172]
Wechsler memory scale	WMS	1	Memory	[173]
Wisconsin Card Sorting Test	WCST	7	Executive functioning	[174]
Working memory task	WM	1	Memory	[153]

Table 4: Cognitive assessments reported in included studies

2.3.3 Memory

Of 52 studies, 50 reported on at least one assessment that claimed to assess memory. These studies reported on a total of 21 assessments of which nine were memory specific and 12 assessed memory as part of a broader cognitive assessment. These assessments varied in their specificity.

Decline in at least one aspect of memory was seen in 28 studies [88, 89, 92, 93, 95-97, 100, 101, 103, 106, 108-111, 120, 122, 124, 126, 131, 133, 134, 137, 175-177]. None of these studies reported decline to reverse over time. Whilst the majority of studies presented this as a decline in assessment score, eight provided a more in-depth break down of which areas of memory were seen to decline. These included delayed recall [106, 131], visual recall [92, 93, 108, 109], and verbal recall [92, 93, 95, 108, 137]. Decline in memory was reported fairly evenly across tumour types.

A lack of sensitivity was seen in some studies that included the mini mental state exam (MMSE). Onodera et al (2014) reported that the result of the Repeatable Battery of Assessment of Neuropsychological Status (RBANS) showed a decline in delayed memory in patients four months after treatment, however, there were no changes observed in MMSE scores [131]. Similarly, Pospisil et al (2017) reported a decline in Rey Auditory Verbal Learning Test (AVLT) scores, yet no alteration in the MMSE [133]. In addition to this, it was seen by Fernandez et al(2012) that even though patients reported a decline in cognitive functioning in a QoL questionnaire, there was no change in MMSE scores [124].

Several of the included studies investigated the way different radiotherapy methodologies affect cognitive functioning. Three studies [111, 122, 175] reported that patients undergoing WBRT experience more memory deficits than those who underwent STR. However, it was reported by Kepka et al (2016) that there was no difference in decline in patients who received WBRT or STR [126]. Furthermore, Keime-Guibert et al (2007) reported that elderly patients (aged 70 or over) that received STR experienced the same levels of decline as those who did not receive radiotherapy [97]. Gondi et al (2014) reported that patients receiving hippocampal avoiding whole brain radiotherapy (HA-WBRT) displayed a preservation of Hopkins Verbal Fluency Test (HVLT) scores [177]. The benefit of reducing hippocampal dose was mirrored by Okoukoni et al (2017) in their comparison of partial RT and WBRT, where they found that a reduction of RT administered to the hippocampus resulted in higher function [100].

Amongst the seventeen studies [90, 94, 102, 104, 107, 113-118, 135, 138, 139, 178-180] that reported no change in patient memory, twelve [90, 94, 102, 104, 107, 114, 116-118, 138, 178, 179] included patients who had undergone STR alone. This could serve as an example of the preservation of cognitive functioning that often results in STR being more favourable above WBRT. However, as previously stated, the lack of sensitivity associated with the MMSE could be misleading. As eight of these studies presented their outcomes based on MMSE scores alone, it is difficult to suggest that this shows a true link between STR and preservation of patient memory.

Six studies [119, 127, 130-132, 181] reported improvement in at least one assessment associated with memory. Of these, two reported improvements in 'immediate memory' exclusively [119, 131]. Although these studies used more extensive batteries of tests, it should be noted that the term 'immediate memory' is often used interchangeably with 'short-term memory' or 'working memory' which could be associated with changes to multiple areas of cognition such as attention and processing speed. However, neither batteries of tests highlighted any other areas of improvement. All studies that reported improvement were cohort studies focused on patients with brain metastasis (BM). Five of the studies [119, 130, 132, 180, 181] that report improvement utilised tissue sparing methods such as STR and brachytherapy. These therefore provide evidence that such methods could work to preserve memory. However, as the majority of BM studies included reported on WBRT, more research is needed to know for certain.

The results demonstrate that the use of memory-specific assessment tools allowed the identification of several key domains of memory. Verbal memory, visual memory, long term (both episodic (recollection of personal experiences) and semantic (recollection of words, concepts or numbers)), and working memory were highlighted as areas in which decline was observed. Studies which used both global and memory-specific assessment tools appeared to demonstrate more sensitivity to change using the task-specific tools, suggesting that the frequent use of global tools such as MMSE may under report memory problems.

2.3.4 Executive functioning

Fifty-one of the included studies reported on assessments that included aspects of executive functioning. These studies utilised a total of twenty-five different assessments. Eleven of these assessments are designed to specifically measure elements of executive functioning. The remaining fourteen assessments include measurements of executive functioning within a broader assessment of cognition. Due to the complexity in categorising which area of cognition working memory fits in

to, I have considered reports of working memory for both memory and executive functioning outcomes.

Decline in areas of executive functioning was reported in 23 studies. The majority of these studies concluded a general decline in executive functioning, however five studies provided further insight into the nature of this decline; the specific areas of executive functioning highlighted to decline were orientation [104, 116], initiation [97], construction [97], calculation [104, 116] and working memory [96, 110]. Most of the studies that reported a decline in executive functioning also reported a decline in memory. Therefore, the relationships identified and reported in the previous section between tumour type, radiotherapy protocol, assessment used, and decline are mirrored.

Twenty-three of the included studies reported on maintenance of scores that could be associated with executive functioning. As with memory, a large portion of these studies (n=11) [90, 105, 107, 118, 135, 136, 138, 178, 179, 182] concluded this from a reduction of MMSE scores alone. Five other studies also reported on only on assessment including the NeuroCogFX (NCFX) [93, 94], the NeuroTrax Programme (NeuroTrax) [119] and the Wechsler Adult Intelligence Scale-Revised (WAIS-r) [92]. The remaining eight [101, 114, 115, 117, 128, 137, 139, 180] utilised multiple assessments to increase sensitivity. No further insight was given into the areas of executive functioning seen to decline. In addition, three of these were cross-sectional studies [92, 101, 114], so no change over time could be determined. However, no studies that reported longitudinal result reported any change in executive functioning over time.

Four studies reported an improvement in test scores that could be the result of an improvement in patient executive functioning. Of these four, two [130, 132] used the MMSE in isolation. The remaining two [123, 131] used multiple assessments. Onodera et al (2014) detailed that improvement was seen in patients' working memory eight months after the completion of WBRT [131].

It is evident that whilst executive functioning is not seen to decline in all cases, many deficits may have been missed by utilising assessments that lack sensitivity. In addition, whilst the presence of reversible acute decline was reported, this improvement over time was only observed in a small number of the included studies. Furthermore, as with any brain tumour-based study, there is no way of comparing functioning to a pre-tumour baseline.

Where specific deficits were identified they were in the areas of orientation, calculation, initiation, construction and working memory.

2.3.5 Motor Dexterity

The assessment of motor dexterity is not a primary outcome in many of the cognitive assessments used. However, motor dexterity is often required to complete tasks presented in assessments. Therefore, patient scores in these assessments could be influenced by patient motor dexterity. A total of 42 studies included at least one assessment that required aspects of motor dexterity. These assessments were the Rey-Osterrieth complex figure (ROCF), Design Fluency (DF), Brief visual special memory test – revised (BVMC-r), Grooved Pegboard Test Dominant (and Non-Dominant) GPTD(ND), Line Bisection Task (LBT), MMSE and Trail making test a + b (TMT(a+b)). Of these tests the GPTD(ND) is the only one that is designed to predominantly assess an individual's motor dexterity.

Thirteen of the studies [88, 89, 91, 97, 108, 110, 111, 120, 122, 126, 127, 133, 134, 175, 183] included reported a decline in assessment scores that could be attributed to a decline in motor dexterity. Of these, four [108, 122, 127, 175] directly assessed motor dexterity with the GPTD and GPTND. Chang et al (2009) reported on a RCT to determine the effect of administering additional WBRT alongside STR [122]. They report that whilst decline was seen in patient GPTD and GPTND scores in those who received WBRT, they did not reach statistical significance. However, as there is no control nor baseline score reported, it is unclear as to how functioning in those who received STR alone is affected.

Twenty-one studies reported a maintenance of test scores that could be associated with motor dexterity [90, 101, 104, 105, 107, 109, 113, 116-119, 124, 127, 129, 131, 135, 136, 138, 139, 178, 182]. Motor dexterity was determined to be maintained from a maintenance of MMSE scores alone in fifteen of these studies [90, 101, 104, 105, 107, 109, 116, 118, 124, 127, 135, 136, 138, 139, 178, 179, 182]. Two studies utilised the GPTD(ND) [109, 127].

Improvement was reported in four studies. Two of which [130, 132] reported an improvement in MMSE scores after treatment. Navarria et al (2017) used several assessments to determine patient cognition and highlighted that whilst most assessment scores remained stable over time, the ROCF and TMTa were seen to improve [180]. Chang et al (2007) reported improvement in GPTD(ND) scores over time [123].

Whilst the GPTD(ND) scores were seen to maintain or improve in a few studies, the majority of studies that used this assessment reported a decline. This shows that, as with other domain areas, domain-specific assessment tools appeared more likely to identify a deterioration in function, with studies using global tools such as MMSE more likely to report stable or improved function.

2.3.6 Language

Language was assessed in 50 of the included studies. This was done using a total of fourteen assessments. The majority (n=9) of assessments used assessed language as part of a more general cognitive assessment. However, five of the assessments used were specific to language. This included the Auditory Naming Test (ANT), the Boston Naming Test (BNT), the Verbal Fluency test (VF) the Controlled Oral Word Association Test (COWAT) and the multiple-choice test of vocabulary knowledge (MWT).

Of these fifty studies, 22 reported a decline in one or more assessments involving language [88, 92, 93, 95, 97, 100, 104, 108, 111, 120, 122, 124, 126, 127, 133, 134, 137, 175, 177, 182, 183]. In general, studies that reported on a decline in language did so with the use of multiple assessments with only six studies reporting language decline through a decline in MMSE score. Whilst the MMSE is a general assessment of cognition, Yavas et al (2012) reported a specific decline in patient language skills with the use of the MMSE [104].

Twenty-five studies described a maintenance in scores associated with patient language [90, 94, 96, 101, 105, 107, 109, 110, 113-115, 117-119, 123, 128, 129, 131, 135, 136, 138, 139, 180]. As with other domains, maintenance was observed as a maintenance of MMSE score in several studies. However, Salander et al (1995) reported MMSE results alongside the results of a language specific assessment [101]. Maintenance of language associated functioning was seen in both the MMSE and VF scores. The remaining two studies in this group report an improvement of language related scores. Both Pham et al (2016) and Nakazaki et al (2013) demonstrate an improvement in language through the increase of MMSE scores in patients following radiotherapy [130, 132].

Whilst language is a part of only fourteen of the assessments reported in included studies, at least one of these assessments was reported in almost all of the included studies. This along with the multiple assessments used in many of the studies could indicate that language is the domain with the most thorough representation. The proportion of studies reporting a decline or maintenance of language can be seen to

showcase the variation of cognitive symptoms that could be experienced by patients. It can therefore be concluded that patients may experience speech and language difficulties once their treatment is complete.

2.3.7 Attention and processing speed

As attention and processing speed are integral elements to all cognitive processes, the assessment of attention and processing speed is observed throughout all of the included studies. Eight of the assessment reported claim to include assessments of attention, including the brief test of attention (BTA) and the test of attentional performance (TAP) which are designed to assess attention specifically. Habets et al (2014) [184], Gui et al (2020)[95], Yavas et al (2012) [185], Douw et al (2009) [186] and Correa et al [187] all highlight deficits in participant attention and/or processing speed specifically. However, as attention and processing speed can be considered facilitators of functioning, they are required as part of every cognitive process. In addition to this, none of the included studies specified any difference between patients' attention and processing speed.

Study ref	Method	Patient details	Tumour type	Radiotherapy protocol	Cognitive tests used	Time points measured	Cognitive outcomes	PPI	Quality grade
Ahluwalia et al, 2019 [117] USA	A multicentre prospective study of laser interstitial thermal (LITT) ablation in patients with radiographic progression after stereotactic radiosurgery for brain metastases. Cohort	Aged over 18 KPS >60 N=44	Brain metastasis	RT: SRS (dose not specified) Chemo: one patient no details Surgery: 12 patients had undergone prior resection	HVLT-R & MMSE	3- and 6-months post treatment	No significant change was noted in the HVLT-R or MMSE scores between baseline and the 12- or 26-week results for the overall group.	Not reported	Medium
Bauman et al, 2016 [118] Canada	To examine functional outcomes and quality of life of WBRT with integrated fractionated STR for BM treatment. Cohort	Aged over 18 KPS >70 N=87	Brain metastasis	RT: WBRT + STR (WBRT 30Gy, STR 60Gy) Chemo: not detailed Surgery: not detailed	MMSE	Baseline (before treatment) and 6 weeks, 3,6,9 and 12 months after.	No significant alteration in MMSE score after treatment.	Not reported	Medium
Berger et al, 2018 [119] Israel	To prospectively evaluate the neuropsychological effects following post-resection SRS treatment. Cohort study	Aged over 18 KPS >60 N=12	Brain metastasis	RT: STR (22-24Gy, 16-18Gy and 15Gy for cavities less than 20mm, 21-30mm and 31-35mm respectively) Chemo: not detailed Surgery: All patients	NeuroTrax	1 day before RT and 3 months after	Significant improvement in immediate verbal memory after 3 months. Performance maintained in all other tested domains.	Not reported	High
Berk et al, 2007 [120] USA	To determine if high-dose melatonin improves survival over historical controls, and	Aged over 65 KPS not specified	Brain Metastasis	RT: WBRT (30Gy) Chemo: yes in 58 patients. Details not given	MMSE	1,2,3,6,12 and 18 months after RT	Significant decline in overall MMSE score.	Not reported	High

	to determine if the time of day melatonin was given affects its toxicity. Cohort	N=126		Surgery: not detailed					
Brown et al, 2016 [175] USA	To determine whether there is less cognitive deterioration at 3 months after SRS alone vs SRS plus WBRT RCT	Aged over 18 KPS not specified N=213	Brain metastasis	RT: STR alone (20-24Gy) and STR + WBRT (WBRT 30Gy, STR 18-22Gy) Chemo: Not detailed Surgery: Not details	HVLT-R, GPTD, GPTND, COWAT & TMTa+b.	Baseline (post RT) and 6 weeks, 3,6,9,12,16,24,36,48 and 60 months after.	Decline was observed in all domains tested. Scores were significantly lower in patients who had received WBRT	Not reported	High
Chang et al, 2009 [122] USA	To help clarify whether elective WBRT should be given with SRS or deferred RCT	Aged over 18 KPS >70 N=58	Brain metastasis	RT: STR or STR + WBRT (WBRT 30Gy, STR 24 Gy, 18 Gy, and 15 Gy for tumours <= 20 mm, 21-30 mm, and 31-40 mm in maximum diameter Chemo: not detailed Surgery not detailed	HVLT-R, TMTa+b, DSpan, DSym, COWAT, GPTD & GPTND.	Before RT then 1,2,4,6,9,12 and 15 months after RT	Significant decline seen in HVLT-R in patients with WBRT. Decline observed in all other tests but did not reach significance.	Not reported	Medium
Chang et al, 2007 [181] USA	A pilot study to measure neurocognitive function (NCF) in patient with 1-3 BM treated with SRS alone RCT	Aged over 18 KPS >70 N=15	Brain metastasis	RT: SRT (24 Gy, 18 Gy, and 15 Gy for tumors <= 20 mm, 21-30 mm, and 31-40 mm in maximum diameter) Chemo: not detail Surgery: not detailed	WAIS-r, DSpan, DSym, TMTa+b, HVLT-R, COWAT, GPTD & GPTND	Before RT then 1,2,4,6,9,12,15 and 18 months after RT	The majority of patients had stable or improved scores. Improvement seen across executive function, memory and motor dexterity but did not reach statistical significance.	Not reported	High

Fernandez et al, 2012 [124] Portugal	To assess QoL, survival and cognitive impairment for patients with BM 1-3 months after radiation. Cohort	Aged over 18 KPS >70 in 51.3% N=39	Brain metastasis	RT: WBRT (30Gy) Chemo: Not stated Surgery: not detailed.	MMSE and in an unnamed quality of life survey	1 week before RT then 1 and 3 months after	Decline observed in cognition reported through the quality of life questionnaire but no significant change in MMSE	Not reported	Medium
Gondi et al, 2014 [177] USA	To compare memory function in patients receiving HA-WBRT to patients receiving WBRT Cohort	Aged over 18 KPS >70 N=308	Brain metastasis	RT: WBRT (30Gy). Chemo: not detailed Surgery: not detailed	HVLT-R	Baseline then 2,4 and 6 months after RT	Significant decline in HVLT-R scores observed, higher hippocampal does significantly predicted greater decline over time.	Not reported	High
Kepka et al, 2016 [126] Poland	To evaluate if NCF outcomes in patients with resected single BM after STR of the tumour bed are not inferior compared to those achieved with WBRT RCT	Aged over 18 KPS >70 N=59	Brain metastasis	RT: STR (15Gy) or WBRT (30Gy) Chemo: not detailed Surgery: All patients	MMSE	Before RT then 8 weeks and 3 months after.	Decline of MMSE observed in most patients (decline on 3 or more points). No significant difference between WBRT and STR.	Not reported	Medium
Li et al, 2008 [127] USA	To examine the relationship between neurocognitive function and quality of life in patients with brain metastasis after WBRT Cohort study	Aged over 18 KPS >70 N=208	Brain metastasis	RT: WBRT (30Gy) Chemo: none Surgery: Not detailed	COWAT, GPTD, GPTND & TMT a+b	Just after RT, then every 6 months until death	Significant decline observed in all tested domains. Decline was a statistically significant predictor of quality of life decline.	Not reported	Medium
Li et al, 2007 [128] USA	To evaluate the effect of WBRT on	Aged over 18 KPS >70	Brain metastasis	RT: WBRT (30Gy) Chemo: motexafin gadolinium.	COWAT, GPTD, GPTND & TMTa+b	Monthly after RT for 6 months, then	Cognitive test scores were observed to improve or maintain	Not reported	Medium

	neurocognitive function. Cohort	N=208		Surgery: not detailed		every 3 months until death	after treatment unless tumour growth. Statistically significant improvement in executive functioning and motor dexterity.		
Minniti et al, 2013 [179] Italy	To evaluate clinical outcomes of SRS as initial treatment for brain metastasis in patients 70 or older Cohort	Aged over 70 KPS >60 N=102	Brain metastasis	RT: STR (20Gy, 18Gy or 16Gy). Chemo: Not detailed Surgery: not detailed	MMSE	6 and 12 months after RT.	No significant alteration in MMSE score after treatment.	Not reported	Medium
Nakazaki et al, 2013 [130] Japan	To evaluate MMSE scores of patients after Gamma knife surgery. Cohort study	Aged over 18 KPS > 50 N=76	Brain metastasis	RT: STR (median 22Gy) Chemo: none Surgery: 3 patients	MMSE	Before RT then every 3 months after until death.	Significant improvement was observed with time after treatment.	Not reported	High
Onodera et al, 2014 [131] Japan	To investigate whether the neurocognitive function at 4 months could be a relevant primary endpoint in clinical trials dealing with BM Cohort study	Aged over 18 KPS >70 N=27	Brain Metastasis	RT: WBRT (35Gy) (3 or more BM) or STI (25Gy for lesions 1.5cm or less and 28-35 for larger lesions) (less than 3 BM).	RBANS, TMTa+b and MMSE	Before treatment then 4, 8 and 12 months after RT	Statistically significant decline in delayed memory at 4 months after treatment. Significant improvement in immediate memory after 8 months (In WBRT only). No significant change at 12 months from 8. No changes in MMSE score	Not reported	High

Pham et al, 2016 [132] USA	Prospective trial of the impact of intraoperative Cs-131 on neurocognitive function and quality of life in patients with resected brain metastasis. Cohort	Aged over 18 KPS not specified N=24	Brain metastasis	RT: brachytherapy (80Gy). Chemo: not detailed Surgery: All patients	MMSE	Before treatment then every 3 months after for 1 year.	Significant improvement was observed in MMSE scores of patients after treatment	Not reported	Medium
Pospisil et al, 2017 [133] Czech Republic	To evaluate post-WBRT changes in hippocampal concentration of h-tNAA as a marker of neuronal loss and to correlate those changes to NCF cohort	Aged over 18 KPS >70 N=18	Brain metastasis	RT: WBRT (30Gy) Chemo: 75% of ppts Surgery: 44% of ppts	MMSE, AVLT, BVMT-R.	Before RT and 4 months after	Decline in cognition observed with the exception of MMSE scores which showed No significant changes.	Not reported	High
Qing et al, 2020 [188] China	To compare the survival outcomes and neurocognitive dysfunction in non-small cell lung cancer (NSCLC) patients with brain metastases (BM ≤10) treated by whole-brain radiotherapy (WBRT) with sequential integrated boost (SEB) or simultaneous integrated boost (SIB). Cohort	Aged over 18 KPS >70 N=52	Brain metastasis	RT: WBRT (30Gy) with SEB (12Gy) or SIB (40Gy) Chemo: Not detailed Surgery: None	MMSE	At end of treatment and 1, 3 and 6 months after RT.	Significant decline of MMSE scores seen in both arms although WBRT+SEB group showed less impairment.	Not reported	Medium

Regine et al, 2001 [135] USA	To evaluate neurocognitive outcome as measured by the MMSE among patients with unresectable BM randomly assigned to AF or AH WBRT. RCT	Aged over 18 KPS >70 N=359	Brain metastasis	RT: acceleration-fraction (30Gy) or accelerated-hyperfractionated (54.4Gy). Chemo: not stated Surgery: not detailed	MMSE	Before treatment then 2 and 3 months after.	No significant differences in MMSE scores unless tumour growth	Not reported	Medium
Weber et al, 2011 [136] Switzerland	To assess treatment toxicity and patient's survival/QoL after VMAT with SIB for patients with 1-4 BM treated with or without surgery. Cohort	Aged over 18 KPS >70 N=29	Brain metastasis	RT: WBRT (40Gy) Chemo: Not detailed Surgery:	MMSE	Before treatment, during (week 1 and 2) and every 3 months after RT until tumour progression	No significant change in MMSE scores	Not reported	Medium
Welzel et al, 2008 [137] Germany	To prospectively compare the effect of prophylactic and therapeutic WBRT on memory function in patients with and without BM. Cohort study	Aged > 18 KPS >60 N=44	Brain metastasis	WBRT (40Gy) Chemo: Not detailed Surgery: Not detailed	AVLT, MCT, TAP, MWT	1 day before RT, at completion and then 6-8 weeks after.	Statistically significant cognitive dysfunction after WBRT is restricted to verbal memory.	Not reported	Medium
Yamamoto et al, 2017 [189] Japan	To confirm the long-term safety of SRS alone in patients with 5-10 BM Cohort	Aged over 18 KPS not specified N=1194	Brain metastasis	RT: STR (dose not detailed) Chemo: not detailed Surgery: not detailed.	MMSE	4 and 12 months after RT then every 12 months thereafter.	No significant change in MMSE scores	Not reported	Medium

Zhong et al, 2020 [190] USA	To investigate the use of WBRT with a simultaneous integrated boost (SIB) to visible lesions in patients with brain metastases. Cohort	Aged over 18 KPS >70. N=13	Brain Metastasis	RT: WBRT (25 or 37.5Gy) +SIB (45 or 52.5Gy) Chemo: not detailed Surgery: Not detailed	MMSE, MOS & HVLt-R	Before treatment, one month after then every 3 months until study end date.	No significant changes to cognition following treatment.	Not reported	High
Okoukoni et al, 2017 [100] USA	To correlate volumetric radiation doses received by critical neuroanatomic structures to post RT memory impairment. Cross sectional	Aged over 18 KPS >70 N=53	High grade and low-grade primary	RT: partial or WBRT (median 54Gy) Chemo: not detailed Surgery: not detailed	HVLt-R	Once, median 10 months after RT (range 6-26 months)	Hippocampal dose is a significant predictor of cognitive impairment.	Not reported	Medium
Cayuela et al 2019 [89] Spain	Cognitive and brain structural changes in long-term oligodendroglial tumor survivors Cohort	Aged over 18 KPS not detailed N=48	High grade or low-grade primary	RT:STR (dose not specified) Chemo: 79% of patients Surgery: All patients	HVLt-R, ROCF, COWAT & TMTa+b. If inadequate completion was noted due to moderate cognitive compromise, the MMSE was completed.	2-5, 6-10 or over 10 years after RT	Long-term oligodendroglial tumor survivors who underwent standard RT ± CT treatment, mainly >5 years of its completion, present cognitive impairment, statistically significant decline of memory and executive functions, associated with late GM and WM damage	Not reported	High
Younis et al, 2009 [105]	To evaluate the effect of treatment with	Aged over 18	High grade or low-	RT: STR (60Gy)	MMSE	Once, 9 months after RT	MMSE scores remained statistically	Not reported	Medium

Egypt	radiotherapy on cognitive functions and neurological manifestations in patients with brain tumours. Cohort	KPS not detailed N=52	grade primary	Chemo: not detailed Surgery: All patients			unchanged with improvement observed in some scores.		
Archibald et al, 1994 [88] Canada	The sequential neuropsychological testing of two groups of patients with successfully treated HGG. Cohort study	Aged over 18. KPS not measured. N=25	High grade primary	RT: WBRT (35-57Gy) Chemo: All patients other than 1. Surgery: All patients	WAIS-r, DSym, ROCF, SRT, TMTb, MSRC & DF	Interval inconsistent, but each participant assessed 4 times.	Most patients that did not score poorly at baseline significantly deteriorated over time.	Not reported	Low
Choucair et al, 1997 [191] USA	To prospectively test the feasibility of performing QoL and neuropsychological evaluation. Cohort study	Aged over 18 KPS >60 (60% >90). N=126	High grade primary	RT: STR (60Gy) or hyperfractionated (72 Gy). Chemo: Yes Surgery: All patients.	MMSE	Before RT, every 3 months throughout and after the completion of RT.	Scores did not significantly differ.	Not reported	Medium
Corn et al, 2009 [176] Israel	To describe the quality of life endpoints as well as results pertaining to neurocognitive impairment. Cohort study	Aged over 18 KPS <60 N=185	High grade primary	RT: STR (66Gy) Chemo: None Surgery: All patients	MMSE.	Start of RT, at end of RT and 4 months after.	Significant decline in MMSE scores	Not reported	Medium
Davies et al, 2003 [92] UK	To describe patient outcomes and contact with rehabilitation services two years after the diagnosis of	Aged over 18 KPS not specified. N=12	High grade primary	RT: protocol not detailed (45-64Gy) Chemo: 4 patients Surgery: All patients	WAIS-r	Once, at least 2 years after diagnosis	Significant decline seen in verbal and visual memory. Verbal fluency tended to be weak,	Not reported	Medium

	malignant cerebral glioma. Cross-sectional study						but no significant change.		
Flechl et al, 2017 [192] Austria	To evaluate QoL and NC during the course of the disease in GBM. Cohort study.	Aged over 18 KPS not specified N=42	High grade primary	RT: STR (60Gy) Chemo: All patients Surgery: All patients	NCFX	6 times every 3 months at least 4 months after diagnosis	Median summary scores remained were maintained throughout the study period. (No significant change)	Not reported	medium
Flechl et al, 2012 [93] Austria	To assess the sociodemographic characteristics and clinical outcomes. Cross sectional study	Aged over 18 KPS between 90-100 except for 1 patient with 40 N=17	High grade primary	RT: Partial (60Gy) Chemo: yes Surgery: All patients	NCFX	Once at least 3 years after diagnosis	Moderate impairment was observed in cognitive functions including attention, verbal and figural memory and verbal fluency. However, there was no significant change in overall test scores.	Not reported	High
Gui et al, 2020 [95] USA	To prospectively evaluate the impact of limiting radiation dose to the NPC niches on tumor progression, survival, and cognition in patients with glioblastoma. Cohort	Aged over 18 KPS >70 N=30	High grade primary	RT: STR (mean 41.8Gy) Chemo: TMZ Surgery: All patients	WAIS, TMTa+b, COWAT, HVLt-R.	Before RT then 6 and 12 months after	Significant decline observed in areas of processing speed, verbal learning, and memory as measured by TMTa and WAIS. No significant change in other test scores over time.	Not reported	High
Habets et al, 2014 [184] Netherlands	To evaluate cognitive functioning and HRQoL in long-term survivors. Cross-sectional study	Aged over 18 KPS not specified.	High grade primary	RT: Protocol not detailed Chemo: 22 patients	DSym, W CST, Stroop, VVL, MCT & VF	Once. Mean 146 months after diagnosis	Cognitive function was observed to be variable in long-term survivors and	Not reported	High

		N=32		Surgery: Not detailed			significant deficits were observed in working memory, information processing speed, psychomotor functioning, and executive functioning.		
Keime-Guibert et al, 2007 [193] France	To compare radiotherapy and supportive care to supportive care alone in elderly patients. RCT	Aged over 70 KPS >70 N=85	High grade primary	RT: STR (50Gy) Chemo: None Surgery: All patients	MMSE, MDRS	Baseline then every month for 3 months. MDRS administered 60 and 135 days after RT.	MMSE significantly declined over time, nPI did not significantly change and the MDRS remained unchanged except for progressive deterioration in the initiation and construction subscales.	Not reported	Medium
Lombardi et al, 2018 [178] Italy	To evaluate the characteristics in GBM patients with standard first line therapy outside clinical trials. Cohort study	Aged over 18 KPS >70 N=111	High grade primary	RT: STR (60Gy) Chemo: All patients Surgery: All patients	MMSE	2 weeks after surgery, at start of RT then 1, 3, 6 and 9 months after RT	MMSE remained stable unchanged.	Not reported	High
Navarria et al, 2017 [180] Italy	To evaluate hypofractionated radiation therapy (HFRT). Cohort study	Aged over 18. KPS >70. N=97	High grade primary	RT: HFRT (60Gy) Chemo: 96% of patients. Surgery: All patients	TT, PN, VF, DSpan, AVLT, ROCF, IAT, TMTa+b, AMT, Stroop & RPM	Median follow up time was 15.2 months and 20.2 months.	Overall scores remained statistically unchanged after treatment with improvement	Not reported	Medium

Salander et al, 1995 [101] Sweden	To further understand neuropsychological performance in adults with malignant gliomas. Cross-sectional	Aged over 18. KPS not specified. N=11	High grade primary	RT: STR (56Gy) Chemo: Patients randomised to receive. Surgery: All patients	MMSE, DSpan, DSym, Arithmetic, Vocabulary, Reading/recalling, VF, WCST, KB & RPM MoCA	Before RT, 2 months after then 5 months after is no signs of progression seen.	observed in the ROCF, IAT and TMTa. Significant deficit in long-term memory, but no clear impairment in global intellectual abilities.	Not reported	Medium
Wang et al, 2020 [194] China	To identify risk factors for cognitive impairment in patients of postoperative HGG Cohort	Aged over 18 KPS >70 N=229	High grade primary	RT: STR (60Gy) Chemo: TMZ Surgery: Full or partial resection	MMSE MoCA	Before treatment, then 3, 6, 9, 12, 15 and 18 months after.	64.2% had a significant decline in MoCA scores at the end of follow up. Median follow up duration was 9 months.	Not reported	High
Wang et al, 2010 [182] USA	To analyse within-subject longitudinal changes of cognitive function and quality of life, characterise the effects of patient specific factors on cognitive, QoL and survival and explore the prognostic implications of cognitive function and QoL. RCT	Aged over 18. KPS >60. N=289	High grade primary	RT: STR (59.4Gy) Chemo: One treatment arm Surgery: Not detailed	MMSE	Before treatment then 3, 6, 9 and 12 months after. Followed by every 4 months in year 2, every 4 months in year 3 and every 6 months in years 3-5. Then annually until death.	MMSE scores remained stable over time	Not reported	high

Yavas et al, 2012 [195] Turkey	To assess quality of life and cognitive and emotional distress in patients treated for high grade glioma. Cohort study	Aged over 18. KPS >70. N=118	High grade primary	RT: STR (60Gy) Chemo: All patients Surgery: All patients	MMSE	Before RT, at the end of RT, then 3, 6, 12, 18, 24 and 30 months after.	Follow up scores of orientation, attention and calculation, and language significantly decreased.	Not reported	Medium
Sherman et al, 2016 [196] USA	To understand the neurocognitive effects of proton radiotherapy (PRT) in patients with low grade glioma (LGG). Cohort	Aged over 18. KPS >70 N=20	Low grade glioma	RT: Proton radiotherapy (54Gy). Chemo: none Surgery not detailed	WAIS, BNT, ANT, CPT, WMS, TMTa+b, COWAT, WCST, HVLTR & BVMT-R	Before treatment and once a year for 5 years.	Overall, cognition was maintained after treatment.	Not reported	High
Armstrong et al, 2012 [197] USA	To investigate semantic versus perceptual, and versus verbal, memory to determine the most disease-specific measure of RT-related change and understanding the neurotoxicity from radiotherapy to brain. Cohort	Aged over 18 KPS not specified N=70	Low grade primary	RT: STR (Median 54Gy) Chemo: one patient from each group Surgery: not detailed.	AVLT & BFL	Baseline (just before treatment), 1.5 months, 4.5 months and 1 year post treatment.	A decline in memory was identified. Delayed recall and time to recognise were observed to significantly decline and was specific to the retrieval of semantic memory.	Not reported	Medium
Breen et al, 2020 [107] USA	To provide a final update on oncologic and cognitive outcomes of high-dose versus low-dose radiation for low-grade glioma Cross-sectional	Aged over 18 KPS not specified N=203	Low grade primary	RT: STR (50.4Gy or 64.8Gy) Chemo: not detailed Surgery: all patients	MMSE	Every 4 months in years 1-2, then every 6 months years 3-5.	Cognitive function appeared to be stable after radiation as measured by MMSE.	Not reported	Medium

Correa et al, 2008 [198] USA	A longitudinal cognitive follow-up in a subgroup of patients who received RT, chemotherapy, or no treatment. Cohort	Aged over 18 KPS not specified N=25	Low grade primary	RT: STR (54Gy-68.4Gy) Chemo: 5 of 6 patients who had RT. 3 patients had chemo only. Surgery: All patients	BTA,TMTa+b, VF, HVLt-R, BVMT-R.	Start of RT then 6 and 12 months after.	Significant decline observed in nonverbal recall and in executive function. Maintenance seen in all other domains.	Not reported	High
Correa et al, 2007 [187] USA	To assess cognitive functioning in LGG patients who received conformal radiation therapy, chemotherapy or not treatment. Cross-sectional	Aged over 18 KPS not specified N=40	Low grade primary	RT: STR (54Gy-68.4Gy) Chemo: 5 patients Surgery: 3 patients	DF, DSpan, WAIS-r, BTA, TMTa+b, Stroop, ACT9 & 18, VF, HVLt-R, BVMT-R, GPTD, GPTND, BNT & JLO	Once. Time since treatment not detailed	Patients who received treatment had significantly lower scores than untreated patients on psychomotor and non-verbal memory domains. A decline was also seen in attention, executive, verbal memory and language domains but did not reach significance.	Not reported	High
Douw et al, 2009 [186] Netherlands	To assess the radiological and cognitive abnormalities in survivors of LGG at a mean of 12 years after initial diagnosis. Cross-sectional	Aged over 18 KPS not specified N=65	Low grade primary	RT: Protocol not stated Chemo: none Surgery: All patients	DSym, Stroop, WCST, VVL, MCT & VF	Mean 12 years after diagnosis	Patients who received radiotherapy were observed to have significantly lower attentional functioning. Decline was also seen in psychomotor functioning, working memory and information	Not reported	High

Klein et al, 2002 [199] Netherlands	To identify the specific effects of radiotherapy on objective and self-reported cognitive function, and on cognitive deterioration over time. Cross-sectional study	Aged over 18 KPS not specified N=295	Low grade primary	RT: STR or WBRT (Dose not stated) Chemo: Not detailed Surgery: not detailed	DART, LBT, FRT, JLO, DSym, VVL, WM, Stroop, VF & WCST.	Once, 1-22 years post RT.	processing speed, although this was not statistically significant. Patients receiving high fractions of radiotherapy had poorer cognitive performance overall. Significant difference in memory domains only.	Not reported	High
Prabhu et al, 2014 [183] USA	To determine the effect of the addition of chemotherapy to radiotherapy on cognitive function. RCT	Aged over 18. KPS not specified. N=251	Low grade primary	RT: STR (54Gy) Chemo: 125 patients. Surgery: All patients	MMSE	Every 4 months for 1 year, every 6 months for 2 years then once a year thereafter.	No significant difference in MMSE scores between arms but both were seen to significantly decline.	Not reported	Medium
Taphoorn et al, 1994 [114] Netherlands	To determine the QoL and cognitive functions in long-term survivors and the impact of RT on these parameters. Cross-sectional	Aged over 18 KPS >60 N=60	Low grade primary	RT: STR (45-63Gy) Chemo: none Surgery: All patients	Stroop, WISC, AVLT, VF, D2-test, FRT & JLO.	Once, at least 1 year post RT	Treatment was observed to have no negative impact on cognition.	Not reported	Medium
Torres et al, 2003 [115] Canada	To investigate longitudinal cognitive functioning in patients with brain tumours treated with modern highly conformal fractionated partial brain radiotherapy. Cohort	Aged over 18 KPS >60 N=22	Low grade primary	RT: Partial (54Gy) Chemo: none Surgery: All patients	SRT, DSym, WAIS, DSpan, TMTa+b.	Before treatment, then 3, 6 and 12 months after.	Treatment was not associated with cognitive decline through the first 2 years after treatment.	Not reported	Medium

Yavas et al, 2012 [185] Turkey	To evaluate the HRQoL in treated patients. Cohort	Aged over 18 KPA >70 N=43	Low grade primary	RT: STR (60Gy) Chemo: All patients Surgery: not detailed	MMSE	Before RT, then every 3 months for 1 st 2 years and every 6 months for 2 to 5 years	MMSE scores of orientation, attention and calculation were significantly decreased by 18 months. Other domains remained stable.	Not reported	Medium
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Table 5: Studies included in the systematic review.

2.4 Discussion

This review synthesises the existing literature to summarise the areas of cognition in which decline has been reported in patients with brain tumours after the completion of radiotherapy. Whilst results across domains did vary, decline was reported in areas of memory, executive functioning, motor dexterity, attention and processing speed, and language. It was seen that variation of the cognitive outcomes reported is impacted by method of assessment in addition to the tumour type or radiotherapy protocol.

The variation due to the method of assessment used is highlighted by the discrepancies of outcomes. More domain specific tests were often seen to be more sensitive than the MMSE with regard to identifying the presence and specific nature of deficits. In addition to this, various studies of the robustness of the MMSE have concluded that this test is often proven to be insensitive to subtle cognitive changes [200]. This, coupled with the inconsistency of assessments used, prevents any meaningful conclusions being made regarding the relative influence of tumour type, location or radiotherapy protocol on cognitive outcomes in patients.

This challenge regarding determining causation is mirrored in the finding of a systematic review conducted by Lawrie et al (2019). In this, they highlighted the lack of evidence available to suggest that cognitive impairment was associated with radiotherapy. Whilst they did not highlight the inconsistency of assessments to be responsible for the unconvincing nature of the evidence, they mirrored the stance that more comprehensive neuropsychological tests are preferable to the MMSE as they are more likely to be sensitive to more subtle changes in cognitive functioning.

However, attempting to evaluate the specificity of assessments comes with its own challenges. The general ambiguity surrounding the theories of cognitive processes and the overlap between domains makes it difficult for any assessments to be completely clear on what they measure. This is particularly pertinent with regards to attention and processing speed. As processing speed is a measure of the time it takes to process our surroundings and respond accordingly [201], then a decline in this could be attributed to difficulty with any step in that process. Similarly, deficits in areas of executive functioning could diminish a person's ability to remain attentive to a task [202]. This could in turn disrupt their ability to take in information, leading to what could be identified as a memory deficit. However, even though the true nature of decline may be difficult to determine, it can be seen throughout this review that

domain specific assessments may detect decline where more global assessments may not.

With this considered, given that the majority of included studies were focused on the evaluation of treatment modalities, cognitive functioning was often a secondary outcome. Therefore, using a general assessment was usually appropriate for these studies. One of the main benefits of the MMSE is the ease in which it is administered. For this reason, the MMSE is often the assessment of choice in medical and health research [203, 204]. Along with the ease of administering, the MMSE also claims to detect alterations in a wide range of cognitive domains including orientation, registration, attention, flexibility, recall, language, repetition and the completion of complex demands [205]. Therefore, if a study is not focused on detecting subtle changes, the MMSE may be seen as an acceptable measure of cognition. It is also worth noting the use of the Montreal Cognitive Assessment (MoCA) [206] by Wang et al (2020) [103]. Like the MMSE, the MoCA is designed to assess a wide range of domains, however, it has been seen to be more sensitive to mild changes than the MMSE [207]. However, as it is only reported in one of the included studies, no conclusions can be drawn regarding its use in brain tumour research.

There are several limitations to be considered in this review. One of which is a general limitation of any systematic review. The quality of the answer to the review question is directly correlated to the quality of the included studies and is impacted by general publication bias. Overall, the studies included were determined to be satisfactory, however, every study is subject to limitations. One limitation exhibited by even the studies determined to be of high quality was the lack of reported use of PPI. This could be indicative of a lack of insight into the patient experience. The incorporation of PPI could have led to the use of outcome measures that may have catered to the patients' lived experience, thus acknowledging the subjective nature of cognitive decline rather than reaching conclusion based upon general assessment scores alone. That being said, the breadth of the review question allowed for a better understanding how cognition may be affected. The sheer number of studies included in this review allowed for the variation of cognitive outcomes to be explored. In addition to this, the lack of reported PPI could be due to a lack of consistent requirements from journals. Although the value of PPI has been increasingly acknowledged, there is still a clear lack of transparency as to how this is addressed in research. Staniszewska and colleagues published the Guidance for Reporting Involvement of Patients and the Public (GRIPP2) in 2017 [208]. These guidelines were the first international guidance to be developed to improve the quality of PPI

reporting in research papers, indicating that there may be a more structured expectation for the reporting of PPI in the future. However, as many of the studies included in this review were published prior to 2017, and this guidance is not yet mandatory, whilst it can be seen that the included studies do not report PPI, it cannot be assumed that there was none.

Another limitation was the sample size of many included studies. Several studies reported outcomes that did not reach statistical significance and it is possible that this could be due to their limited sample size. For example, Davies et al [92] reported that verbal fluency had a tendency to be 'weak', but there was no significant decline reported. As this was a study of just twelve participants, it is reasonable to question whether a larger sample would identify a significant decline or alter the narrative all together. Small sample sizes limit power to find any statistically significant changes and add to the challenge of generalising findings to the wider population. Therefore, when including studies with small sample sizes, it is important to highlight the implications this has on the overall narrative of the review.

Although conducting a review with such a broad question has enabled the inclusion of a vast amount of patient data, it still comes with its own limitation. Using such a broad question increased the heterogeneity of the eligible studies. This heterogeneity meant that a narrative synthesis was the only method of aggregating the results. A key weakness of conducting a narrative synthesis is the lack of formal guidance on how to correctly synthesise results [209]. However, as previously stated, the inherently subjective nature of cognition means that heterogeneity is something to be expected regardless of the question design. Additionally, although there is a lack of formal guidance available for conducting a narrative synthesis, this review followed the Cochrane guidelines for conducting a systematic review with a narrative synthesis. This enabled patterns in the literature to be explored and key areas of cognition to be exposed in a way that maintained as high a quality as possible.

Overall, the objective of this review was to identify the areas of cognition that have been reported to decline in patients with brain tumours after receiving radiotherapy. According to the studies included patients with brain tumours, regardless of type and grade, are susceptible to experiencing cognitive deficit. This review highlights this and shows how complex these deficits can be, and the need to consider detailed neurocognitive assessment to fully elucidate these rather than relying on generic tools alone. This complexity makes it challenging for health care professionals (HCP) to easily identify the cognitive difficulties individual patients may be facing. This in turn

results in many patients being insufficiently supported in regard to their cognitive symptoms.

2.4.1 Conclusion

The cognitive deficits observed in adults with brain tumours after receiving radiotherapy or combined chemo-radiotherapy are memory, executive functioning, attention, processing speed, language and motor dexterity. In the following chapter, these domains will subsequently be used to guide the development of a survey to further understand how such deficits may impact the day to day lives of patients. As this review has encompassed various brain tumour types, the next stage of this thesis will aim to better understand how the cognitive processes identified are affected in patients with HGG specifically.

In addition, this review has shown that there is still much to be done with in regard to the biological underpinning of cognitive decline. Therefore, there is no evidence to suggest that the administration of a potential screening tool should be dependent on tumour location.

Chapter 3: Changes in everyday memory and processing in patients with high-grade glioma after radiotherapy – A public online survey

3.1 Introduction

In this chapter, I will report on the development and results of an online, public survey that was conducted to investigate which cognitive deficits, identified in the systematic review, are most commonly experienced by HGG patients following palliative radiotherapy.

As the aim of this PhD is to develop a screening tool that is focussed on patients with HGG, it is necessary to further explore the experiences of this patient population. This chapter will report which deficits are experienced by patients with HGG. I have taken a multi-perspective approach to encompass the observations and opinions of health care professionals (HCP's) and the lived experiences of patients and their families. The results presented are a snapshot only of the experiences of patients who are living with the combined burden of the disease and any potential side effects caused by radiotherapy, rather than a method of determining which is the cause of cognitive decline.

The systematic review (Chapter 2) provided an understanding of the nature of cognitive deficits reported in studies involving brain tumour patients who have received radiotherapy. It is now understood that areas of memory, executive functioning, motor dexterity, attention and processing speed, and language have been seen to be impacted in patients with HGG. To obtain a better understanding of how this may impact patients with HGG, it was deemed most appropriate to engage with a large sample of this population via a public survey.

Surveys are a method of collecting information by asking specific questions to a well-defined population. Surveys can be conducted in person, by mail, over the phone or online. Dependent on the target population and the circumstances surrounding recruitment, it is important to consider which method is appropriate for a particular study [210].

Surveys are being increasingly utilised in medical research. They are a valuable aspect of social research; however, they are not limited to this area. Surveys can be developed to be used in a multitude of disciplines including medical research. This method of research serves to provide evidence on practice, attitudes, and knowledge

[211]. Survey methodology can provide an opportunity to directly ask patients questions, that they may not be able to via other methods. A survey is a minimally invasive method of enhancing the quality of care by taking the patient experience to the centre of the research [212].

In person surveys include the physical presence of an interviewer who will ask the survey questions and be able to assist the participant in their response. This enables more complex and richer data to be obtained. This must however, be considered with the increase in logistical costs and how the physical presence of an interviewer causes the a higher possibility for potential bias [213]. This could include social pressures guiding the participants response. Logistical costs may be reduced with the use of over the phone surveys, however this does not reduce the added risk of bias. The use of mail surveys, whilst more costly than over the phone surveys, will have less cost than in person surveys. Mail surveys also allow the respondent to complete the survey, free from potential bias set upon by an interviewer.

The use of online surveys allows participants to answer without the presence of an interviewer. This in itself provides several benefits to participants. Firstly, it allows for the possibility of anonymous participation. Allowing participants to respond anonymously may help in facilitating them sharing their experiences without the presence of societal pressures [214]. Participants may feel pressured when interacting with an interviewer to respond in a way that they think the interview expects. In addition to this, the lack of interviewer ensures that all respondents receive the survey questions in the same way. Thus removing any unintentional bias from the interviewer [215].

The strengths and limitations of the various methods of conducting a survey were considered and the use of a digital online survey was deemed most appropriate due to the lack of time restraint on respondents (as they are able to complete these at their own pace), ease of dissemination and low costs. The benefits that come with the use of online surveys are particularly favourable when considering this patient population. Due to the nature of the topic, it is necessary that the survey is presented in a way that allows patients to take part at their own pace, as to not put any additional pressure on them [216].

The ease of dissemination associated with online surveys, was beneficial in this study as recruitment of patients with HGG is challenging. This is due to the prevalence, symptom burden and prognosis associated with such a diagnosis. Recruitment of such a specific population is difficult and whilst HCP's and family members were also

recruited, patients were limited to the point in which they had completed radiotherapy, but were fit enough to take part. Therefore, conducting a survey that lacks geographical borders enables for a wider outreach. However, it is necessary to acknowledge the lack of control researchers have on who is taking part [217].

Online surveys work to almost completely remove additional logistical costs and the potential bias added by the presence of an interviewer. However, it is not without its limitations. Whilst online surveys are becoming increasingly popular [218], they may exclude participants with limited internet access. In addition to this, the absence of an interviewer means that more attention must be paid to ensure that questions can be clearly understood, and the lack of prompts may result in misinterpretation. These limitations must therefore be taken into account when designing and drawing conclusions from any online survey.

3.1.1 Aims

The primary aim of this survey was to determine which of the deficits highlighted in the systematic review are relevant for patient with HGG in their personal experience. The secondary aim was to work towards developing an understanding of how deficits are described by patients and their families.

3.2 Methods

3.2.1 Establishing a research paradigm

In order to conduct high quality research, it is important to establish an understanding of the underlying philosophical assumptions researchers have regarding the nature of reality and how knowledge is attained [219]. To identify which research paradigm this research belongs to, I will first identify the ontological and epistemological beliefs that influence this.

3.2.2 Ontology

The concept of ontology centers around the nature of being and existence. There are two distinct ontological positions; realism and idealism. Realism is the claim that there is a definitive 'truth' or 'real world' regardless of how this is perceived. Therefore, the truth is believed to be objective. Taking a realist approach in research would therefore involve trying to remove subjective perception to try and reach the 'truth'.

In contrast to this, idealism is the belief that the 'truth' or 'reality' is inseparable from human perception. This defines the truth as being subjective. Therefore an idealist approach in research requires an emphasis on how the outcome (or 'truth') is perceived in order to evaluate its existence.

A key aim of this PhD is to look into how patients and their families perceive changes in cognition. As we are interested in the subjective perception of how cognitive decline impacts QoL, this would indicate that an idealist stance would be taken. However, as previously stated, cognitive psychology is built upon the understanding that knowledge is attained through the senses, and the entire notion of cognitive decline is defined by an alteration of this process that skews how individuals react to the outside world. Therefore, this PhD was conducted with an acknowledgement of both objective and subjective truths.

3.2.3 Epistemology

Epistemology focuses on the nature of knowledge and ways of obtaining knowledge. The two main branches of epistemology are positivism and constructivism. Positivism adheres to the claim that knowledge is only 'factual' and 'trustworthy' if it is obtained through measurement. In research studies following this, findings are usually observable and quantifiable. On the other hand constructivism focuses on knowledge that is influenced by social constructs and draws conclusions based upon subjective experience rather than objective observation. Studies with a constructivist approach would more likely use qualitative methods.

As cognition is the way in which a person perceives and interacts with the external world around them, it is important to consider the ideas surrounding constructivism. However, as it was initially planned that the domains of cognition experienced to decline in patients should be quantified, this PhD was conducted using a mixed-method research design.

3.2.4 Research paradigm

Considering the aims of the PhD, it was clear that both qualitative and quantitative methodologies would be needed. There are advantages and limitations to both approaches. A quantitative approach lends itself to the rapid analysis of precise data, however, this may lead to important contextual factors being disregarded [220]. A qualitative approach on the other hand, provides opportunity for a more in depth examination. This knowledge however, cannot be generalised in other contexts [221].

In order to attempt to quantify the cognitive domains seen to decline in patients and further understand the best way of identifying these, a mixed-method approach was required. From a philosophical point of view, I have adopted a pragmatic approach for this research. The purpose of this research is work towards changing practice. Therefore, it was necessary to structure the research in a way that used the information available in a practical way, rather than it being guided by assumptions

about how knowledge is obtained [222]. There are arguments against using pragmatism as philosophical justification, such as the critique from Hall (2013). Hall argued that you cannot determine if a methodology works before the research has been conducted [223]. However, taking a pragmatic approach involves the selection of methodologies based on their proposed purposes, strengths and limitations in order to identify which method serves which purpose, rather than the anticipation of the results they will yield [220]. For this research, each method used has been guided by the findings of the previous stage.

3.2.5 Study design

This was a mixed method, cross sectional, observational study. This survey was open to the public from the 10th of September 2020 until the 1st of December 2020.

3.2.6 Participants

Inclusion criteria

The survey was designed to obtain information regarding patient experience after receiving radiotherapy. This is from the perspective of either the patient themselves, a family member or close friend, or health care professional interacting with high grade glioma patients. Participants were invited to identify as one of these groups. Participants were required to be over eighteen and either:

- A patient with a confirmed diagnosis of HGG and completed at least one course of radiotherapy
- A close friend or family member of an adult who had completed at least one course of radiotherapy to treat HGG
- A health care professional HCP with regular direct contact with HGG patients

3.2.7 Recruitment

This survey was launched as a public online survey. Participants were recruited online through social media (Twitter, LinkedIn, Facebook and Reddit) and charity run forums and newsletters (*brainstrust*, the Brain Tumour Charity 'BRIAN' forum, and Tenovus Cancer Care). The advertisement used on social media platforms can be seen in figure 5. Participants were informed that a printed Welsh version of the survey would be available upon request.

Participants Required

How is everyday memory and processing altered in patients with high-grade glioma after radiotherapy?

We are conducting a short survey looking into the day-to-day experiences of patients after receiving radiotherapy

If you are

- A **patient** diagnosed with high-grade glioma
- A **close friend or family member** of a patient diagnosed with high-grade glioma
- A **healthcare professional** with direct and regular contact with patients with high-grade glioma

we would like to hear about your experiences.

<https://cardiff.onlinesurveys.ac.uk/how-is-everyday-cognitive-performance-altered-in-patients-4>

Canolfan Ymchwil Gofal Lliniarol
Marie Curie
Palliative Care Research Centre
CARDIFF, CAERDYDD

CARDIFF
UNIVERSITY
PALLIATIVE CARE
RESEARCH CENTRE

Marie Curie Palliative Care Research Centre,
Division of Population Medicine,
Cardiff University School of Medicine

Email: mazzaschi@cardiff.ac.uk
Twitter:
@MCPCCCardiff
@FMazzaschi

Figure 5: Survey recruitment advertisement used for social media platforms

3.2.8 Participation

As I was not testing any hypothesis or looking into any correlations, there was no defined sample size. We aimed to describe the experiences of individuals and in order to do this, convenience sampling was utilised. Targeted recruitment was to be implemented if numbers of a group were particularly low in comparison to the other groups. The use of targeted recruitment was planned to assist in generating a sample that was representative of the target population to allow for the results to be generalised.

For this survey, participants were self-selected following survey promotion. A more targeted approach followed to increase participation in underrepresented groups once the survey was launched. The front page of the survey detailed that participation was voluntary and the participant was not obliged to answer any questions that they would like to decline. The completion of the consent agreement following the participant information and data usage page confirmed that the participant was not lacking capacity to consent, and that they had read and understood the relevant information provided.

Participants were invited to respond to a short series of questions regarding their eligibility. If they did not meet the inclusion criteria, they were redirected to the end of the survey, where they were informed that they did not meet the eligibility criteria.

Contact details of FM were also provided should the participant have any questions, as well as multiple links for cancer support and advice.

3.2.9 Questionnaire development

The review findings highlight alterations of memory (verbal learning, long term memory (both episodic and semantic, figural memory, and working memory), executive function (flexibility, orientation, initiation, and construction)), both visual and auditory attention, calculation, verbal fluency and motor dexterity. These terms are used as defined in Table 6 which has been generated with the use of definitions stated in the American Psychological Association online dictionary [224]. These definitions were also discussed and agreed with two neuropsychologists based at the University Hospital of Wales in Cardiff.

Cognitive Processes	Definition
Verbal Memory	Memory of verbally presented information.
Figural Memory	Memory of visually presented information.
Working Memory	The temporary maintenance of information that is no longer present in the environment for use in ongoing cognition.
Flexibility	Mental ability to switch between thinking about two different concepts, and to think about multiple concepts and to think about multiple concepts simultaneously.
Orientation	The function of the mind involving awareness of 3 dimensions: time, place and person.
Initiation	The process of starting a task.
Construction	The ability to see an object or picture as a set of parts and then to construct a replica of the original; from these parts is known as visuospatial constructive cognition.
Attention	The ability to choose and concentrate on relevant stimuli.
Calculation	The ability to process numbers and calculations.
Verbal fluency	A cognitive function that facilitates information retrieval from memory to form language.
Motor dexterity	Hand eye coordination.

Table 6: Definitions of cognitive domains addressed in the survey

To ensure that the questions were presented in a way that participants found both easy to understand and relate to, questions focused on the type of daily activities that involve these areas of cognition. In order to ensure that the intended areas of cognition were represented, the survey questions were adapted from existing tools that included questions that had been validated for detecting cognitive decline. Each question of the survey represents at least one area of cognition highlighted in the systematic review. Adaptation was required to ensure that the questions were presented in a way that would be most relevant and understandable for prospective participants. As specific aspects of memory and executive function have been

highlighted in the review, questions from two separate questionnaires were adapted to ensure that the survey questions had the specificity required. Two neuropsychologists were consulted on the use of these preexisting tools and it was agreed that they would be appropriate.

The situations presented in questions 1-13 are adapted from the everyday memory questionnaire [225]. This questionnaire assesses various domains of memory and attention in an everyday context and has been validated with neurological patients [225]. Questions 14 and 15 are adapted from questions included in the Dysexecutive Questionnaire-revised (DEX-r). The DEX-r was chosen as it contextualises domains of executive functioning and attention to real-life situations [226] and has been validated with patients with acquired brain injury [227]. Questions regarding calculation and motor dexterity have been derived from tasks used as part of the mini mental state examination (MMSE) [228]. Whilst this is an older tool, it is still commonly used by clinicians [229] and is reported in papers included in the systematic review (chapter 2). Table 7 lists the questions adapted for use in this survey. The full survey is available in supplementary appendix b.

Question adapted for this survey	Tool
Having to check whether you have done something	the everyday memory questionnaire
Forgetting when it was that something happened	the everyday memory questionnaire
Finding that a word is 'on the tip of your tongue'	the everyday memory questionnaire
Completely forgetting to do things you said you would	the everyday memory questionnaire
Forgetting important details of what you did	the everyday memory questionnaire
Forgetting to tell somebody something important	the everyday memory questionnaire
When reading a paper, being unable to follow the story	the everyday memory questionnaire
Getting the details mixed up	the everyday memory questionnaire
Repeating to someone what you have just told them	the everyday memory questionnaire
Starting to read something you have read before	the everyday memory questionnaire
Forgetting where things are normally kept	the everyday memory questionnaire
I find it difficult to start something	Dex-R
I find it difficult to do or concentrate on two things at once	Dex-R
'Participants are asked to write a sentence'	MMSE
'Participants are asked to copy a simple design'	MMSE

Ask the patient to begin with 100 and count backwards by 7. Stop after five subtractions (93, 86, 79, 72, 65) MMSE
--

Table 7: Questions adapted from existing tools

Situations which focus on memory are presented in seven questions; “Having to double-check that they have done something” (Question 1), “Being unable to recall events in the order that they occurred” (Question 2), “Being unable to recall something they were told in the last week” (Question 3), “Getting halfway through reading something before realising they have already read it” (Question 4), “Forgetting to do something they had planned and wanted to do” (Question 7), “Having difficulty remembering details of what happened the day before” (Question 8), and “Misplacing items around the home” (Question 13).

Executive functioning was the key focus of eight of the questions; “Having to re-read something to fully understand the meaning”(Question 5), “Losing their train of thought whilst speaking”(Question 9), “Being unable to stay engaged when listening to someone talking”(Question 10), “Finding themselves getting detail of what someone has told them mixed up or confused”(Question 11), “Not knowing ‘where to start’ when undertaking a task”(Question 14), “Being unable to efficiently multitask”(Question 15), “Being unable to solve addition and subtraction calculations”(Question 18) and “Being unable to solve multistep calculations”(Question 19).

As this survey was designed to investigate into how deficits are experienced in the context of everyday situations, motor dexterity was considered in the way in which it may affect communication through writing or typing. Therefore domains of motor dexterity and language are grouped together into the category of communication. Four questions presented situations that have implications on a person’s ability to communicate effectively; “Getting the feeling that a word is ‘on the tip of their tongue’” (Question 6), “Realising that you have repeated yourself or asking the same questions” (Question 12), “Having difficulty to write by hand or draw” (Question 16), and “Having difficulty typing on a computer or phone keyboard” (Question 17). Once the questions were designed, they were presented to two neuropsychologists who confirmed that they were representative of the intended cognitive processes.

In addition to questions focusing on cognitive functioning, patients and family members were asked to provide information on the patients’ diagnosis, treatment undertaken, and tumour location. This was to determine which specific patient groups

were being represented by participants. As this survey was conducted to aid in the designing of a screening tool for all adult HGG patients, it was important that the data obtained represented the patient group. As HCP's were asked to provide a general opinion on patient they had seen, they were not required to provide specific patient details. Instead they were asked to identify their primary profession.

3.2.10 Piloting

Whilst the protocol of this survey was reviewed by two PPI research partners, face validation of the initial survey design was conducted. This was done by seeking review from two different groups. Group One (n=3) comprising family members and health care professionals with knowledge of the topic area to evaluate if the survey successfully captures the topic. Group Two (n= 3) comprising public contributors to assess acceptability of language and format.

This ensured that the survey not only covered areas of interest, but that it is acceptable to the target population. Based upon the feedback provided, changes to wording and layout were made to the survey before it was launched. One of the key changes made was the division of survey paths to allow participants to answer questions specific to their point of view. This was changed following feedback from the research partners.

3.2.11 Survey layout

The sequencing of questions was selected to provide the most streamlined experience for the participant. Following the recommendations of Tourangeau et al [230], Slattery et al [231] and Orionzi et al [232], questions relating to demographic data were placed at the end. This is recommended for two reasons. Firstly, the potential perception of intrusion should the questions be asked first. Secondly, demographic questions are generally easier to answer and therefore less demanding on the participant who may experience a decline in attention as they work through the survey questions. The survey map is shown in figure 8.

The closed questions focusing on cognitive functioning were ordered in a way that gradually transitioned from one domain to another. As flexibility is one of the cognitive domains of interest for this study, and as task switching is a key element to cognitive flexibility it is necessary to present questions to patients in a way that does not put extra strain on this function. For example, questions looking at memory were asked in succession rather than being separated by questions assessing motor function or calculation. In addition to this, each closed question was accompanied by a free text box in which participants could provide any further information if they wished to. This

was done to prompt participants to give examples of how deficits may impact them/ the patient. Framing these boxes around the closed questions was done to encourage participants to provide further information on a single question. This was done to allow participants to fully consider questions one at a time, instead of having to reflect on the questions retrospectively at the end of the survey.

The survey comprised of 19 questions and it was estimated to take approximately 10 minutes to complete.

As the focus was experience post- radiotherapy, it was important that participants answer questions as a comparison to pre-radiotherapy functioning. For this purpose, answers for closed questions directed at patients and family members were formatted as Likert type scales to describe any changes from pre-radiotherapy functioning. Many health care professionals, whilst in regular contact with patients, may not have information on patient functioning prior to the completion of treatment. Due to this, questions for these participants were designed to investigate how often they observe changes or are informed of changes by the patient or those close to them.

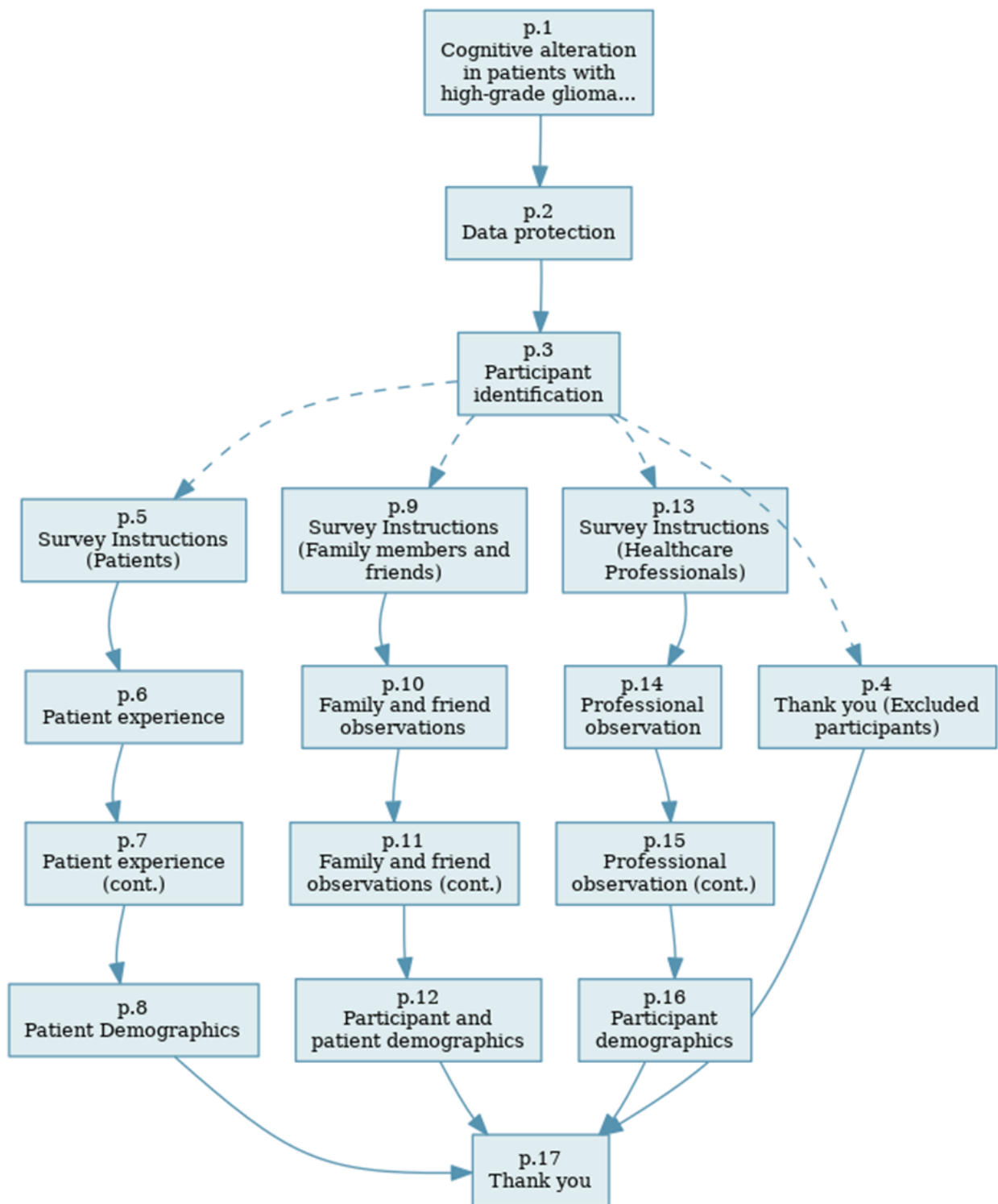


Figure 3: Survey map

3.2.12 Ethical and regulatory consideration

Ethical approval

This survey was conducted according to the principles of good research practice, the General Data Protection Regulation (GDPR) and the UK Policy Framework for Health and Social Care Research (2017). This study received ethical approval from the Cardiff University School of Medicine on the 2nd September 2020 (SMREC 20/69).

Ethical considerations

It was important to consider that, due to the sensitivity of the topic, some participants may find subject matters addressed in this study to be distressing. For this reason, it was stressed that participants could stop the survey at any time. Participants were directed to the webpages and contact numbers of Marie Curie and Macmillan that offer information and support.

Patients were also informed that the data would be anonymised and failure to complete the survey would not result in any change in their care.

Confidentiality

This study was conducted in adherence to the principles of good clinical practice as outlined in the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). It was conducted in compliance with the protocol, the Declaration of Helsinki (South Africa, 1996), and other regulatory requirements as appropriate.

Data Management

All data will be retained for at least five years post study closure. Data will be archived in accordance with Cardiff University's policy of retaining postgraduate and staff research records and data from clinical research projects.

Consent

The front page of the survey gave a brief overview of the subject background for context. Participants were also given information on the purpose of the survey and were informed that the survey would take approximately 10 minutes to complete. Before progressing to the survey questions, participants were asked to read through information on the policies of the data protection and usage, privacy, data handling and participation practices that were followed in the launch and analysis of the survey. Participants were required to confirm their understanding of this information, confirm

that they were over 18 and consent to take part in the survey before proceeding. The use of this relies on the participants assurance that they have understood, and whilst this cannot be guaranteed for this survey, participants were encouraged to seek the support of their families if they were unsure of their participation.

3.2.13 Data analysis

As this was a mixed methods survey, both quantitative and qualitative data was obtained.

Quantitative data

Likert type questions were utilised for the presentation of daily situations. Each situation (i.e. Being unable to recall events in the order that they occurred) was presented with a scale ranging from 1 to 5. For patient and family participants 1 corresponded to 'much less often' and 5 to 'much more often'. For HCP's 1 corresponded to 'never' and 5 to 'very frequently'.

Analysis was conducted using descriptive statistics to summarise the findings in a meaningful way to enable the identification of patterns. The data from the closed questions were analysed using IBM SPSS 26 [233] to determine which of the domains highlighted in the systematic review are of importance for patients with HGG. This statistical software was used to work out the mean, median and range of responses to each of the changes are seen in each daily situation.

The median was used to identify the central tendency of responses. Whilst the mean may not offer any direct meaning with regard to Likert type scales, the mean was also calculated to identify if the average response was above or below the neutral response (3 'same as before').

Additionally, as the results from the systematic review were indicative of variation in patients, it is important that every reported experience is accounted for. For this reason the range in results was reported.

Qualitative data

For free text responses, data was handled in NVivo (NVivo12) [234]. A thematic approach [235] was used to identify themes in qualitative data. A portion of the data (10%) was double coded by AN. Once a preliminary coding framework was generated, the final coding framework was agreed by both FM and AN. This is done with the aim of interpreting the data by identifying any patterns and describing them in context to the subject areas. As suggested by Braun and Clarke, a six step approach was undertaken to identify and review common themes:

1. Familiarisation with the data
2. Generating initial codes
3. Searching for themes among codes
4. Reviewing themes
5. Defining and naming themes
6. Producing the final report

Reflexivity and facilitators

When researching patient experience, it is important to acknowledge how personal circumstances may be a cause of bias. My mother was diagnosed with a grade 1 ependymoma in 2005, and whilst this is accompanied by a very different prognosis, I understand that this has shaped how I perceived symptoms of brain tumours and their subsequent treatments. I am aware that when discussing symptom burden with participants, I must try and remain neutral and set aside any preconceived ideas of what patients could be experiencing.

It was planned that two PPI research partners would help in facilitating the group, however due to the unforeseen school closures due to the COVID-19 pandemic, neither were able to attend. However, AN and SS both attended the focus group and acted as facilitators. This helped to ensure that any attendees that wanted to speak were acknowledged and given the opportunity to do so. In addition to this, as I was previously inexperienced in conducting a focus group, they were both able to assist in making sure the conversation stayed on track.

3.3 Results

3.3.1 Participation

A total of 148 people responded to the survey between the 15th of September 2020 and the 24th of November 2020. Recruitment was steady throughout the study period. There is a large spike in recruitment on the 29th of October. On this day fifty-seven responses were submitted which accounted for approximately 39% of respondents. Prior to this, the highest number of responses in a day was eight. This increase in response corresponds with the advertisement and survey link being sent via email through the Brain Tumour Charity 'BRIAN' forum. The rate of responses can be seen

in figure 9. Table 8 shows the number of participants recruited from each recruitment avenue.

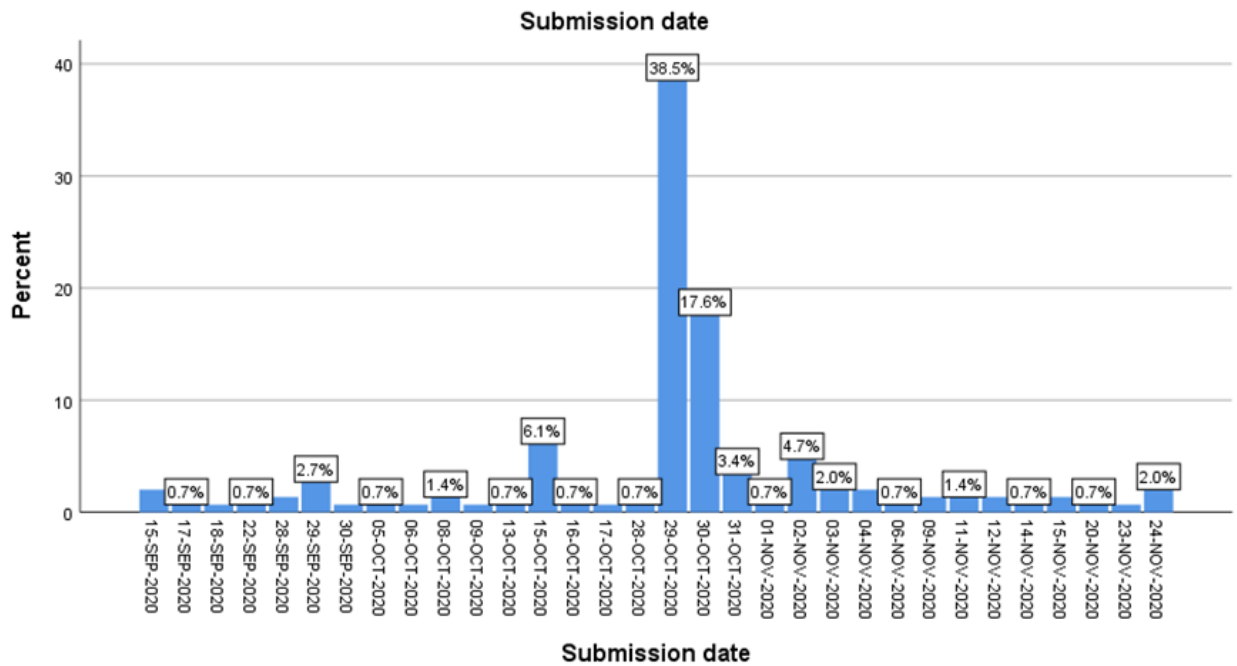


Figure 4: Rate of response submission

Method of recruitment	Number of participants		
	Patients (n=91)	Family (N=46)	HCP (n=5)
Brain Tumour Charity	73	18	0
<i>brainstrust</i>	2	1	0
Reddit	4	9	0
Twitter	0	3	0
Word of mouth	1	4	3
Not detailed	10	9	2

Table 8: Recruitment methods for survey participants

Ninety-one patients (61.5%) , 46 family and friends of patients (31.3%), six health care professionals (4.1%), and five respondents who did not meet the eligibility criteria (3.4%) responded to the survey. Due to the anonymity of respondents, it was unclear if there were any relationships between participants. Individual patient data as reported by patients and, family and friends of patients, is presented in Table 10. Of the six healthcare professionals who completed consent and screening questions,

five proceeded with the rest of the survey; these included: neuro-oncology doctors (n=2); oncology nurse (n=1); physiotherapist (n=1); clinical neuropsychologist (n=1).

Patient data (n=137)		
	Patient reported n=91(66.4%)	Family reported n=46(33.7%)
Gender		
Male	39	25
Female	52	16
Other	-	-
Prefer not to say	-	-
Age		
18-25	-	3
26-35	20	4
36-45	22	-
46-55	31	14
56-65	13	17
66-74	5	6
75+	-	-
Tumour Location		
Frontal lobe	34	16
Parietal lobe	22	6
Occipital lobe	7	2
Temporal lobe	13	10
Cerebellum	1	2
Brain stem	2	4
Unknown	8	4
Completed full course of radiotherapy?		
Yes	87	41
No	3	3

Table 9: Patient data as reported by patient and family members

3.3.2 Quantitative results

Responses were received from both male and female patients and family members. It can be seen that there were more female patients that took part, accounting for 57% of patient respondents. Additionally there were male patients reported by members that took part (54%). The ages reported show that the most commonly reported age by patients was between 46 and 55 (34%) and family members most

commonly reported on patients aged between 56-65 (36%). As this aim of this PhD is to develop a screening tool for patient with HGG regardless of tumour location, the identification of tumour location was included to identify if the data was representative of all tumour types, rather than to be used to determine any correlations. As seen in table 9, tumour location is fairly varied, however the most commonly reported location is the frontal lobe, which was reported for 50 patients, accounting for 36% of the patient data.

The majority of questions were answered by all patients. Three questions were not answered by all participants in this group: "Getting the feeling that a word is 'on the tip of your tongue'" (Question 6: n=2/91); "Losing your train of thought" (Question 9: n=1/91); "Misplacing items" (Question 13: n=1/91). In the family and friends group, there were two questions which were not answered by all participants: "Having to double check that they have done something (i.e. locking the door)" (Question 1: n=1/46); "Having difficulty remembering details of what happened the day before" (Question 8: n=1/46). The HCP's answered all but two questions: "Being unable to solve addition or subtraction calculations" (Question 18: n=1/5); "Being unable to solves multistep calculations" (Question 19: n=1/5). All questions were optional, therefore responses were not required in order to progress in the survey. As there were no more than 2 responses missing from questions, missing data was omitted from the final analysis.

Memory

Variation was observed in all patient responses to memory focused questions. Responses ranged between 1 ('Much less often') and 5 ('Much more often'), with the exception of Questions 1 ("Having to double-check that they have done something") and Question 7 ("Forgetting to do something they had planned and wanted to do") which ranged between 2 ('Slightly less often') and 5 ('Much more often'). The mean and median responses of patients were all observed to be 3 ('Same as before') or above (see Table 11).

Variation was observed in all family and friend responses ranging between 1 ('Much less often') and 5 ('Much more often'), with the exception of Question 2 ("Being unable to recall events in the order that they occurred") and Question 13 ("Misplacing items around the home") having responses ranging between 2 and 5. Mean and median responses were 3 ('Same as before') or above (see Table 11). This indicates that patients may experience a degree of difficulty with tasks that rely on memory but with significant differences in experiences amongst the sampled participants.

HCP responses showed responses to be 2 ('Rarely') or above for all questions associated with memory. Question 3 ("Being unable to recall something they were told in the last week") and Question 13 ("Misplacing items around the home") had responses ranging from 2 to 5 ('Very frequently'). Question 1 ("Having to double-check that they have done something"), Question 2 ("Being unable to recall events in the order that they occurred"), Question 7 ("Forgetting to do something they had planned and wanted to do") and Question 8 ("Having difficulty remembering details of what happened the day before") ranged between 2 and 4 ('Frequently'). Responses to Question 3 ("Being unable to recall something they were told in the last week") had the least variation, with responses ranging between 2 and 3 ('Occasionally'). The median response for all questions was 3. Mean responses were all above 2 (see Table 9). This shows that difficulty with tasks associated with memory are susceptible to decline, but it is not consistent across patients.

Executive Functioning

Patient responses ranged between 1 and 5 for most questions that focused on elements of executive functioning. This is with the exception of Question 5 ("Having to re-read something to fully understand the meaning") (range: 3-5) and Question 11 ("Finding themselves getting detail of what someone has told them mixed up or confused") (range: 2-5). Mean and median responses were all 3 or above (see Table 11).

Family responses also ranged between 1 and 5 for the majority of questions excluding Question 5 ("Having to re-read something to fully understand the meaning") (range: 3-5) and mean responses were all above 3. The median response from the majority of questions was 4 apart from Question 18 ("Being unable to solve addition and subtraction calculations") and Question 19 ("Being unable to solve multistep calculations"), where the median was reported to be 3.

Responses of HCP's ranged between 2 and 5 for Questions 15 ("Being unable to efficiently multitask"), Question 18 ("Being unable to solve addition and subtraction calculations") and Question 19 ("Being unable to solve multistep calculations"). Question 11 ("Finding themselves getting detail of what someone has told them mixed up or confused") and Question 14 ("Not knowing 'where to start' when undertaking a task") received responses ranging between 2 and 4. Responses to Question 5 ("Having to re-read something to fully understand the meaning") ranged between 2 and 3. Responses varied between 3 and 5 for Question 10 ("Being unable to stay engaged when listening to someone talking") and all respondents answered 3 for Question 9 ("Losing their train of thought whilst speaking"). The majority of questions

had a mean response of 3 or above, apart from Question 5 which had a mean of 2.60. All questions had a median response of 3.

As with memory, it can be seen that tasks associated with executive functioning may become more challenging for patients, but this will vary amongst patients.

Communication

For Question 12 (“Realising that you have repeated yourself or asking the same questions”) Question 16 (“Having difficulty to write by hand or draw”) and Question 17 (“Having difficulty typing on a computer or phone keyboard”) patient responses ranged between 1 and 5. Responses for Question 6 (“Getting the feeling that a word is ‘on the tip of their tongue’”) ranged between 2 and 5. Mean responses were above 3 for each question. Median response was 4 for Question 6 and Question 12 and 3 for Question 16 and Question 17. Family responses ranged between 1 and 5 for all questions. Mean response was above 3 for every question and the median response was 4 or above for each question. HCP’s responses ranged from 2 to 3 in all questions excluding question 6 (range: 2-5) and the mean response for all questions was above 2. The median response was 3 for all questions excluding Question 17, which had a median response of 2 (see Table 11)

It can be seen that all tasks involving communicative skills are susceptible to decline and as with memory and executive functioning, this difficulty is variable across patients.

		<i>Patients</i> <i>N=91</i>	<i>Family</i> <i>N=46</i>	<i>HCPs</i> <i>N=5</i>
<i>Having to double-check that they have done something</i>	<i>n (%)</i>	91	45	5
	<i>Mean</i>	3.98	4.04	3.00
	<i>Median</i>	4.00	4.00	3.00
	<i>Range</i>	2-5	1-5	2-4
<i>Being unable to recall events in the order that they occurred</i>	<i>n (%)</i>	91	46	5
	<i>Mean</i>	3.52	3.96	3.00
	<i>Median</i>	3.00	4.00	3.00
	<i>Range</i>	1-5	2-5	2-4
<i>Being unable to recall something they were told in the last week</i>	<i>n (%)</i>	91	46	5
	<i>Mean</i>	3.92	4.11	4.00
	<i>Median</i>	3.40	4.00	3.00
	<i>Range</i>	1-5	1-5	2-5
<i>Getting halfway through reading something before realising they have already read it</i>	<i>n (%)</i>	91	46	5
	<i>Mean</i>	3.37	3.87	3.00
	<i>Median</i>	2.40	4.00	2.00
	<i>Range</i>	1-5	1-5	2-3
<i>Having to re-read something to fully understand the meaning</i>	<i>n (%)</i>	91	46	5
	<i>Mean</i>	4.00	4.04	2.60
	<i>Median</i>	4.00	4.00	3.00
	<i>Range</i>	3-5	3-5	2-3
	<i>n (%)</i>	89	46	5

<i>Getting the feeling that a word is 'on the tip of their tongue'</i>	<i>Mean</i>	4.31	4.15	3.40
	<i>Median</i>	4.00	4.50	3.00
	<i>Range</i>	2-5	1-5	2-5
<i>Forgetting to do something they had planned and wanted to do</i>	<i>n (%)</i>	91	46	5
	<i>Mean</i>	3.93	3.93	2.80
	<i>Median</i>	4.00	4.00	3.00
<i>Having difficulty remembering details of what happened the day before</i>	<i>Range</i>	2-5	1-5	2-4
	<i>n (%)</i>	91	46	5
	<i>Mean</i>	3.90	3.96	3.00
<i>Losing their train of thought whilst speaking</i>	<i>Median</i>	4.00	4.00	3.00
	<i>Range</i>	1-5	1-5	2-4
	<i>n (%)</i>	90	46	5
<i>Being unable to stay engaged when listening to someone talking</i>	<i>Mean</i>	3.98	3.91	3.00
	<i>Median</i>	4.00	4.00	3.00
	<i>Range</i>	1-5	1-5	3-3
<i>Being unable to stay engaged when listening to someone talking</i>	<i>n (%)</i>	91	46	5
	<i>Mean</i>	3.59	3.78	3.40
	<i>Median</i>	3.00	4.00	3.00
<i>Finding themselves getting detail of what someone has told them mixed up or confused</i>	<i>Range</i>	1-5	1-5	3-5
	<i>n (%)</i>	91	46	5
	<i>Mean</i>	3.87	4.04	3.20
<i>Realising that you have repeated yourself or asking the same questions</i>	<i>Median</i>	4.00	4.00	3.00
	<i>Range</i>	2-5	1-5	2-4
	<i>n (%)</i>	91	46	5
<i>Misplacing items around the home</i>	<i>Mean</i>	3.76	3.61	2.60
	<i>Median</i>	4.00	4.00	3.00
	<i>Range</i>	1-5	1-5	2-3
<i>Not knowing 'where to start' when undertaking a task</i>	<i>n (%)</i>	90	46	5
	<i>Mean</i>	3.81	3.63	3.20
	<i>Median</i>	4.00	3.00	3.00
<i>Being unable to efficiently multitask</i>	<i>Range</i>	1-5	2-5	2-5
	<i>n (%)</i>	91	46	5
	<i>Mean</i>	3.48	3.78	3.00
<i>Having difficulty to write by hand or draw</i>	<i>Median</i>	3.00	4.00	3.00
	<i>Range</i>	1-5	1-5	2-4
	<i>n (%)</i>	91	46	5
<i>Having difficulty typing on a computer or phone keyboard</i>	<i>Mean</i>	3.76	4.11	3.00
	<i>Median</i>	4.00	5.00	3.00
	<i>Range</i>	1-5	1-5	2-5
<i>Being unable to solve addition and subtraction calculations</i>	<i>n (%)</i>	91	46	5
	<i>Mean</i>	3.63	3.80	2.80
	<i>Median</i>	3.00	4.00	3.00
<i>Being unable to solve multistep calculations</i>	<i>Range</i>	1-5	1-5	2-3
	<i>n (%)</i>	91	46	5
	<i>Mean</i>	3.65	3.83	2.40
<i>Being unable to solve multistep calculations</i>	<i>Median</i>	3.00	4.00	2.00
	<i>Range</i>	1-5	1-5	2-3
	<i>n (%)</i>	91	46	4
<i>Being unable to solve multistep calculations</i>	<i>Mean</i>	3.48	3.48	3.25
	<i>Median</i>	3.00	3.00	3.00
	<i>Range</i>	1-5	1-5	2-5
<i>Being unable to solve multistep calculations</i>	<i>n (%)</i>	91	46	4
	<i>Mean</i>	3.60	3.63	3.25
	<i>Median</i>	3.00	3.00	3.00
<i>Being unable to solve multistep calculations</i>	<i>Range</i>	1-5	1-5	2-5

Table 10: Mean, Median and Range of responses for Likert type scale survey questions

No table legend here. Also may want to consider clustering the questions according to domains of memory, exec functioning and communication

3.3.3 Thematic Analysis of Qualitative Data

As a result of the thematic analysis of the free text boxes, themes of memory, communication, executive functioning, symptom triggers and causes, coping mechanisms and mood and affect were highlighted. Due to a lack of response from HCP's, the following themes were generated from patient and family responses. Figures 7 and 8 show the themes highlighted from the patient and family data sets respectively.

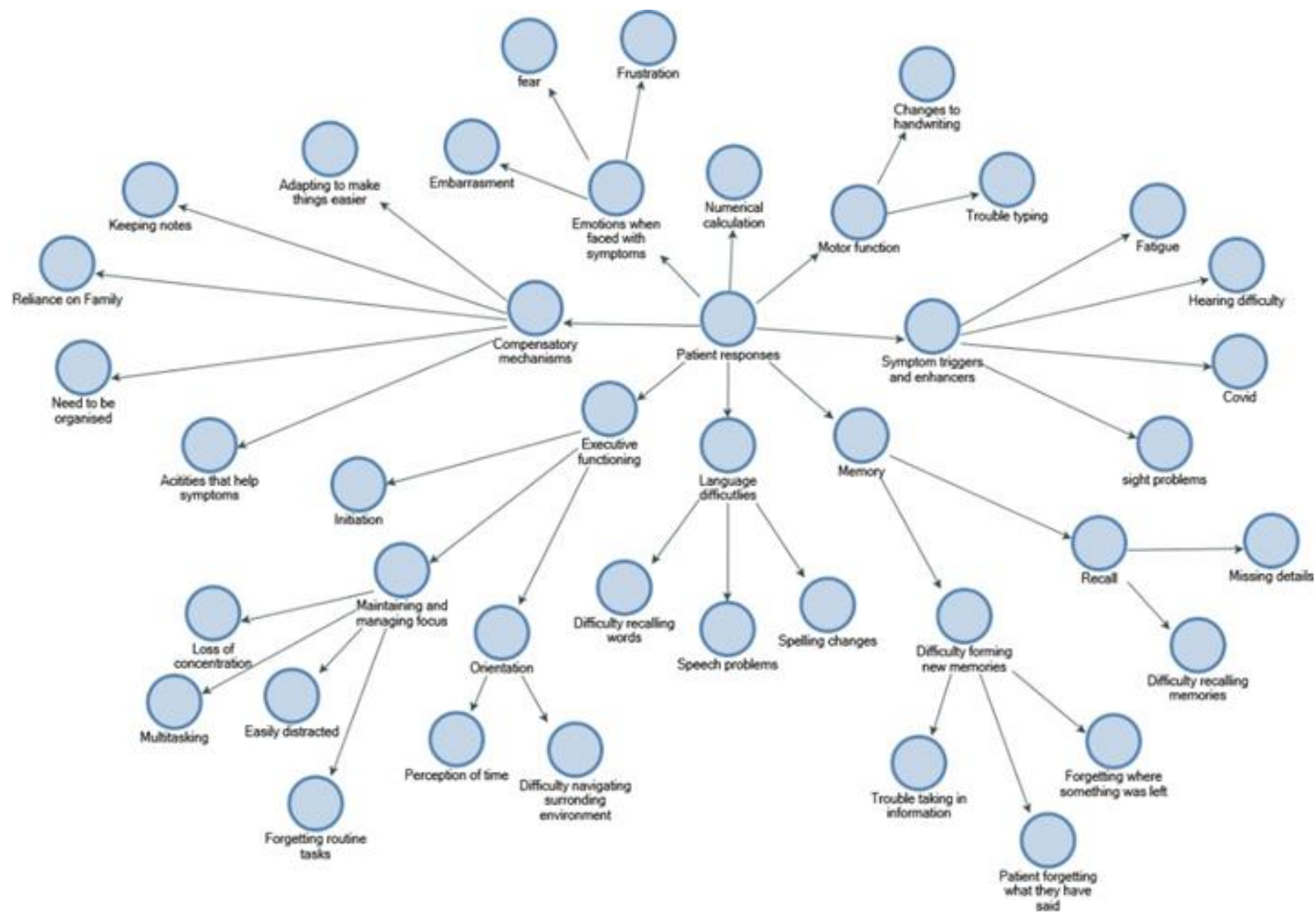


Figure 5: Map of themes highlighted in patient free-text responses

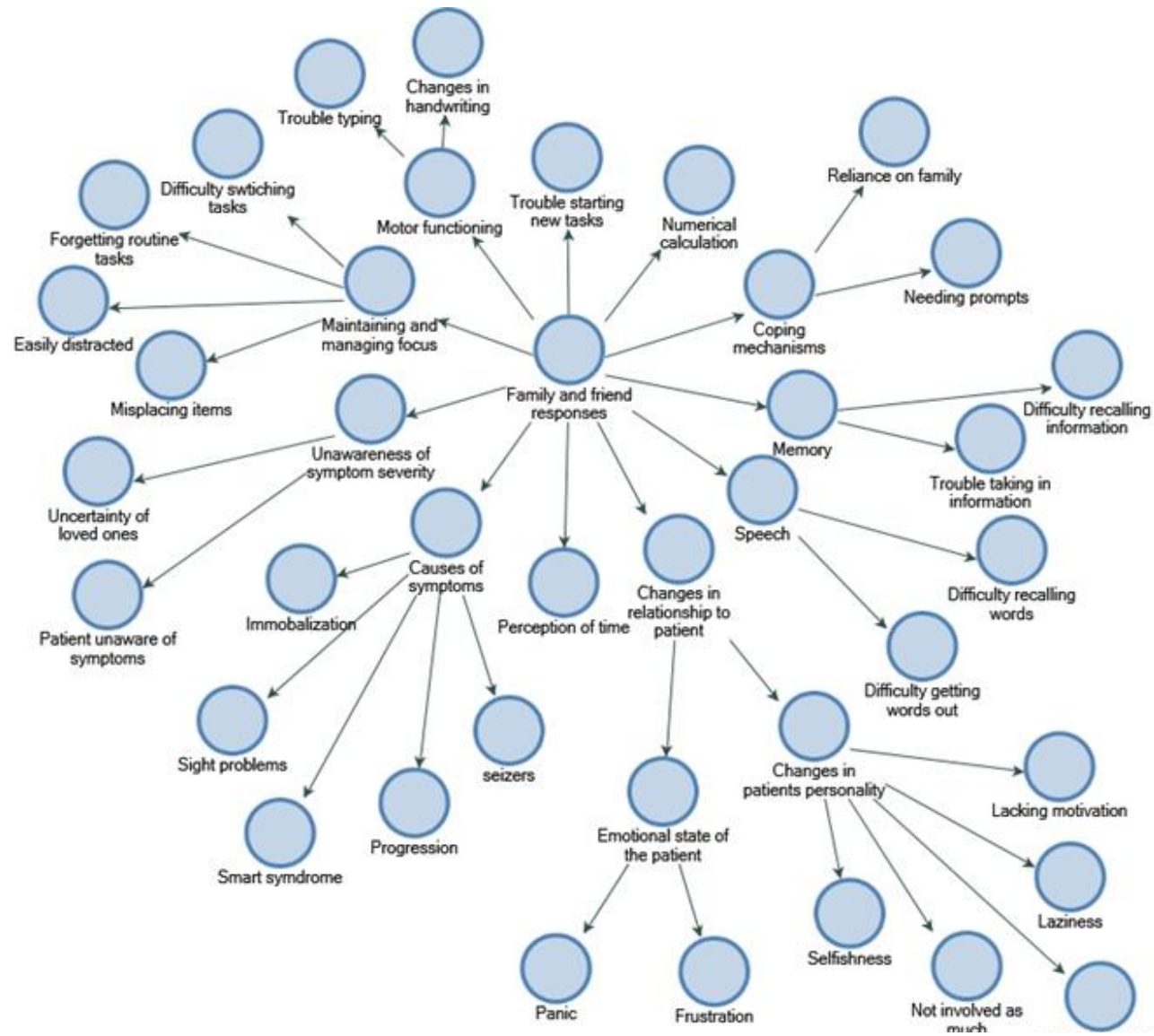


Figure 6: Map of themes highlighted in family free-text responses

Memory

This theme encompasses the reported experiences of participants associated with any process involved with the brain's ability to store information from external stimuli and retrieve this information when necessary. Participant reports on memory were grouped into two sub-themes: Difficulty recalling memories; and Trouble forming new memories.

Difficulty recalling memories was mentioned by both patients and family members. Both expressed that there was difficulty in both recalling entire events, and with missing details. Whilst responses were mirrored across these groups, patients went into more detail. There was a general acknowledgment among patients that recalling information took more effort.

"Have to think harder about what has happened no(w)."-Participant no. 120. Patient Group

Several patients also indicated that recall was only possible when prompted.

"When someone says the answer again I'm like oh yeah I knew that!"-Participant no. 91. Patient Group

Similarly, with regards to trouble forming new memories, family members were able to identify difficulty with this. Family members reported that the patient needed information repeated, or that the patient lacked the interest or focus to take in new information.

"Long term memory is really good. Facts about countries , music he's spot on with but anything new doesn't hold interest for him"-Participant no. 99. Family Group

The need for repetition is also identified within the patient group. Many participants mentioned how they need to either reread text or have verbal information repeated for them to be able to retain it. In addition to this, it was also stated that patients will often repeat what they themselves have said.

"In a week mine memory recall is terrible over an hour or sometimes minutes e.g. I can be told a date and I time and unless I have written it down I would have to ask the person to repeat at least once"- Participant no. 64. Patient Group

The idea of being uninterested was not echoed in the patient responses, however as with recall, it was acknowledged that patients have to focus to assimilate new information.

"really concentrate to take on board information"- Participant no. 64. Patient Group

Communication

Whilst communication is often understood as a process that allows individuals to exchange information, this theme looks at any responses detailing challenges to the patient's ability to express their thoughts, opinions and needs. Two sub-themes were identified: Speech and language; and fine motor function (handwriting and typing).

Responses of patients and family groups were very similar in the way that they described issues with communication. Changes to patient speech and language were mainly focused on difficulties in getting words out. Most commonly, respondents reported patients knowing what they wanted to say, but struggling to retrieve the word. Many patients explained how they would have to actively try to think of the correct word.

***"I either do a mental look around my brain or just try and let it go or settle for a word that isn't really reflective of what I wanted to say."-Participant no. 18.
Patient Group***

While other patients stated that they often resort to inventive means of describing what they wanted to say. Once patient gave the following example:

"ice cubes became 'freezer squares'"-Participant no. 58. Patient Group

Additionally, it was reported that patients may struggle with forming the words rather than just the retrieval of words. Issues such as stuttering and slowed speech were mentioned by patients.

***"I sometimes struggle to get my words out without stuttering. I have to think of what I'm trying to say before I speak or even write it down so I don't mess it up"-
Participant no. 53. Patient Group***

Issues with patients' fine motor functioning was expressed as a difficulty, and changes to patient typing and handwriting. Most patients who had changes to their handwriting commented that their writing was more difficult to understand, with one patient stating:

"It now looks like a two year old is writing"- Participant no. 62. Patient Group

Furthermore, patients also observe trouble with typing. This was most commonly described as issues with accurately typing on smart phones and smaller keyboards.

***"Always making typos in texts. Not so bad on pc." Participant no. 62. Patient
Group***

It can therefore be seen that both verbal and written communication may be affected in a way that effect patients ability to confidently communicate and make themselves understood. It can also be seen that patient communication may be affected in

different ways. Issues with speech, language and motor dexterity have a negative impact on verbal and written methods of communication.

Executive functioning

Executive function refers to a set of neuro-cognitive processes that support purposeful, goal-directed and future-orientated behaviour. This includes processes that aid in the understanding of external stimuli and the planning of responses to these. Sub-themes reported were initiation, maintaining and managing focus and orientation.

Difficulty with initiation was reported by both groups, however it was described as a general feeling of confusion or apprehension. This was expressed by one patient as feelings of anxiety when faced with complex tasks.

“anxious and stressed when attempting something ‘big’” -Participant no. 58. Patient Group.

One participant from the family group explained how difficulty at the beginning of a task is what prevents the patients from undertaking tasks.

“confused at start point” -Participant no. 106. Family Group

Issues with spatial orientation were only commented on by a small number of patients. These patients expressed difficulty when navigating their surroundings causing them confusion. Changes to patients' perception of time was the most commonly reported change to orientation.

“Returning from a run and relaying my route I become muddled, causing frustration.” Participant no. 80. Patient Group

Patients describe losing track of time whereas family members observed timeline issues in patients. This is described by one participant as a confusion when recalling when events occurred.

“recalling things that happened months or sometimes years beforehand and insisting it happened yesterday”-Participant no. 99. Family Group

Most commonly, a deficit in executive functioning was described by both patients and family members, as a difficulty in managing and maintaining focus. This sub-theme captured an insight into how mental flexibility is affected in patients. This was described as problems with multitasking and becoming easily distracted. It was noted by both groups that an interruption to a task can completely derail progress of a task.

“is ok if not interrupted , once interrupted thought process is lost”- Participant no. 76. Family Group

This is particularly troubling for patients who feel frustrated as a result of this. One patient expressed that any disruption in their thoughts is a cause of irritation.

“quite annoyed when I am interrupted” -Participant no. 121. Patient Group

It was also mentioned by one participant that an interruption may be as subtle as ‘background noise’. Such issues were also linked to patients’ omission of out routine tasks, which was causing some patients to miss their medication and on some occasions forget to eat.

“Taking tablets was a problem.”-Participant no. 58. Patient Group

“I was losing weight and couldn't work out why, it turned out that I was just forgetting. I live on my own so I had nothing to prompt me”-Participant no. 107. Patient Group

This shows that issues believed to be associated a decline in executive function can impact most aspects of patients’ lives and are often a source of frustration. The lived examples given indicate that whilst this is a very broad and complex domain, participants are able to identify changes to patient executive functioning through issues with managing focus and processing multiple sources of information at once.

Symptom Triggers and Causes

As well as giving an insight into the way patients experience and family members perceive cognitive changes, responses in the free text boxes give further understanding to the causes participants attribute to various changes. Sub-themes identified were varied between patients and family. Patients highlighted fatigue, hearing difficulty and sight problems as causes of the difficulties faced. Whilst family members also reported sight problems, they also highlighted stroke-like migraine attacks after radiation therapy (SMART) syndrome and tumour progression as causes of deficits. Both groups identified that difficulty with accomplishing certain tasks was due to tumour induced sight problems. This was stated as being mostly detrimental to the patient’s ability to read and type.

“Language and eyesight have both been affected by tumour, so reading is difficult”-Participant no. 21. Family Group

“Typing is an issue esp on small screen and mix up words when typing”- Participant no. 141. Patient Group

Some participants in the patient group attributed difficulties with comprehension to hearing changes. This is mentioned as the cause of having to have information repeated to them.

“I have an increased loss of hearing in my right ear as a result of the radio therapy, which means I do not always hear what is said correctly.”-Participant no. 98. Patient Group

The most common symptom trigger mentioned by patients was fatigue. Whilst fatigue was presented as an exacerbating factor to nearly all areas of deficit, it was most commonly said to be detrimental to the patients' ability to maintain and manage focus.

“I get quite tired trying to listen to someone talking, sometimes tune out”- Participant no. 121. Patient Group

One participant also mentioned that the government enforced COVID-19 lockdown measures had negatively affected their cognitive functioning.

“I think the added lockdown/covid situation has exacerbated matters too”- Participant no. 40. Patient Group.

Responses from family members focussed more heavily on the causes of cognitive changes, rather than exacerbating factors.

“has severe cognitive impairment since suffering from smart syndrome”- Participant no. 76. Family Group

In this participant group, symptoms were most commonly said to be caused by progression and as an after effect of seizures experienced by the patient as a result of their tumour.

“Only with very advanced disease”-Participant no. 33. Family Group

This provides several examples as to the breadth of the symptom burden faced by patients. This also shows that the challenges with specific tasks may be exacerbated by symptoms other than cognitive decline.

Coping Mechanisms

Participants often described coping mechanisms that they or their family members employ to aid in dealing with the changes they experience. It was affirmed by both patient and family groups that the patient being able to rely on those around them serves as a substantial support to the patient. Patients often mentioned that they try to have family members present during important conversations to ensure that they understand what has been said. One patient described how they relied on their spouse taking notes, to make sure they could revisit conversations in their own time.

“I had to record potentially important conversations if my spouse wasn't present. When he was there he would write things down for me to look at later if I was confused.”-Participant no. 10. Patient Group

Many patients expressed a dependence on note-taking. This was often coupled with a need to become organised, with one patient stating that their organisation skills have improved as a coping mechanism.

“...become a lot more organised since treatment”-Participant no. 52. Patient Group

In addition to these methods of coping with symptoms, a small number of participants revealed that they try to be proactive in managing their symptoms by taking part in activities that they believe to help such as completing crosswords to help maintain their ability to focus.

“Undertaking crosswords helped me to focus and again enjoy reading.”-Participant no. 80. Patient Group

The reporting of self-implemented coping mechanisms indicates that methods can be undertaken to ease day to day burden and that patients and their families are seemingly left to navigate these on their own.

Mood and affect

The impact that cognitive decline has on patients was evident through the survey responses. These symptoms come with a substantial emotional burden which may be perceived by those around them in a number of different ways. Patients expressed feelings of fear, embarrassment and frustration. Patients feel fear when they identify changes in themselves.

“I have noticed changes and it worries me. However other people haven't noticed much change.”-Participant no. 114. Patient Group

This is described as a fear of being unable to do things that they could have previously, and the fear of not knowing if these symptoms are normal. One participant expressed gratitude for having their symptoms acknowledge, explaining how acknowledgment of symptoms alone may help to reduce anxiety.

“Thank you for the questions! I feel comforted by knowing this happens to others in my position”-Participant no. 48. Patient Group

Embarrassment was often experienced by patients in situations where they felt that their deficits were obvious to others. This was most commonly experienced as a result of forgetting something.

“Tend to be aware it's happening and then try to cover up to minimise embarrassment”-Participant no. 79. Patient Group

Feelings of frustration were reported in patients by both groups. This often occurred as a result of being interrupted, thus disrupting the patients thought process. It was also reported as a result of the patient become frustrated at themselves for struggling.

“frustration with being interrupted, lose my train of thought”-Participant no. 121. Patient Group

Changes to patient mood where most commonly observed by family members as affects defined as the outward expression of feelings and emotion. Family members observed changes to the patient’s personality. The most frequently observed change was a lack of motivation, with patients being described as being “less involved” with activities that they normally would want to take part in.

“Steadily increasing confusion over last 12 months has resulted in less involvement in group conversations and general reduction in communication due to confusion.”-Participant no. 73. Family Group

This same situation was described by a small number of participants as “laziness”, indicating that they believed the patient had some aspect of control on the situation.

“Not forgetting but saying 'I will do that' and not doing it at the end. Maybe related to more laziness, not sure.”-Participant no. 22. Family Group

This idea was echoed by other participants who felt as though the patient had become ‘selfish’ and in once case, the patient was described as becoming self-centred to the point that it was detrimental to the family as a whole.

“Only would do what he wanted to do. No concept of the wider needs of the family”- Participant no. 33. Family Group

The impact that cognitive decline has on patients and their families is clear from these responses. This indicates that cognitive decline may have a detrimental impact on the psychological wellbeing of patients and those around them.

3.4 Discussion

The results of this survey confirm that the cognitive deficits reported in the systematic review are relevant to many participants specifically with HGG following radiotherapy. The results not only give us quantitative evidence, but also explore the differing ways patients and family members describe the deficits, what consequences these have of the personal lives of both the patient and those around them, and how at present they use ‘trial and error’ approaches in self-managing their impacts.

The results show that all the areas of cognition highlighted by the systematic review, are applicable to HGG patients. This was shown by the maximum response being 'much more often' in all questions completed by the patient and family groups. Considering this along with the range of responses observed, it also reveals variation between patients. There are several potential causes of this variation.

Firstly, there is was a range of reported tumour locations. There are many theories of functional localisation [236] of the brain. Exploring and furthering our understanding the level of impact each area of the brain has of certain actions and the mechanisms in which these are carried out is a substantial, multidisciplinary area of research. However, it is generally agreed that the location of the tumour will impact the nature of the symptoms experienced by the patient in some way [19]. Despite the advancement of radiotherapy protocols designed to limit exposure to healthy tissue, some proportion of healthy tissue will be destroyed [237]. This, therefore, expands the injury site beyond the margin of the tumour. Additionally, the level of connectivity between regions of the brain may mean that injury to one area, could affect the functioning of another [238]. However, this claim cannot be assessed with the data obtained from this survey, although participants had been asked to give details of the tumour location, this was primarily done to ensure representation from a range of participants. With consideration to the complexity of neural connectivity and the lack of current understanding surrounding this, patients should be considered at risk of cognitive deficits even if they are not commonly associated with the location of their tumour. For this reason, the investigation of any correlation between tumour location and deficits was not deemed to be a priority. The quantitative analysis of this survey was done to provide a snapshot of function across all patients. The inclusion of tumour location in the demographic questions was done to ensure representation across multiple tumour locations. However

Secondly, variation could be due to differing living situations. Reliance of patients on those around them was a commonly reported coping mechanism. Therefore, patients that live alone, or have more complex relationships with those around them, may struggle more with different activities. This view is mirrored in the reported concerns of those diagnosed with Alzheimer's disease who live alone. Patients reported uncertainty with how to navigate difficulties alone especially with regard to increased cognitive difficulty [239]. Furthermore, family members who are not as closely involved with patient, may not notice deficits that others may.

Thirdly, participants were required to compare functioning to before the completion of treatment, but this may be subject to recall bias [240]. Whilst this may limit our understanding of the level of changes, the key focus of the entire study is to identify cognitive deficits experienced by patients overall.

The results of the Likert type scale questions were generally consistent across groups, however the free text questions offered a further insight into the similarities and differences between experiencing and observing symptoms. Both patient and family groups were able to identify the negative effect that cognitive symptoms have on the patients. There were several recurring themes on how patients and family members may refer to changes and it was highlighted that there was a general uncertainty as to the precise nature of the patients' cognitive decline. This is somewhat reminiscent of the lack of information of the nature of cognitive decline reported in many of the studies included within the systematic review. However, as participants were still able to describe these changes indicates that whilst understanding may be limited, which may reduce the chances of them reporting issues to their care team, they are able to identify alteration when prompted.

The differences between the responses of patients and family members highlighted the unique perspectives of these groups. These distinct perspectives were clear throughout most of the responses, however, it was particularly notable in regard to mood and affect, and the use of compensatory mechanisms. The results show that there are elements of change resulting from cognitive decline that the patient may be unable to identify. This was highlighted by the changes in personality observed by the family group. Whilst patient are mostly aware that they have extra challenges to deal with, they may not realise that despite their efforts to mitigate or even conceal these, there is still a noticeable change. Personality changes have also been reported in patients with other brain injuries. Dwan et al (2019) report how changes to patient personality after a stroke often contributes to a decline in overall QoL [241].

Finally, there are often mitigating techniques employed by the patient, that those around them may not be aware of. Even though many family members play an active role in caring for the patient, they are still onlookers to the patients' experience. Whilst this limits how much they can understand the actual experiences of the patient, they are able to observe the outward effects of these experiences in a more objective manner. Although this may facilitate the identification of changes that either the patient or family member may not pick up on, this gap in perspective could cause

difficulty in the relationships between patient and family member. This difficulty may be further exacerbated by an increase in reliance of patients of those around them.

There are several limitations that need to be acknowledged when considering the findings presented. An even distribution of participants was initially planned and although targeted recruitment was utilised, with HCP and family member specific advertisements being circulated, this was not achieved.. This was most likely due to the recruitment strategies implemented. A large majority of participants were seen to be recruited through the Brain Tumour Charity 'BRIAN' forum, which is exclusive to patients. Recruitment through charity social media platforms and mailing lists proved to be successful for this survey. This is likely due to the trust established between well-known charities and patient.

Had this survey recruited participants in NHS settings, the number of HCP's taking part may have been higher, as this would have enabled a more direct method of recruitment. However, throughout the planning of this survey, there was uncertainty around the feasibility of recruitment . Due to COVID-19, there was an understandable priority to process applications for COVID-19 related research. Therefore, it was unclear if ethical approval and permissions would have been attainable with regard to the project time scale. Additionally, given that the survey was conducted in the midst of the COVID-19 pandemic, recruitment would have been limited due to the strain on all HCP's.

Whilst social media was most successful with the help of the charities involved, the use of Reddit was unexpectedly positive. As this is a platform that is based around online conversation, it worked as a place to not only advertise the survey, but also promote conversation. Potential participants appeared to be more comfortable to enquire about participation than on any other platform. There are also functions available on Reddit that allow people to set reminders on posts as well as 'up vote' posts to promote them. A reminder was used by one person who had explained that they were just coming to the end of their radiotherapy, so they were able to remind themselves to take part a month later, once they could evaluate any potential changes. Whilst this proved to be a useful method of recruitment, the publicity of platforms like Reddit and Twitter mean that anybody can advertise for anything, which may cause potential participants to be wary of taking part.

Another key limitation of the study is associated with the use of online public surveys. These naturally mean that researchers have a lack of control over participation. Whilst this was addressed with the use of screening questions, there was no way of verifying

these responses whilst maintaining the anonymity assured to potential participants. There is also the further limitation of online access. As participation in this survey was determined by accessibility to the internet as well as a certain level of confidence in using it, this survey had a degree of bias towards younger, less cognitively impaired participants. Therefore, the impact of cognitive decline may be greater than what is reported here. This bias is further enhanced by the heavy use of social media recruitment.

The reliance on social media recruitment may create a bias towards individuals that will be seeking information on such platforms [242]. Whilst many HCP's have a social media presence, this is often utilised as a way to share their own work, or to interact with patients and their families. They may not view it as an opportunity to take part in research and will therefore may not often interact with posts that are aiming to recruit participants. Whilst the use of social media recruitment may have increased the bias in favour of participants who are younger or in less advanced stages of their illness, the use of online participation did have some mitigating factors. The use of public platforms meant that participation was not subject to gatekeeping, a common recruitment problem in advanced disease [243, 244].

Additionally, the use of an online survey allowed participants to carry out the survey in their own time. Whilst the survey completion time was estimated to be approximately 10 minutes, this estimate was given under the assumption that participant would not take breaks between questions. Given that this was a substantial survey of 19 questions plus demographic and screening questions, along with the symptoms associated with this patient population, this was an important consideration. Had the survey been conducted face to face, patients may have become more easily fatigued, and had the survey been posted, that may have impacted the completion rate as submission of completed surveys would have been more complicated. In addition to this, it can be seen from the high completion rates and low missing data points, that this survey was constructed in a way that was acceptable to participants.

It is important that limitations are acknowledged when considering the generalisability of the data. The Central Brain Tumor Registry of the United States (CBTRUS) statistical report on primary brain and other central nervous system tumours diagnosed in the United States in 2014–2018 saw that, in adults, gliomas are most commonly found in the supratentorial regions of the brain [36]. The results presented in this chapter mirror this with higher numbers seen in areas like the frontal, parietal

and temporal lobes and lower instance in areas infratentorial regions such as the cerebellum and brain stem. However, the CBTRUS report states that GBM (which is stated in the report to be the most commonly diagnosed malignant primary brain tumour in adults) is 1.6 times more common in males than females and is most commonly seen in older adults. Contrary to this, patients responding to the survey were more likely to be female representation be aged between 26 and 65. This age distribution may be a result of the afore mentioned bias caused by the use of social media recruitment. Furthermore, the higher female representation despite glioma incidence being higher in males, could be a result of male attitudes towards help seeking. As previously stated, the use of social media recruitment may have led to a bias in favour of those who are looking to seek out information. In addition to this, it has been seen that males are less likely to engage in help-seeking as a result of conforming to masculine norms [245]. This idea is further supported by the fact that family member participants reported on more male patients than female, however, patients taking part themselves were more often female.

As well as the limitations associated with the use of an online survey, there are also the limitations associated with the use of a thematic analysis. Whilst thematic analysis is an appropriate way of bringing together and understanding qualitative data, there are still aspects that need to be considered relating to research rigour. The flexibility and freedom given to the researcher conducting the analysis is useful for interpretation to best suit the study aims. However, this flexibility presents the potential for inconsistency which may make it difficult to coherently develop themes [19]. In order to limit the presence of such issues, a proportion of the thematic analysis was double coded by a second member of the research team. When evaluating the data obtained and analysed from the free text boxes, it is also important to acknowledge the potential limitation that may arise from arranging these around the closed questions. Free text boxes are designed to allow the participants the opportunity to expand on matters beyond the scope of the closed questions. However, having them around such focussed questions may mean that participants are discouraged from considering elements of interest because they may feel they are irrelevant to the question. In the hopes of mitigating this, an additional free text box was presented at the end of the survey, however, it should also be acknowledged that participants, especially those with cognitive decline, may have experienced fatigue by this point, and therefore may have been less inclined to provide any in depth information.

Furthermore, this limitation may be seen to be exacerbated by the closed questions presented being designed from the results of the systematic review. This means that the cognitive deficits explored in the survey, are limited to those identified in the review. Whilst the results of this meant that all areas of cognition that were assessed in studies included in the review were included in this survey, it still needs to be considered that the limitations of the assessments used in the included studies, as discussed in chapter 2, are carried through to the questions presented in this survey.

3.4.1 Conclusion

This survey has enabled us to confirm that the cognitive deficits highlighted by the systematic review are applicable to a population of HGG patients specifically. It has also given a further understanding of the lived experiences of patients and their family members. This information will help to design a screening tool that not only captures relevant deficits, but it also gives us an indication as to how this could be designed in a way that prompts participants to consider the potential of cognitive deficits using terminology that they themselves can identify with.

The unique insights of patients and family members points towards the potential value of giving both patients and family members the opportunity to raise any concerns they may have about cognitive functioning. In order to further understand how this may be best utilised, the next step in this project is to look further into these finding in a more direct way by explicitly asking potential tool users about their experiences.

Chapter 4: Stakeholder meeting to aid the development of a screening tool for the cognitive deficits experienced by patients with high-grade glioma after receiving radiotherapy: A UK based online focus group

4.1 Introduction

In this chapter I will present the findings of a focus group that was conducted to further explore how cognitive deficits and their impact on patients' QoL are described by stakeholders. The analysis of these data will allow a better understanding of how the results of the survey could be used to draft a screening tool that is representative of the lived experiences of those affected by HGG.

The results of the survey (chapter 3) confirm that the areas of deficit highlighted by the systematic review (chapter 2) are specifically applicable to HGG patients. The results also provide an insight into how patients and family members of patients describe deficits, and the subsequent effects on the lives of patients and those around them.

In order to utilise this information to design a screening tool that is both representative and relevant the purpose of the stakeholder meeting is to further investigate the current support available to patients; understand how deficits impact QoL and any potential barriers preventing patients and their families from seeking support; explore the way in which participants describe deficits and their impact on QoL in order to refine the terminology to be used in a potential screening tool.

Additionally, a further understanding of currently available support for cognitive deficits will help to prevent screening of deficits that are already commonly addressed in this patient population to minimize duplication. Furthermore, looking into barriers that may be preventing patients and their families from seeking support will inform understanding of how a potential screening tool could be designed in a way that addresses these issues. This will help to ensure that any screening tool is developed to be as inclusive as possible.

To achieve this, a focus group was conducted to obtain first hand experiences of individuals involved with, and affected by, these issues. While there are many other methods of obtaining these experiences, a focus group was deemed to be the most appropriate method for this stage of the study. Focus groups are used to gain an understanding of the knowledge, perspectives and attitudes of individuals regarding

a specific subject [246]. They are used as a method of data collection for qualitative, quantitative and mix-methods studies [247]. This is done through group discussion facilitated by the researcher [248]. The use of a single meeting to achieve this was particularly useful considering the time restraints of the study. Additionally, it has thus far been established that there is a wide range of cognitive deficits that can be experienced by patients with HGG. These deficits cover processes associated with memory, executive functioning and communication. Furthermore, the survey results show that the severity and presentation of deficits in patients are highly variable. The use of group discussion allows for participants to not only share their experiences, but also consider the experiences of others, which may or may not vary from their own. As the overarching aim of this thesis is to work towards developing an easy to use screening tool, understanding the patient experience and the language used by patients' and their families to describe deficits is a key objective. In addition, allowing participants to discuss their experiences with one another allows for the identification of differences, which in turn enables the screening tool questions to be as inclusive of as many experiences as possible

Other methods, such as individual interviews would require several weeks to complete, which would have limited subsequent stages and added to participant burden. In addition to this, further understanding the sort of language and terminology used by patients and their families was of particular interest for this stage of the study. Therefore, it was important to allow participants the opportunity to vocalise their experiences rather than expressing themselves through text, as would be required if a further survey was conducted.

When carrying out a focus group, some individuals may dominate conversation and opinion. This is a common issue associated with focus groups which can be mitigated by careful sampling of homogenous groups [8]. The constituency of homogenous groups has been subject to debate [249], with some scholars recommending that groups be homogeneous in regard to areas such as age, sex, class and occupation [250]. However, others have reported that there are minimal differences associated with the homogeneity of a group [251]. When attempting to conduct a focus group that includes the insights of individuals with direct experience of a specific element of a specific illness, it becomes a challenge to maintain homogeneity whilst dealing with appropriate number of participants, time limitations and available resources [252]. Therefore, maintaining a pragmatic approach, it was decided that homogeneity would not be prioritised as part of this focus group, but that efforts should be made to ensure individual participant interaction.

In order to do this, the focus group was designed using elements of consensus building methodology. Consensus methods are being increasingly used for clinical application and whilst they are not methods of creating new knowledge, they enable optimal use of already available information [253]. Whilst the outcome of the focus group will be an exploration of expert stakeholder opinion, incorporating aspects of methodologies used in consensus building ensures that each participant will have their opinion heard and therefore represented.

Aspects of the Nominal Group Technique (NGT) were used when planning the structure of this focus group meeting. The NGT is a structured variation of a group discussion to reach consensus. This method combines the individual generation of ideas and group discussion to encourage all group members to participate in order to obtain results that are representative of the whole group [254]. Although, the aim of this study was not to obtain consensus, these aspects of the NGT were used in this focus group meeting in order to ease facilitation of discussion. The maintenance of structure throughout the meeting would therefore help in ensuring that the necessary topics are covered and each individual is able to contribute.

4.1.1 Aim

The aim of this focus group was to prioritise and further explore the results of the systematic review (chapter 2) and survey (chapter 3). This was done to form an outline of the key components needed to develop a simple screening tool to trigger a specialist referral for HGG patients experiencing cognitive deficits after receiving radiotherapy.

There were three key objectives:

1. To determine which changes highlighted by the survey would be benefit from a specialist referral.
2. To determine the best methods of screening for these changes.
3. To gain further insight in the ways stakeholders describe cognitive deficits and their effects on QoL in order to refine the any wording used in a potential tool.

4.2 Methods

4.2.1 Recruitment

Participants were required to be aged over 18, proficient in the English language and fall into one of the following categories:

- A patient diagnosed with HGG
- A family member or friend of a patient with HGG (bereaved family members were not excluded)
- A healthcare professional with direct interactions with HGG patients (i.e Neuro-oncologist or Neuro-oncology nurse)
- A healthcare professional that would be involved in the referral process (i.e GP, Neuropsychologist, or nurse)

Participants were recruited either via social media (Facebook group and Twitter account) or the *brainstrust* Charity contacts (with email list). Figure 12 shows the recruitment advertisement circulated on Twitter with original posts being shared from FM's personal account (@FMazzaschi) and the Marie Curie Palliative Care Research Centre Cardiff account (@MCPCCardiff). Once potential participants showed an interest in taking part, an invitation email was sent to them which included details of the event including time, date, the participant information sheet (Supplementary appendix C), and a consent form (Supplementary appendix D). Participants were also sent the meeting invitation and instructions on how to use the application from a computer or smartphone. All public facing documents including recruitment advertisements, consent form and participant information sheet were reviewed by an ethics committee, and two PPI research partners.

Expert opinion needed

Following on from a recent survey looking at everyday memory and processing in patients with high-grade glioma, we are working to form an outline of the key components needed to develop a simple screening tool to trigger a specialist referral.

On the 2nd of February 2021, we will be inviting UK based stakeholders to share their knowledge and experience to form an outline of the key components needed to develop a simple screening tool to trigger a specialist referral .

If you are:

- A patient diagnosed with high-grade glioma
- A family member or friend of a patient with high-grade glioma
- A healthcare professional with direct interactions with high-grade glioma patients (i.e Neuro-oncologist or Neuro-oncology nurse)
- A healthcare professional that would be involved in the referral process (i.e GP, Neuropsychologist, or nurse) and would be willing to share your knowledge, please get in touch!

Email: mazzaschifi@cardiff.ac.uk
Twitter: FMazzaschi

Canolfan Ymchwil Gofal Lliniarol
Marie Curie
Palliative Care Research Centre
CARDIFF. CAERDYDD

MARIE CURIE
Palliative Care Research Centre
CARDIFF. CAERDYDD

CARDIFF UNIVERSITY
PRIFYSGOL
CAERDYDD

Figure 7: Recruitment Advertisement

4.2.2 Study setting

This focus group took place on the 2nd of February 2021. Due to the COVID-19 restrictions in place at the time of the meeting, this event took place online using 'Zoom' the video call application. The session was scheduled for two and a half hours and included an interactive element using Mentimeter, a voting software programme (Cardiff University app). As the meeting was scheduled to last two and a half hours, it was envisaged that participants may have difficulty staying engaged. The Mentimeter application enabled participants to be involved with every aspect of the meeting. Whilst there are currently no studies on the feasibility of using Mentimeter in studies including this particular population, it has proven to be successful in keeping large groups of students engaged in lectures [255].

4.2.3 Ethical approval

This study was conducted according to the principles of good research practice, the General Data Protection Regulation (GDPR) and the UK Policy Framework for Health and Social Care Research (2017). This study was granted ethical approval from the Cardiff University School of Medicine Research Ethics Committee (SREC reference: SMREC 20/115).

4.2.4 Ethical considerations

It was important to consider that, due to the sensitivity of the topic, some participants may find subject matters addressed to be distressing. For this reason, it was of utmost importance that participants knew that they were able to sign out from the meeting at any time. After the meeting, participants were contacted to thank them for their participation. This email (supplementary appendix E) contained links to the webpages and contact numbers of Marie Curie, The *braintrust* and Macmillan that offer information and support.

Participants were informed that participation was confidential and any opinions or information given throughout will not result in any change in any treatment to be undergone by themselves or their loved one. As this meeting was recorded, participants were required to send the completed consent form prior to joining the meeting. Participants were required to consent to the recording of the meeting and the analysis of any responses submitted on Mentimeter throughout the meeting.

4.2.5 Focus Group Plan

Upon joining the meeting, participants each introduced themselves and were given the opportunity to connect to Mentimeter to take part in the interactive elements of the meeting. Whilst also promoting participant engagement, Mentimeter was used to conduct a variation of a NGT, allowing every participant equal opportunity to

contribute to the discussion. Once participants had the opportunity to connect and ask any questions, the meeting was started.

The meeting was divided into three parts. The first part was a brief presentation delivered to give an overview of the PhD. Background information was given about the systematic review and the survey results, and participants were told how the focus group would contribute and assist with the goal of developing a screening tool. Participants were given the opportunity to ask any questions they had.

Once the background and purpose of the focus group was established, the interactive elements of Mentimeter were utilised. Participants were first asked questions about their current care and presented with the same lists of situations that were presented in the survey. Questions asked in this part of the meeting focused around the services that are currently available to patients and their families. The questions asked focused on the following:

- Deficits they believe would be identified by their healthcare team without prompting from themselves. Participants were asked to consider this in regard to the healthcare professional they have the most contact with.
- Deficits they would report to their healthcare team without prompting.
- Areas they feel they or their loved one would be able to receive adequate support for, should a deficit be identified .
- If they or their loved one had received any support over the course of their illness for difficulty with any of the situations listed.

After each vote, the live results were used to guide discussion so that participants could give more detail on their answers and reasons behind them.

In the third part of the meeting, participants were asked to consider the effects that cognitive deficits have on overall QoL. Firstly, participants were asked to rank the effect on QoL of each deficit. Participants were presented with a set of Likert type scales ranging from one to five, with 1 representing 'no effect' on QoL and 5 being 'very detrimental' to QoL.

These questions were split to be presented over two slides. This was done to make sure each question was presented to be large enough to easily see. Once participants had been given the opportunity to respond, the results were used to guide discussion to determine the reasoning behind their answers. Lastly, participants were asked to

consider the points of discussion covered and vote on which areas of deficit they believe would benefit from further screening.

In preparation to carry out this focus group two practice runs of the meeting were conducted. Firstly, with the supervisory team and secondly with the Marie Curie Palliative Care Research Centre (MPCRC) team. The first was to practice the content of the focus group and the second was to test the practicality of using Mentimeter.

4.2.6 Data Analysis

The data extracted from Mentimeter was analysed using descriptive statistics via Microsoft Excel 365. Bar charts were generated to visualise participant votes for section two. Mean, median and range of Likert type scale responses were calculated.

The audio recording of the meeting was transcribed by a university approved transcription service 'Essential Secretary'. The transcription was then uploaded to NVivo (NVivo 12) for coding, and analysed thematically as described in chapter three. As the results of the focus group were designed to supplement the results of the survey, maintaining the same method of data analysis allowed for not only the addition of new themes, but also the expansion of themes highlighted by the survey.

4.3 Results

4.3.1 Participation

A total of eight participants took part in the focus group, which had a duration of 2 hours and 30 minutes. Participants included patients (n=5) and family members of patients (n=3) of whom two were bereaved. At the start of the meeting, one of the family member participants notified us that they may have to leave the meeting at short notice as they were at work. Whilst no specific demographic questions were asked, most participants offered information on their circumstances and experience of HGG. Table 12 details the information given by participants. Over the course of the meeting, several other participants (n=4) left the meeting, two of which excused themselves in the Zoom chat function and two emailed their apologies shortly after detailing issues with connectivity. Time attended is detailed in table 12.

Information provided by participants	Number of participants
Relationship to patient	8 (100%)
Patient	5 (62.5%)
Sibling	1 (12.5%)
Widowed	2 (25%)
Time since diagnosis	5 (62.5%)
<1 year	1 (20%)
1-5 years	2 (40%)
5-10 years	1 (20%)
10+ years	1 (20%)
Time attended	8 (100%)
<30mins	8 (100%)
30 mins- 1 hr	8 (100%)
1hr-1.5hr	8 (100%)
1.5hr-2hr	7 (80%)
2hr-2.5hr	4 (50%)

Table 11: Focus Group Participant information

4.3.2 Mentimeter results

Of the eight focus group participants, seven took part in the interactive elements of the meeting through Mentimeter. The participant who was unable to take part was unable to connect to Mentimeter whilst staying on the call. Whilst seven participants took part, respondents were not recorded for individual questions if they did not vote for any of the options. Participants were asked to confirm they had completed.

Current Care

Figure 13 shows the results of the votes on questions surrounding current care. Question one (If you or your loved one were to experience problems in any of the following areas, which do you feel would be picked up on?) can be seen in figure 13. All seven participants voted for at least one option. It can be seen that the item 'taking in information' had the highest number of votes (n=4/7) and the items: numerical calculation, writing and typing, and starting new tasks, received no votes.



Figure 8: Number of votes for question 1

The results of question 2 (If you/your loved one were to experience problems in any of the following areas, which would you tell your doctor or nurse about?) are shown in figure 14. Six (86%) of participants voted for at least 1 option. Problems with 'misplacing items', 'recalling details' and 'recalling events' were seen to be the most commonly voted, with each receiving 4 votes (57%). None of the items received less than 2 votes (29%).



Figure 9: Number of votes for question 2

Four (57%) participants voted for at least one option for question three (If you/your loved one were to experience problems in any of the following areas, which do you feel that you would get adequate support for?). The results shown in figure 15 show that at least one person (14%) voted for each option. 'Misplacing items', 'Speech and language', 'Recalling details' and 'Taking in information' were the options with the most votes, with each receiving 2 votes (29%). One (14%) participant voted in question four (Which of the following have you/your loved one received support for?). Figure 16 shows that very few participants or their loved ones had received support. Participants reported that support had been received for issues regarding 'Recalling details', 'Maintaining focus' and 'Recalling events' were reported to be supported, with each receiving one vote each (14%).

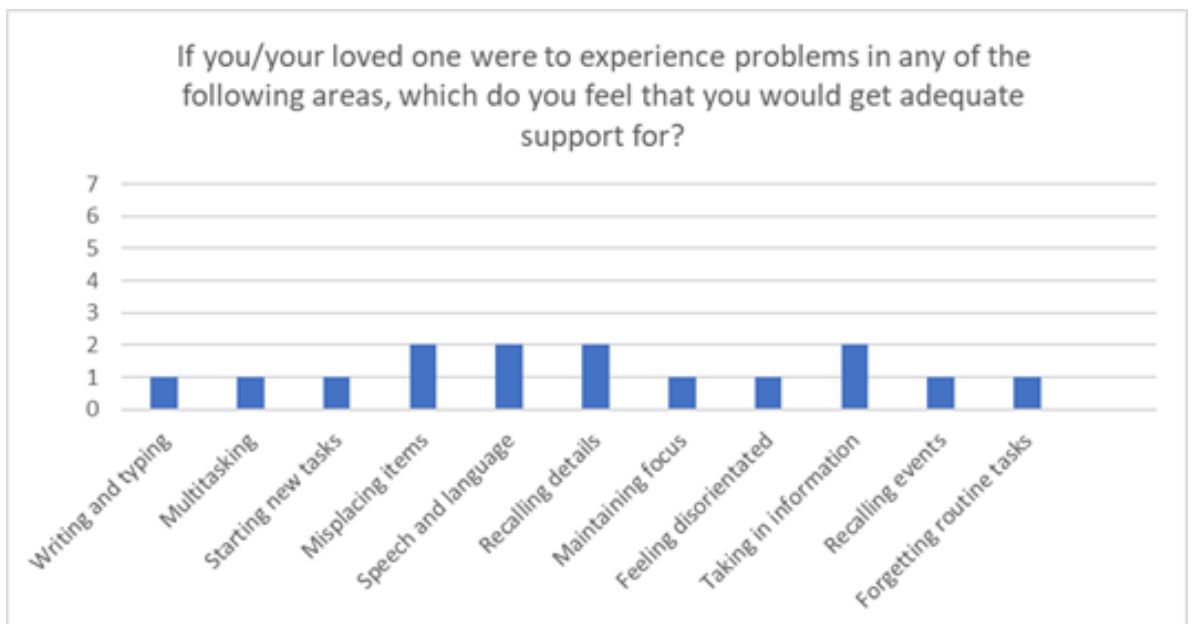


Figure 10: Votes received for question 3

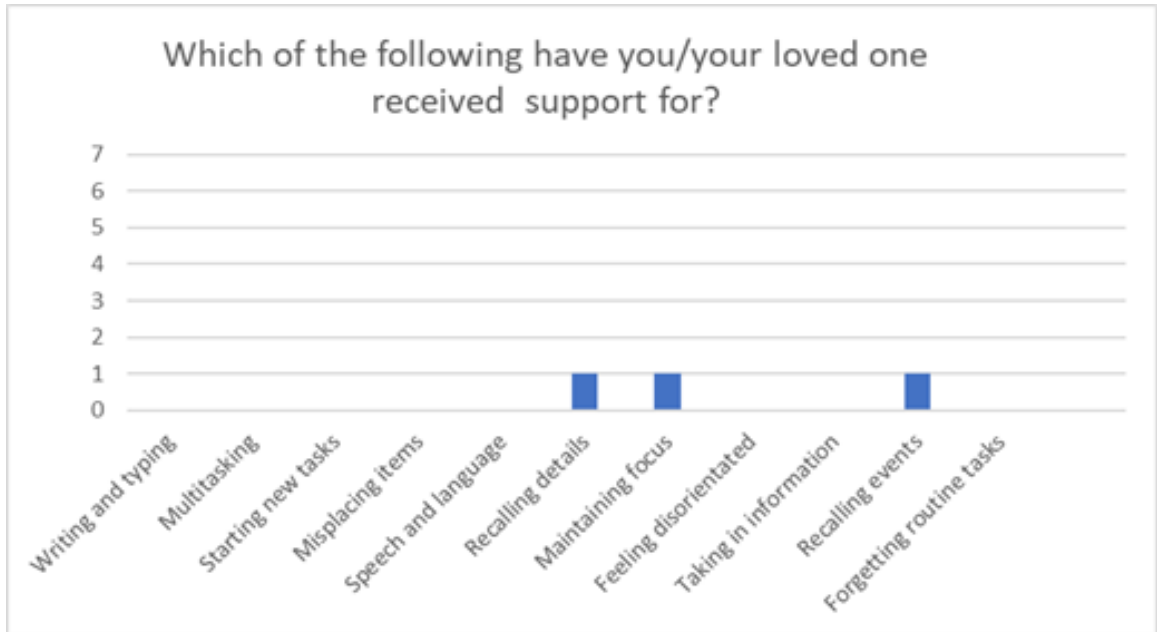


Figure 11: Votes received for question 4

Impact on Quality of Life

The results from the Likert type scales presented in part three of the meeting are presented in table 12. Participants were asked to rank the effect of listed cognitive deficits on overall patient QoL. All seven participants that took part in the Mentimeter questions took part in the first set of questions, but one participant dropped out of the session in the discussion of the first six questions. Therefore six participants took part in the second set of questions.

On a scale of 1 to 5 (with 1 being no effect and 5 being very detrimental) overall, participants voted that numerical calculation to have the least effect on patient QoL. This is shown by a mean response of 2.29 and a median of 2. However, it should be noted that at least one respondent answered 5. The area reported to have the highest impact on QoL was speech and language. Similarly to numerical calculation, responses ranged from 1 to 5. The rest of the areas highlighted all scored generally high over all, with all other means reported being above 3.43.

Task	Measurement	
Numerical calculation	<i>n</i> (%)	7 (100%)
	<i>Mean</i>	2.29
	<i>Median</i>	2
	<i>Range</i>	1-5
Writing and typing	<i>n</i> (%)	7 (100%)
	<i>Mean</i>	3.71
	<i>Median</i>	4
	<i>Range</i>	2-5
Multitasking	<i>n</i> (%)	7 (100%)
	<i>Mean</i>	3.57
	<i>Median</i>	4
	<i>Range</i>	1-5
Starting new tasks	<i>n</i> (%)	7 (100%)
	<i>Mean</i>	3.43
	<i>Median</i>	4
	<i>Range</i>	1-5
Misplacing items	<i>n</i> (%)	7 (100%)
	<i>Mean</i>	3.71
	<i>Median</i>	4
	<i>Range</i>	2-5
Speech and language	<i>n</i> (%)	7 (100%)
	<i>Mean</i>	4.43
	<i>Median</i>	5
	<i>Range</i>	1-5
Recalling details	<i>n</i> (%)	6 (86%)
	<i>Mean</i>	3.83
	<i>Median</i>	4.00
	<i>Range</i>	2-5
Maintaining focus	<i>n</i> (%)	6 (86%)
	<i>Mean</i>	4.00
	<i>Median</i>	4.00
	<i>Range</i>	3-5
Feeling disorientated	<i>n</i> (%)	6 (86%)
	<i>Mean</i>	3.83

	<i>Median</i>	4.00
	<i>Range</i>	2-5
Taking in information	<i>n(%)</i>	6 (86%)
	<i>Mean</i>	3.83
	<i>Median</i>	4.00
	<i>Range</i>	2-5
Recalling events	<i>n(%)</i>	6 (86%)
	<i>Mean</i>	3.67
	<i>Median</i>	3.5
	<i>Range</i>	3-5
Forgetting routine tasks	<i>n(%)</i>	6 (86%)
	<i>Mean</i>	4.00
	<i>Median</i>	4
	<i>Range</i>	2-5

Table 12: Likert type scale responses rating impact of decline on quality of life

The range of responses seen indicate that the perceived impact of decline that various cognitive deficits have is variable amongst participants. Furthermore, a decline in numerical calculation is generally reported to be the least detrimental to patient QoL.

4.3.3 Thematic analysis of transcript

During the course of the focus group, participants repeated references to areas of interest at various points across the meeting, therefore, a transcript of the entire meeting formed the case for analysis in preference to analysing data per question. The transcript was analysed by FM. Once a preliminary coding framework was drafted. AN double coded a proportion of the transcript (10%) and a final coding framework was agreed. The thematic analysis of the audio transcript gave rise to three key themes. These were: Key domains for screening tool, Family support, and Barriers to reporting cognitive deficits. Figure 17 shows how these themes are separated into subthemes.

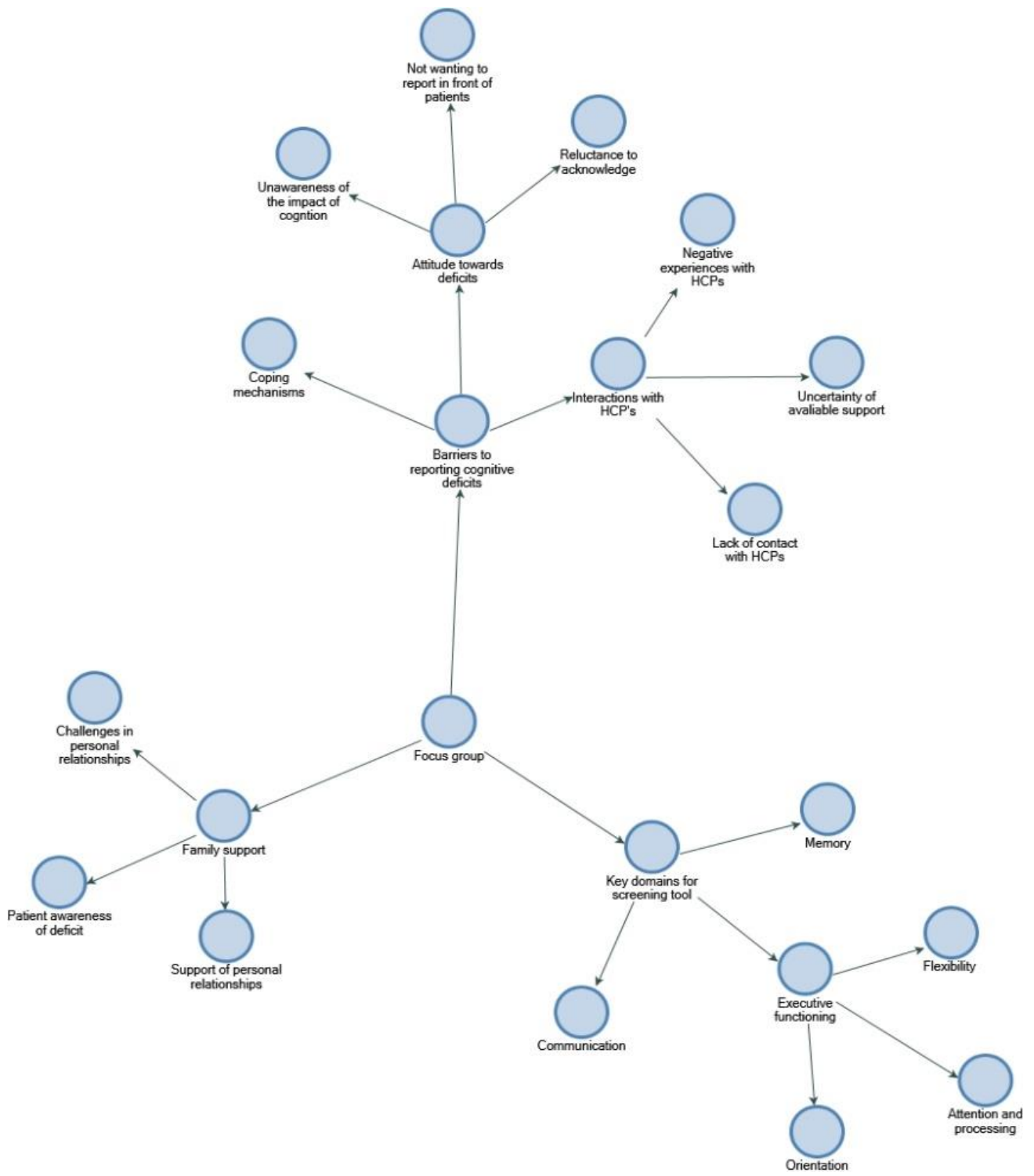


Figure 12: Themes highlighted in the thematic analysis of the meeting transcript

Key domains for screening tool

This theme comprises of three subthemes: Communication, Executive functioning, and Memory.

Communication

Communication was generally regarded to be an essential aspect of a patient's life and it was agreed by all participants that preservation of communicative skills was paramount to maintaining QoL. Participants reported that communication was key in enabling patients to seek help and support and a fundamental part of every aspect of life. Difficulty with communication, was described by several participants as being one of the most frustrating and distressing symptoms experienced by patients.

“communicating what your needs are, um, well it's, it's paramount really isn't it, to your existence, to getting your wants, needs, thoughts across to people, and to be able to you know, to support you.” -Participant 5 (Widowed)

“it's key isn't it, communication is key really?” -Participant 4 (Patient)

“I think of all of (their), disabilities and symptoms, this was by far and away the most distressing.” – Participant 5 (Widowed)

Trouble with word recall was one of the key points raised by the group. This was reported to be experienced by patients in both verbal and written communication resulting in frustration and the need for support from others. Many participants make a clear distinction between their past and present lives, highlighting losses to their sense of self and normality.

“My whole world was about communicating with people, and it's one of the most frustrating things that I found, um, was the word finding, it's the trying to explain, I mean, sometimes my husband, I'll be trying to explain something so, so simple, um, and he tries to go really slowly and get me to sort of almost go back to the beginning again.” -Participant 4 (Patient)

“I've lived my whole life writing everything down, and typing and um, that's one of the things that I feel really difficult is that sometimes you've got it up here, but you can't get it down on paper, um, what you want to say” -Participant 6 (Patient)

It was clear that most of the participants, or their family members, had experienced difficulty with communication to some degree. However, it was also evident that these

difficulties could be caused by a range of different cognitive deficits. One participant described how their relative had potential issues with mental flexibility, expressing difficulty with switching focus.

“I’ll say to her every morning, what, you know, what would you like for breakfast, and if she just happens to glance at the clock and said, I’ll have a half 10” - Participant 3 (Sibling)

Another participant described how they often struggle to remain on track in a conversation and often forget what they were talking about. There is a clear distinction made between the way they comprehend a task and their ability to verbalise. This highlights a specific deficit regarding verbal recall, rather than a more generalised memory deficit.

“Because halfway through talking to them I’m just going to go no, I’ve forgotten what I’m saying now. But doing the task is fine, but I can’t explain it to them, and that’s a, that would be a problem” -Participant 2 (Patient)

Executive functioning

Issues with domains of executive functioning were commonly reported by participants. Due to the broadness of this subtheme, further coding was applied in relation to ‘Flexibility’, ‘Orientation’, and ‘Attention and Processing’. One participant explained how issues with mental flexibility have resulted in their family member having to change their way of life:

“She was a busy person, having lots of things you know, spinning lots of plates, um, you know, and now that’s not the case.” -Participant 3 (Sibling)

The importance of mental flexibility in everyday life was reiterated by another participant. They gave an example of the importance of keeping up with the responsibilities of day to day life. This shows the importance of mental flexibility in maintaining normality.

“...and just kind of planning the timetable of getting the bus, and all of those things you need to multitask don’t you? Because you need to think about while I’m on the bus, I’m texting my children to check that they’re doing their home schooling. Um, so it’s all of those things, because you know, we have got some

different responsibilities that we have to do really, and keep up to date with, I suppose.” -Participant 4 (Patient)

Whilst challenges with attention and processing can directly effect a patients mental flexibility (and vice versa), participants often described overwhelming issues with attention and processing as distinct from concerns about flexibility. It was described by one participant as a type of 'sensory overload'.

“...at Christmas in the supermarket, and it was just a sensory overload” – Participant 8 (Patient)

A similar description came from another participant who reported a difficulty with processing multiple stimuli and a feeling that they are often over stimulated by information.

“My brain just can't work fast enough, to process all the information” -Participant 4 (patient)

The impact of these challenges was made evident throughout the meeting. It was clear that these deficits directly led to lifestyle changes. One participant stating that it was a difficulty in maintaining focus that led to them having to retire from work.

“I'm not even allowed to work now, because er, the, my inability to stay focused on the technical details of what I'm discussing is now significantly lacking.” - Participant 2 (patient)

Difficulty with orientation was described by participants as challenges with navigation. Participants indicated that it requires more effort to navigate routes that they had previously been familiar with. One participant went on to describe the changes they had noticed in regards to their regular cycling routes.

“I'm a cyclist as well, so I'm used to finding my way places, um, obviously now it's harder. Um, but even places I know, I haven't kind of got that bird's eye view of where I am, to plan where I'm going, I find that really difficult now.” – Participant 4 (Patient)

Memory

Memory deficits were experienced by patients in various ways. One participant gave an example of how their memory deficits affect their daily living by causing them to forget to do or take part in activities that they had planned.

“I'm just apologising for being late, um, it's a classic example of my memory I'm afraid” -Participant 8 (Patient)

One participant reported that they often misplaced items, which was described as particularly frustrating. However, they went on to explain that they not only felt frustrated at the loss of the item, but also felt distressed as they felt situations like this highlighted the fact that they had deficits as a result of their tumour and subsequent treatment.

“Silly little things like a tee shirt, or you've had it in your hand, and then you've gone upstairs, and it's just not there anymore. And you just cannot remember what you've done with it, where you've put it, and I mean, that to me again, is such a huge thing, because not only is it the fact that you've lost the item, but it's that um, sort of highlighting the cognition side of things.” -Participant 4 (Patient)

Although participant 2 described the effect that declined verbal recall had on their ability to communicate, it was also expressed that their challenge is not one of verbal fluency, but rather disengagement from the conversation. They explained that their difficulty is mostly due to being unable to retain information regarding the purpose and context of a conversation, rather than difficulty with remembering the information and verbalising what they wish to say.

“I still know all the information, I can still get it all out, but I can't remember what I'm talking about, to be able to do that.” -Participant 2 (Patient)

The importance of memory on QoL was made known by all participants. It was expressed to be a key element of all areas of daily life.

“And the memory and you know, it's um, it's such a huge, huge thing. And also it impacts on all the other areas as well, um, I think” -Participant 3 (Sibling)

Role of family members

Understanding the challenges faced by patients experiencing cognitive deficits requires a full understanding of both the patients functioning, and their circumstances.

Throughout the meeting the importance of gaining proxy insight from family members was very clear, however, it was also evident that relationship dynamics between patients and their families may be challenging. This theme includes subthemes of 'Challenges in personal relationships' and 'Support of families'.

Challenges in personal relationships

This subtheme encompasses the views expressed by participants about how deficits can impact on the relationships between patients and their families. Several participants explained how the additional responsibilities they found themselves dealing with, shifted the dynamic of their relationships with the patient. One participant described how they were no longer to prioritise their own needs.

"Your focus is just completely on the patient and managing the 14 medications, and the trips to radiotherapy every day, you know, you do sort of shut off from your own priorities." – Participant 5 (Widowed)

This was agreed by the other participants who were family members of patients. One explained how both the relationship dynamic and the nature of the patient cognitive deficits can have an effect on the experience of both the patient and their families.

"If you're lucky in your relationship and in the kind of neuro psychiatric implications of the diagnosis, it can be easier." -Participant 7 (Widowed)

Support of personal relationships

Patients often form a support system with their families. This theme encompasses the viewpoints of participants on the roles of personal relationships when supporting patients throughout the course of their illness. One participant spoke about how they would work to compensate for their spouses deficits. This description of partnership was also expressed with gratitude for the support of a spouse.

"tasks that both of us needed to do, were sort of put together, and whatever deficit (she) had, I could step in for. Um, and so er, you know, perhaps that was fairly fortunate." -Participant 5 (Widowed)

"I feel incredibly lucky, because I have a wife who supports whatever I decide to do. So if I'm er, not very well, she'll make sure I'm okay, and when she's not very well, I'll try and look after her as much as I can." -Participant 2 (Patient)

Reluctance to report issues

Even though both patient and family participants expressed that cognitive deficits are detrimental to patient QoL, there were also reasons given for why some people may

be reluctant to report any issues to their health care team. This theme covers these reasons given in three subthemes, 'Attitude towards deficits', 'Coping mechanisms' and 'Interactions with HCP's'.

Attitude towards deficits

Whilst both patient and family member participants acknowledged that cognition is commonly affected in this patient population, it was not always evident that patients fully understood the extent of their deficits. There was a general understanding that patients are aware that there is something wrong as explained by participant.

"We're really aware of it, aren't we, I think more aware than anyone what we can't do." -Participant 4 (patient)

However, it was clear that some patients may attribute difficulties to causes other than their tumour and treatment, therefore unintentionally underestimating the full impact of their symptoms.

"I've put down I occasionally forget you know, tasks and occasionally I can't remember where I've put something down. But I'm assuming like most 50 year olds would have that sort of issue" – Participant 8 (patient)

This was reinforced by the experiences of another participant. They explained how their spouse would often use mitigating language to justify not declaring issues, often surmising that their deficits are directly caused by fatigue. However, they would be more inclined to report on more physical symptoms. The view that cognitive deficits are linked to a patient's fatigue levels was mirrored by other participants.

"I think he might declare the physical things, um, but not declare the cognitive things, I suspect. You know, it's a bit like I'll be better after a night's sleep. Lots of mitigation language." – Participant 7 (Widowed)

"I think some things are variable, and I think some cognitive activities do change according to fatigue" -Participant 4 (patient)

There was also a general sense of acceptance amongst patients, with several of them describing the challenges they face as aspect of their lives that are now part of everyday life.

"it's just all part of parcel of the disease isn't it?" -Participant 8 (Patient)

"I think in our experience it's part of normal life" – Participant 4 (Patient)

The use of mitigating language was also reported to be associated with feelings of embarrassment in patients regarding their cognitive deficits.

“In terms of kind of neuro psychiatric manifestations, there isn't an easy way. Um, it can be really undignified in terms of what's happening, and so you mitigate, you hide, you work much harder, um, but yes, it massively affects quality of life, all of these things.” -Participant 7 (Widowed)

It was then explained further that family members of patients who deal with symptoms in this way will often refrain from declaring issues in order to avoid making their family member uncomfortable. When asked if they would have declared any issues if directly asked, they answered that it would be depended on if the patient was present.

“...your coping strategy are often as a family. So you hide and you support, and you kind of are aware of the changes, but you don't declare them, because that's what keeps things comfortable.” -Participant 7 (Widowed)

“It depends if I was with him” -Participant 7 (Widowed)

Coping Mechanisms

Due to the lack of support offered and available, many participants reported that they had coping mechanisms in place in order to work around the challenges they face. One participant explained how they have written reminders around them in order to compensate for memory loss.

“...we've got um post it notes, they're all, they're dotted everywhere. Um, so I'm not to be unaware of what's going on.” -Participant 1 (Patient)

Other participant expressed how they no longer view their deficits as problems that need the attention of their healthcare team, as they have ways of compensating for them.

“And as long as I can hit that level daily, that I'd ticked a few number of boxes in the house, that keeps me fairly stable.” -Participant 4 (Patient)

This was mentioned specifically in terms of numerical calculation. One participant highlighted that issues with this are very easy to handle and are therefore not as detrimental.

“...in all honesty there's ways round it. I mean, you've got a calculator on your phone, so if you couldn't work things out in your head, it wouldn't matter. I guess if you're in a role or something in your life where you needed numerical calculations on a daily basis, it would be more of an issue, but I think most people now have moved away from that haven't they?” -Participant 6 (Patient)

Interactions with HCP

Participants viewpoints on the availability of support was dependent on their experiences with HCP's. This theme includes the reported experiences of participants. A lack of interaction was a commonly reported occurrence .

“Well, she doesn't see anybody, they've discharged her unfortunately.” – Participant 3 (Sibling)

Participants highlighted how access to services can be very limited for patients. One participant explained how support for those living outside of cities are unlikely to have the same support as those who do not.

“Most people can't drive, so if you live in a city with a group, access skills is very, very different. You know, Wales is huge, very rural, your ability to join a group would be minimal frankly, if you lived in mid Wales somewhere.” -Participant 6 (Patient)

However, it was then stated by another participant that even those living in cities, may not have access to the required resources. It was then expressed that patients and their families often feel as though the availability of support is inconsistent and a matter of luck.

“I don't think you even have to be in rural areas, because ...we had nothing. So I don't think you really even have to be in rural areas, not to get any support...it's a bit of a postcode lottery isn't it?” – Participant 3 (Sibling)

It was also reported that even when there are regular interactions with HCP's, the extent of those interactions are not enough to show the full impact of symptoms on both the patients and families QoL.

“I don't think the neuro oncology team who might see you for 10 minutes a week, in the clinic, really understand the impact of the 24/7 challenge of caring for someone with glioblastoma.” -Participant 3 (Sibling)

Along with a lack of contact time with HCP's, a lack of enquiry from HCP's into the cognitive deficits that may be experienced often leads to patients and their families not being forthcoming with information of these symptoms.

"we've never been offered any support for any of those issues, um, and actually we've never been asked if there are any of those issues either, so we've never kind of volunteered that information." – Participant 3 (Sibling)

"I've never asked for any support...I've not been asked, so I don't tell them." - Participant 2 (Patient)

It was also mentioned that a negative interaction with HCP's can make patients and their families reluctant to seek out further support. One participant explained how it is difficult to forget how a negative interaction with a HCP makes you feel, especially when dealing with such a challenging situation.

"...we had a fairly uncaring response, and his words were, 'there is no pill I can give you for that.' and these things just get branded into your mind, you know, you don't forget them." -Participant 5 (Widowed)

It was then discussed amongst the group that willingness to declare deficits is dependent on the confidence you have in the HCP you are dealing with.

"I think it's also about how confident you are in the professional that you're dealing with." – Participant 6 (Patient)

4.4 Discussion

The focus group explored the opinions and experiences of five patients and three family members of HGG patients. It was highlighted that deficits experienced in all areas of cognition explored in the focus group can have a detrimental impact on patients' and caregivers' QoL. It was also identified that the input of family members could play an important role in identifying deficits due to their insights as to how their relationship with their family member has changed. Furthermore, it is clear that there is a sense of uncertainty as to what support is available, with participants noting a lack of support from HCP's regarding cognitive issues. This was reported by participants to be caused by a lack of contact with HCP's and inconsistent resource availability across the UK.

In establishing which of the changes highlighted in the survey (chapter 3) would benefit from specialist referral, the results of this focus group indicated that there is no consistent support currently available for any areas of cognitive deficit highlighted in the survey. Therefore, the benefit of specialist referral should be based on the impact changes have of QoL. All deficits were expressed to have a detrimental impact on QoL. However, the fact that a deficit in numerical calculation was reported to not be as detrimental as other areas, could indicate that this is not as high a priority to patients and their families. In studies of older populations, it was a decline in both simple calculation and complex number processing can be associated with a decline in mental flexibility [256, 257]. Additionally, this has also been seen to be attributed to other challenges with executive functioning, such as processing speed and construction [258]. Therefore, it could be surmised that a deficit in numerical calculation that is a result of cognitive decline would be detected through enquiry into other areas of executive functioning. It would not be necessary to explicitly include numerical calculation in a potential screening tool.

While the results show that each participant had a unique experience of cognitive deficits, looking into how they describe the effects of deficits on quality of life enabled for the grouping of very specific and complex issues into broader terms. For example, when participants report issues regarding word recall or difficulty with losing track of what they wanted to say, they are two separate and complex issues, but they can both be recognised as barriers to effective communication. The use of general statements to flag up cognitive decline is seen in studies of subjective cognitive decline (SCD) [259]. In recent years, SCD has been increasingly recognised as the earliest symptomatic manifestation of Alzheimer's disease [260]. This shows that it is technically possible to detect the presence of specific deficits with more general questions. However, these questions must be representative of the challenges posed to QoL.

In determining the best methods of screening for changes, several barriers to reporting deficits were identified. Firstly, there is a clear lack of information given to patient and their families as to the cognitive symptoms they may face. The lack of information given can make patients feel as though their symptoms do not need to be reported, and can often give rise to feelings of embarrassment. The stigma surrounding cognitive decline and the unsocial behaviors associated with it are acknowledged with regard to dementia care [261]. Stigma associated with cognitive impairment is seen to have a negative impact on relationships, interactions with HCP's and attitudes towards service utilisation [262]. Therefore, patients may not

wish to declare symptoms, especially if they feel that their experiences are isolated. A person's cognitive capabilities are what guide the way they acquire, retain and use information [263] and is therefore immensely personal. This, along with the social stigmas associated with decreased cognition are often a source of distress for patients [264]. Therefore, it should not be the responsibility of the patient to report deficits unprompted. Additionally, if patients are not informed of the cognitive symptoms they may experience, it may lead to them either assuming deficits are caused by other factors, leading to further confusion, or may cause patients to feel as though they must accept and deal with these symptoms without the possibility of support.

As highlighted by the survey results, there is a clear benefit to acknowledging the insights of those closest to the patient. The value of family member input for the assessment of cognitive impairment is demonstrated in patients with mild cognitive impairment (MCI) where it is seen to give insight into the changes family member experience to their daily realities [265]. However, as previously stated, the personal nature of cognitive decline can make patients reluctant to report deficits. It was also a point of discussion in the meeting that family members will often hold back from reporting any issues that their loved one chooses to withhold. This is done to prevent both them and the patient from feeling uncomfortable, however, it was also determined that if asked independently from the patient, they would answer honestly in the hope of getting support. This supports the case for the requirement of a two-part screening tool in order to give both patients and family members the opportunity to independently disclose any difficulties.

There were several key limitations in this study. The most prominent being the lack of HCP representation. One of the aims of this focus group was to get an expert opinion on how cognitive decline could be best screened. Therefore, further input from HCP, who will no doubt be involved in the screening process, would have been a valuable contribution. This is particularly relevant to discussion points raised regarding the lack of information given by HCP's. It was seen in the survey results that HCP acknowledged the presence of cognitive deficits in HGG patients, therefore the question must be asked as to why this is not further discussed with patients.

The lack of HCP representation was caused by a combination of reasons. Firstly ethical approval was met through the Cardiff University School of Medicine Ethics Committee. Whilst this enabled for recruitment to take place over public platforms, this does not grant access to NHS recruitment routes. The decision to not seek NHS

ethics approval was concluded on the basis of time restraints. Each stage of this thesis was designed pragmatically and was directly influenced by the results of previous stages. Therefore, the focus of this meeting could not be determined prior to the analysis of the survey data. As the NHS ethical approval process is a lengthier process, and the fact that the survey was open until December 2020, it would have been difficult to ensure that there would be sufficient time to carry out any subsequent stages of the project.

In addition to this, the meeting took place on a weekday and was scheduled to last over two hours. Even in the event that NHS ethical approval was granted, the challenge of finding a time that would be convenient for multiple HCP's would prove to be difficult. However, it is important to note that whilst the presence of HCP's would have potentially clarified some questions that arose, the data obtained from this focus group allows us to see how cognitive deficits in this patient population effect the day-to-day lives of patients and those around them. The reported expressions and opinions reported are therefore not influenced by professional opinion.

Another key limitation of this study is the challenges faced when conducting an online focus group. Over the last year and a half, online meetings have become a necessity for many. This rise in use has accentuated both the benefits and limitations of remote meetings [266]. It was clear throughout the meeting that communication was not as streamlined as it would have been had the meeting been conducted in person. There were many instances where it was difficult to determine when to join in with group discussions. This led to occurrences where participants unintentionally would speak over one another. There were also challenges caused by connectivity issues. By the end of this meeting four participants had dropped out with two participants later reporting that this was due to connectivity problems.

These difficulties are further exacerbated by any cognitive impairments patient-participants may be facing. Over the course of the COVID-19 pandemic, a study conducted by Bennet et al (2021)[267] examined the 'videoconference fatigue phenomenon' which they defined as the degree to which people feel exhausted, tired, or worn out attributed to engaging in a videoconference. This study found that videoconferences that lasted 'for extended periods' are likely to cause this. As established in the survey, patients often experience fatigue. Whilst it is unclear how this impacts patient cognition, the addition of this made it a particular challenge to engage this patient population for duration of the meeting. In addition to this, the use of an online focus group leads to a participant bias in favour of patients who have

better functioning. Therefore, although the family members who attended all had experience of caring for a patient with advanced illness, their first hand experiences were not able to be explored. Although these factors need to be taken into account when considering the outcomes of this study, it is also important to acknowledge, that the use of an online platform meant that participants who would have otherwise been unable or unwilling to travel to attend.

Although this meeting was designed to ensure all participants had the opportunity to contribute, there were still instances in which individual participants dominated the conversation. While this is a common occurrence within focus groups [268], this may have been exacerbated by the loss of inhibition due to HGG and subsequent treatments. This was explicitly mentioned by one participant, who had a significant amount of damage to their frontal lobe as a result of the resection of their tumour. This loss of inhibition, whilst understudied, has also previously been proposed to arise in patients with orbitofrontal damage [269]. In addition to this, as discussed throughout this chapter, patient with HGG may experience difficulty with communication. Therefore, this may have influenced some participants willingness to contribute to conversation. This was especially challenging given the personal and sensitive nature of the topics raised. The challenge in managing this was in drawing the conversation back to the group without dismissing the points raised by the individual. This was a particular challenge considering my lack of experience in conducting focus groups prior to this. However, the use of the voting system and support from the facilitators (both throughout the meeting and being able to do a practice run before hand) meant that it was easier to ensure all points were discussed and no points of view were lost if the discussion varied from the intended focus.

In addition to these limitations, it is important to acknowledge the quantitative data presented in this study must be interpreted with caution. The small number of participants makes it difficult to generalise the findings presented to the wider population. This challenge is further heightened by the way in which the quantitative questions were presented. It was expressed that those who did not respond to the Mentimeter questions did not due as they did not feel that any of the responses were applicable to them. However, it is unclear as to whether or not participants were confident in their answers. With this considered, it would have been useful to include a 'Don't Know' option to questions. This may have opened up conversation into areas beyond that of the cognitive domains presented or served to highlight other gaps in current care. However, as stated previously, these quantitative elements were incorporated primarily to help guide conversation and were based upon the results of

the survey, which was representative of a much larger sample of the population. Furthermore, most of the conclusions presented in this chapter, are drawn from the rich qualitative data of this select group and are brought forward in subsequent chapters as such.

4.4.1 Conclusion

This focus group worked to further explore the findings of the systematic review and survey by exploring the perceived experiences of a group of stakeholders. It was discussed that all cognitive deficits identified in the systematic review and survey, could have a detrimental effect of patient QoL. However, it was raised that deficits that may be easily compensated for, may be less troublesome if experienced in isolation. It was also reported that participants experienced a lack of support offered, which often left them feeling unsure as to the cognitive symptoms they may face and furthermore, unaware of any available support. . This lack of support and understanding was one of the main reasons that participants have not report any difficulties faced. As well as this, family members reported feeling as though they were unable to report deficits if the patient did not do so first, however, it was also reported that if directly asked about cognitive symptoms, they would answer honestly in the hopes of getting access to support.

Chapter 5: Screening tool question development and Face Validation using cognitive interviews.

5.1 Introduction

This chapter describes how the results of the survey (chapter 3) and focus group (chapter 4) have been utilised to formulate a draft question set. This chapter will present the face validation of two sets of questions to be used as a screening tool to highlight if patients may be experiencing cognitive deficits that are detrimental to their QoL. In the previous chapters, the areas of cognition reported to be affected in patients with HGG after the completion of radiotherapy are described, including how these are experienced by patients and observed by those around them.

It was seen that all areas of cognition including memory, executive functioning, language and motor dexterity can all be affected in this population. Further, long term memory and working memory were often identified as separate processes. Executive functioning was described in terms of challenges with managing attention, and processing information in a way that could lead to a meaningful conclusion or decision. Language was reported by patients and family members of patients in terms of their effect on the communication skills of the patient. A decline in motor dexterity was also reported to affect patient communication skills through its consequences to written and typed communication.

This understanding of patient and family perspectives has been used to guide the drafting of prospective screening tool questions. It is therefore necessary to determine how the drafted questions are subjectively viewed and interpreted by potential tool users. In order to do this, these questions have been tested for face validation.

There are multiple levels involved in the process of validating a screening tool. The four main types of validity are construct, content, face and criterion-related validity. Content validation works to assess how well a prospective tool measures the intended outcomes [270]. In order to produce valid results, the measurement must cover all relevant aspects of the construct. Construct validity is described by Messick (1989) as “an integration of any evidence that bears on the interpretation or meaning of test scores” [271]. This is often done by comparing a test to other tests that are designed to measure similar qualities [272]. Criterion-related validity is the evaluation of how much a test or measurement relates to or predicts the results of a single measure that is supposed to be a direct measure of elements being tested [273].

However, in order to be able to assess any of these, it must first be established that the questions are correctly understood. Especially when considering a patient and family focused set of questions, it is important to acknowledge that the opinion of service users may vary from those of professionals. The concept of face validation is centered around the evaluation of test items to assess how they are understood and interpreted by respondents [274].

The value of face validation can be recognised in both terms of practicality and an ethical stance. Practically, face validation offers assurance that respondents are being asked questions in a way that prompts respondents to consider the deficits that they are designed to highlight. This means that any questions that then undergo content validity are being assessed with regard to the correct outcomes. From an ethical point of view, the use of face validation keeps the core principle of patient experience at the forefront of this project. The aim of this PhD is to work towards developing a screening tool for patients that is focused on the experiences of patients. Ensuring that patients and their families are satisfied and comfortable with completing the questions is therefore a priority.

In order to face-test the drafted questions, a method of cognitive interviewing was utilised. Cognitive interviewing is a process that aims to understand how respondents interpret and understand the questions, and how they think through the answers they give. The use of cognitive interviewing as a method of pretesting questions is used by a wide variety of researchers [275-278]. It is a process that asks respondents to explain further their understanding of questions and how they arrived at their answers [279]. Cognitive interviewing is a methodology originally developed to aid in understanding the thought processes of participants when they complete survey questions specifically. This is utilised to detect any sources of response error [280]. Whilst it is possible to use the cognitive interviewing format as a form of structured interview, the use of it presented in this chapter more mirrors that of their original purpose. Although it has not been used for survey questions, its use has been to determine item comprehension, information recall and judgement of screening tool items to detect sources of response error.

Cognitive interviewing can be conducted following several different techniques. These various techniques may be used in isolation or in combination in order to best fit the aims of the study. These methods include observation, think aloud, scripted probes, and unscripted probes [281]. Observation is a method that helps to frame spontaneous (unscripted) probes. It involves the interviewer giving the respondent

time to answer the questions without interrupting, taking note on how they answer the questions and formulating probes based on these observations. The 'think aloud' method encourages respondents to verbalise their thought processes when answering questions. This allows for further insight into respondent interpretation in real time, rather than a retrospective interpretation.

The use of probes, allows interviewers to easily direct the interview to meet the study aims. Scripted probes allow the interview to be conducted with a specific guide. These probes are designed prior to the interview. Unscripted probes are used to further explore points that are raised throughout the interview. This can be through observation or to prompt the respondent to expand of point of interest.

For the purposes of establishing face validation of the drafted questions, the cognitive interview technique will utilise a combination of all four techniques. Due to the nature of the topic area, it is expected that patients who are participating may have some existing cognitive difficulties. The combined use of observation, unscripted probes and talk aloud techniques, will help to capture the first impression of the respondent without relying on them having to remember their thought processes. In addition, scripted probes will help to keep the interview on track. Carrying out a structured interview will not only help in ensuring the aims of the study are met, but also help to keep the interview concise. It is commonly known that HGG patients often experience fatigue [282]. Therefore, preventing the interview from becoming too long may serve to limit participant fatigue.

5.1.1 Aims

The aim of this chapter is to present the face validation of a drafted screening tool with potential tool users (patients with HGG and family members of patients)

There are three key objectives to this study:

1. To construct a set of simple questions for use as a screening tool for the cognitive deficits experienced by patients with HGG after receiving radiotherapy
2. To establish if the screening tool is understandable with regards to wording, sentence structure and content
3. To determine whether the proposed questions are relevant and suitable to participants

5.2 Methods

5.2.1 Screening Tool Design

The questions presented in the screening tool were designed using the results of both the survey (chapter 3) and the subsequent focus group (chapter 4). Whilst these two steps of the projects determined that all areas of cognition highlighted by the systematic review (chapter 1) were of importance to the quality of life of patients with HGG, these steps proved to be valuable in understanding the way in which patients and their families described deficits. This in turn allowed for the included questions to be designed using the same phrasing.

The key findings from previous chapters are summarised in the following points, to be used as a guide in drafting the questions:

- Views of family members may offer a unique perspective, which may highlight difficulty that patients may not report themselves. It is therefore recommended that, where applicable, family members be offered the opportunity to report cognitive changes observed in their family members.
- Motor dysfunction overall, is usually addressed by a patient's health care team if gross motor dysfunction is identified. However, fine motor functioning which may affect handwriting and typing may not be reported. This is predominantly identified as problematic in terms of a patient's ability to communicate. Therefore, such deficits would be identified as a communicative issue.
- Speech and language difficulty are not always thought of as a result of cognitive deficit. However, issues with this were seen to be the most distressing as it impairs patients' ability to communicate confidently and effectively.
- Whilst memory deficits may be different among patients (some have issues with forming new memories and others are unable to recall events prior to their diagnosis) the way in which patients and family describe issues is fairly similar. Patients and their family members used the word 'memory' to refer to both the process of recalling details correctly and remembering entire events, however, there was a distinction made between this and the ability to form new memories. It is therefore important to make this distinction in any questions asked.

- Issues with executive functioning were common but not well understood. Most problems were described as a lack of focus, being unable to concentrate, being disorientated, or becoming frustrated or overwhelmed when interrupted or when making decisions.
- Family members often observed changes in the patient's personality. Becoming less motivated, more selfish, and lacking empathy were all reported. This indicates that family members may not fully understand the cognitive deficits the patient is facing, but the impact of these may affect their relationship with the patient.
- Both patients and family members often attributed changes to different factors, so in order to capture the broader experience, it is important to not use language in questions that attribute symptoms to a specific cause.

In order to ensure the questions asked are representative and considerate of the experience of the individual answering, it was decided that having separate patient-facing and family-facing questions would be required. This was decided for two key reasons. Firstly, it would aid in the identification changes in patients' personality observed by family members. As changes were not reported by patients themselves, it would not be of benefit to include this in a patient-targeted tool. Secondly, designing the questions to be applicable to both patients and family members may lead to some ambiguity as to who the questions were designed for. This was an issue highlighted in the focus group, where one participant struggled with processing questions that addressed both groups of participants.

As with the questions presented in the survey, once these questions had been drafted, Dr Alicia Eccles, a neuropsychologist who specialises in brain tumour patients, was consulted. The questions were presented alongside the summary of findings presented above. This was done to get feedback from Dr Eccles to ensure that the drafted questions were inclusive of all the required elements. This was done to once again ensure that the questions were representative of the cognitive processes of interest.

5.2.2 Recruiting Participants

Participants were recruited either via social media (Twitter), the *brainstrust* Charity contacts (including an email list, Facebook group and Twitter account), the Brain Tumour Charity 'BRIAN' forum contact list, or by invitation to focus group attendees. Figure 18 shows the recruitment poster used on social media platforms. We aimed to recruit 10 to 15 participants in total for each phase of cognitive interviewing. This

sample size has been established following the recommendations of Willis [283]. As the purpose of conducting cognitive interviews is not to reach statistical estimation, variety amongst participants was prioritised above quantity. Therefore, every effort was made to recruit roughly equal numbers of patients and family members.

The advertisement features a blue background with yellow flowers and a central graphic of a brain with a lightbulb. The text is arranged in several sections:

- Participants needed** (written in red, slanted text)
- Evaluation of a screening tool developed for the cognitive changes experienced by patients with high-grade glioma after receiving radiotherapy.**
- We are developing a short set of questions, designed to detect any problematic changes to patient cognition after the completion of radiotherapy as treatment for high-grade glioma. This is being done with the goal of helping patients get access to the support and care required for their specific needs.**
- We are inviting UK based Patients aged over 18 diagnosed with high-grade glioma who have undergone radiotherapy AND Family members of a patients aged over 18 diagnosed with high-grade glioma who has undergone radiotherapy to help test a potential screening tool**
- For more information on how to get involved, please get in touch!**
Email: mazzaschifi@cardiff.ac.uk
Twitter: FMazzaschi
- Canolfan Ymchwil Gofal Lliniarol Marie Curie Palliative Care Research Centre**
CARDIFF CAERDYDD
- CARDIFF UNIVERSITY**
PŵL YSGOL CAERDYDD

Figure 13: Recruitment advertisement used on social media platforms

5.2.3 Inclusion Criteria

Patient Criteria:

- Have had radiotherapy as part of treatment for HGG (grade 3 or 4)
- Be over the age of 18
- Be able and willing to give informed consent to participate in the study
- Be able to understand and communicate to the extent needed to participate in the interview

Family member Criteria

- Be a family member who lives with/has daily contact with a patient who has received radiotherapy as part of treatment for HGG (grade 3 or 4)
- Be over the age of 18
- Be able and willing to give informed consent to participate in the study;

- Be able to understand and communicate to the extent needed to participate in the interview.

Patients were eligible for participation, regardless of if they felt as though they had been experiencing cognitive decline. Having cognitive impairment as an inclusion criteria could lead to the exclusion of patients who are experiencing difficulties, but are unaware that their challenges are caused by cognitive impairment.

5.2.4 Exclusion Criteria

If any of the following apply, participants will not be eligible to take part in the study:

- Are bereaved family members
- Are patients/ family members of patients with other underlying neuropsychological issues.
- Don't have access to an internet enabled device with a camera
- Are under the age of 18 or family members of a patient under the age of 18.
- Patient is still undergoing radiotherapy or chemoradiotherapy

Whilst it was not possible in the scope of this study to access the information required to verify whether patients had any other underlying neuropsychological issues, or proof that they were not still undergoing radiotherapy or chemoradiotherapy, participants were asked to self-select with consideration to this.

5.2.5 Approaching participants

Participants were invited through the aforementioned recruitment strategies. Potential participants were given contact details of FM. Once participants expressed interest, a date and time that suited them best to conduct the cognitive interview was organised over email.

5.2.6 Informed Consent and Ethical Issues

Online data

Interviews were conducted online and were recorded. Any personal data obtained was kept confidential in line with the Data Protection Act (2018). No identifiable information is included in the data that is reported. Individual details such as diagnosis, treatment, and occupation details will not be included in the report, and data was stored in a secure folder on the Cardiff University Network, only available to the research team.

Consent

Once participants put forward an expression of interest, and an interview date and time have been agreed, a participant information sheet (supplementary appendix F) was sent to them at least 24 hours prior to the interview. This was sent alongside a consent form (supplementary appendix G) asking for their consent to record the meeting and analyse their responses. Participants were required to complete and return this before joining the meeting. Participants were reminded of the recording of the meeting and the use of their responses and were given the opportunity to withdraw should they wish to do so. Although the interviews were all to be conducted in English, Welsh translation of any documents was available upon request, in line with Cardiff University regulations. This was not requested.

Ethical approval

This study was conducted according to the principles of good research practice, the General Data Protection Regulation (GDPR)(2016) and the UK Policy Framework for Health and Social Care Research (2017). This study obtained ethical approval from the Cardiff University School of Medicine (SMREC 21/51).

Ethical considerations

Due to the sensitivity of the topic, some participants may have found the subject matter addressed in this study to be distressing. For this reason, it was a priority that participants know that they may withdraw from the meeting at any time. After the event, participants were contacted to thank them for their participation. This email (supplementary appendix G) also contained links to the webpages and contact numbers of Marie Curie, The *braintrust* and Macmillan as agencies that offer information and support.

5.2.7 Patient and Public Involvement (PPI)

Two PPI research partners offered feedback and advice throughout this study. During this stage, they were consulted on the appropriateness of the research methods, wording and presentation of the participant information sheet, consent form, thank you emails and advised on the efficacy of the recruitment avenues.

5.2.8 Cognitive Interviewing

Participants were asked to complete the draft screening tool relevant to them. As developed by Ericsson and Simon (1980) [284] cognitive interviews were conducted as a method of pre-testing this draft tool. This study employed elements from the following interview styles:

- Think Aloud Interviews: Participants were asked to think aloud as they answered the questions. This enabled an understanding of their thought process and which areas they may be unsure of.
- Observation: Participants worked through the questions, any signs of hesitation, confusion or discomfort were noted for discussion.
- Probe Interviews: Participants were asked specific questions by the interviewer to explore specific areas that the participant may have not considered.

A combination of scripted and spontaneous probing was used. Spontaneous probes allowed the interviewer to explore ideas or concerns raised by the participant as well as any non-verbal cues such as signs of discomfort or confusion. It would have been optimal to conduct these interviews face-to-face, however, due to COVID-19 restrictions, video calling was used for this.

Scripted probing followed a master interview schedule with questions and prompts developed specifically for these questions (supplementary appendix c and d). Probes were developed following the categories suggested by Willis [285] including:

- Comprehension (e.g., 'Did the wording make sense?')
- Paraphrasing (e.g., 'Can you tell me in your own words what the phrase 'effectively communicating your thoughts, needs or opinions' means to you?')
- Confidence judgement (e.g., 'How sure are you of your answer?');
- Recall (e.g. 'How easy or difficult was it for you to remember how you felt over the past few weeks?');
- Specific probes (e.g., 'Might it cause upset?');
- General probes (e.g., 'You seem a little uncertain about that question, what were you thinking when you tried to answer it?').

Interviews were conducted using the video conferencing platform Zoom. Participants were asked to try and connect from a quiet area. It was preferred that the participant be interviewed alone, however, participants were able to have a friend or family member present if they wished to do so. Any data from the additional party was not analysed. The interviews were scheduled to last between 30 minutes to an hour. However, if the participant was thought to be fatigued or became unwell the interview would have been terminated earlier.

Interviews were conducted in two phases. The first of which served to assess the question drafted from the previously mentioned guide. The second phase was then conducted to assess the changes made as a result of phase one. Participants that took place in phase one were unable to take part in phase two to ensure those changes made were beneficial to the way in which the question was asked, rather than based off of the preferences of the individual.

5.2.9 Data Analysis

The analysis of the interview data was conducted following a deductive thematic analysis methodology. The screening tool drafts completed by participants were assessed through the analysis of the responses to the scripted probes which covered areas of comprehension, recall, paraphrasing, and confidence, as well as question specific and general probes. For each interview, the responses for each question were coded into these categories.

5.2.10 Data Collection

At the beginning of the interview, participants were asked about their, or their family members, diagnosis to ensure participants fit the inclusion criteria for the study.

Interviews were transcribed by FM as an edited transcription. As a deductive thematic analysis was the chosen method of data analysis, the use of an edited transcription was more practical as it enabled the omission of any irrelevant sections of audio whilst still maintaining the meaning of the text. For example, one participant was distracted by an incoming email which led to approximately 5 minutes of audio that held no relevance to the research topic.

5.3 Results

5.3.1 Tool design

Following the guidelines developed from the results of the survey and focus group. Questions were drafted as 'yes or no' questions that covered areas of memory, executive functioning and communication using terminology highlighted in the survey and focus group. The following questions were developed for patients (figure 19) and family members (figure 20). These questions were presented to a neuropsychologist, who confirmed that they covered the intended cognitive processes. Therefore, no changes were made as a result of that consultation.

Please read through the following questions and answer 'yes' or 'no':

- 1. Have you been experiencing any recent difficulty with effectively communicating?**
- 2. Have you had any concerning changes to your memory or ability to take in new information?**
- 3. Have you had any increased difficulty with concentrating or maintaining focus?**
- 4. Do you feel frustrated or overwhelmed when making simple decisions?**

Figure 14: Patient-facing questions developed from survey and focus group findings

Please read through the following questions and answer 'yes' or 'no':

- 1. Have you found any recent difficulty in understanding their thoughts, needs or opinions?**
- 2. Have they shown any concerning signs of memory loss or difficulty taking in new information?**
- 3. Has the patient shown any recent signs of difficulty with concentrating, maintaining focus or decision making?**
- 4. Have you noticed any recent changes in the patients personality that affect your relationship with the patient or the patients quality of life?**

Figure 15: Family-facing questions developed from survey and focus group findings

5.3.2 Phase one

Participants

All participants that took part in phase one of the interviews were recruited through the *brainstrusts* Facebook group and email lists. Nine participants contacted the *brainstrusts* with an expression of interest and where then put in direct contact with FM. Of these nine, eight went on to take part in the interview.

Participants included; six patients and two family members. Patients and family members confirmed a diagnosis of grade 4 (n=7) or grade 3 (n=1) glioma. Median time since diagnosis was thirteen and a half months with times ranging from seven months to sixteen years.

Patient facing questions

Question 1: Have you been experiencing any recent difficulty with effectively communicating?

Comprehension

The majority of participants understood the question to be asking about how well others are able to understand the points or ideas they are trying to express. One participant described this in terms of verbal communication:

“To me it would mean that the person you’re speaking to would understand what you’re saying” -P05

This was mirrored by another participant who specified that they understood that the question can represent both verbal and written forms of communication.

“So I guess it’s being able to construct in somebody else’s mind the same thing I have in my own through speech or text. So avoiding ambiguities to ensure that what I want to communicate has been done.” -P02

However, the term ‘effectively communicating’ did not always prompt participants to consider how they expressed themselves. One participant understood the question to be asking if the general point of what they want to say is understood, and therefore answered no despite having difficulty with word recall.

“I feel I can get over what I want to say. Occasionally I will struggle to think of a word and I do panic”-P08

One participant interpreted the question as asking them to evaluate how their communicative priorities have changed and the emotional support they receive from those around them. They understood the term ‘effectively communicating’ to be communication that enhances their lives. They explained how they felt they were doing everything alone and have therefore had to prioritise who they chose to communicate with in order to maintain a positive outlook.

“When you, the question is about communicating and I am almost feeling like I’m communicating on my own.” -P01

“I can control my life by identifying relevant people and learning how to not communicate to non-relevant people.” -P01

Paraphrasing

Paraphrasing proved to be the most challenging element of the interviews for participants to complete. Several participants offered no paraphrasing, explaining that they could not think of a way to improve on the wording.

“Ah ok. It looks pretty good to me.” -P02

“I can’t think of anything that needs to go in there.” -P08

One participant explicitly stated that they were unable to think of any other words that could be used. They explained that this was an issue that has developed as a result of their tumour.

“I’m sorry I don’t know the answer. This is where the brain stops working. Before my problems I wouldn’t have had any problem at all.” -P03

One participant paraphrased the question with an emphasis on simplistic conversing.

“Can you have a conversation with someone?” -P04

Whilst other participants did not offer a full question in their own wording, one did state how they would change the wording to better explain effective communicating.

“I think I would word it as making yourself understood.” -P05

Recall

All participants compared their situations now to how they were prior to their diagnosis and treatment, meaning that their answers were based upon this comparison.

“I think life before the diagnosis. My life fell off a cliff after that. So since my treatment, it all went into one.” -P03

“Just before my diagnosis comparing to afterwards and now” -P05

Confidence

Whilst most participants stated that they were confident in their answers, several had some uncertainty. One participant mentioned that whilst they did not feel that there was any difficulty, they could not guarantee that they were communicating effectively.

“I don’t really know the answer to that. I probably can’t, but to me I can.” -P03

In addition to this, there was some ambiguity reported around the use of the term 'recent'. Whilst this was not picked up on the initial answering, this term led participants to second guess their answers.

"When you say recent do you mean after radiotherapy? Do you mean straight after?" -P04

"I suppose 'recent'. Is that this week, this month this year? For me it's this decade. I continue to have the problem."-P02

However, one participant stated that use of the word 'recent' was important for determining a time frame, and that its inclusion made them more confident in their answer.

"I think having the recent in there is a good idea though because my answer would have been different before"-P08

Participants also explained how they believed most patients would feel comfortable in answering this question honestly, if it meant that there would gain access to the help and support they need. However, it was mentioned by several participants that patients may be wary of this information being passed on to employers.

"Yeah, it's a question of trust to some extent. So if you're wanting to get back to employment then you might well be guarded in what you say and not understand the limits of communication of who you speak to."-P04

"I'm putting myself in the place of the person who's thinking about who it will reach. I think you could change your answer to different audiences. If you were being asked by your boss at work you might give a different answer. So if there would be some words at the start of this to detail privacy because that would be good." -P02

Specific Probes

Specific probes explored if and how the term 'effectively' helped participants to answer the question. In general participants expressed that it was helpful in specifying that they were being asked about how much they are able to make themselves understood.

"Yeah, I guess, you can communicate with no problem, but if no one understands you there's no point really."-P05

However, one participant did mention that the inclusion of this word could make others second guess themselves.

"Well, I suppose it depends on how effectively. If it's only a small difficulty you probably won't say yes to it."-P02

General Probes

Most participants were able to answer question one fairly easy, however, one participant who answered 'no' went on describe the challenges faced when communicating with their spouse.

“But on the other side communicating with wife was and is that’s probably the hardest level of communication.” -P01

Question 2: Have you had any concerning changes to your memory or ability to take in new information?

Comprehension:

Most participants understood the question to be asking them about any changes to their memory or how they are able to process information. One participant stated that they felt the question was 'self-explanatory'.

“Remembering small things or long-term memory. Self-explanatory, being able to keep in information.”-P04

Another participant explained how they understood the term 'concerning changes' to be changes that would cause them to worry.

“It means just that any changes that worry you.” -P05

However, the term 'concerning' was a challenge for one participant on the first read through. This led to confusion as to the definition of the word.

“Ah ok, right I think there’s some slight ambiguity in the word concerning. Because concerning could mean related to or concerning the meaning of worried about. Um I think this probably means worried about. But it could be a lesser word in a sense.”-P02

Paraphrasing:

As with question one, paraphrasing this question was challenging to most participants. Participants generally expressed that they were happy with the wording of the question. However, one participant did mention that the word 'concerning'

should be removed from the questions. It was stated that its use may cause patients to dismiss more mild symptoms.

“Maybe don’t say concerning changes. Because then I would have answered yes. I do have a problem but I don’t always think about them. I do think that word needs to come out because people might dismiss it.”-P08

Recall:

Participants were mostly able to recall times in which they felt their memory had been affected from recalling times when those around them had brought their attention to it. One participant explained how they often repeated conversations or elements of conversations with those around them.

“There are times, with my sister. We’ll have a conversation then the next day I’ll ask her a question that she answered.”-P08

Confidence

The only element that was seen to cause patients to lack confidence in their answers was the use of the word ‘concerning’. This hesitance was particularly obvious in one participant who explained how they had noticed changes in their memory, but they felt that the problem was not frequent enough to be considered a concern.

“I’d say yes but I’m not sure how concerned I am of that... It’s not constantly but its odd times. So for concerning changes I’d say no. People may say no if they don’t think it’s particularly bad.”-P08

As with question one, participants felt that patients would generally feel comfortable with answering this question.

“With me it doesn’t matter, but I don’t think anyone would mind. But I don’t know.”-P03

The only thing that was identified as a potential reason for not wanting to answer honestly was personal pride.

“Um yeah, personal pride to some extent. I’m very open but I’m not sure... I can only answer personally and I wouldn’t take offence.”-P02

Specific probes:

As this question asks participants to consider if they have changes in their memory 'or' ability to take in information, specific probes for this question aimed to ensure that participants answered yes even if they felt they only had changes with one element. All participants were able to consider both parts of the question and answer accordingly.

“FM: If you had changes to your memory, but no changes in your ability to take in new information, how would you answer this question?”

P02: I think I could answer yes.” -P02

General Probes:

The uncertainty mentioned with regard to the use of the word 'concerning' served to highlight the use of compensatory mechanisms. One participant explained how they have had substantial changes to their memory, but as they have developed ways to counteract this, they do not feel concerned.

“Yes I’ve had massive changes to my memory purely based on the illness but I record everything... I am now on book number 14 and I have my children have camcorders each so I do that. One of those each.” -P01

Question 3: Have you had any increased difficulty with concentrating or maintaining focus?

Comprehension:

All participants understood the question as intended. Many understood the terms 'concentrating' and 'maintaining focus' to be focused around engaging and staying on task. One participant defined it in terms of lacking distraction.

“Being able to stay with one thing and not being distracted by anything.” -P04

Most of the participants struggled to distinguish between concentrating and maintaining focus.

“Yeah, I think the two terms are similar. Like concentrating is sort of the same as focus.” -P05

However, one participant felt as though they were able to maintain focus, but not concentrate deeply.

“I can maintain focus but concentrating, I’m making a clear distinction. The first time I realised my powers of concentration and capability for making inference was limited, was when I gave some roles to people for an event then someone else gave conflicting roles to those people and I sat and tried to resolve this, so simple a task really, and bringing those two sources of information together, I spent about an hour thinking about it.” -P02

Paraphrasing:

Once again, paraphrasing this question was a challenge for most participants. However, participants did highlight some differences that they believe would help others to answer more easily. One participant drew attention to the inclusion of the word ‘increased’. They explained how others may interpret this as an assumption of preexisting difficulty, which could lead to confusion.

“I mean you’re saying any increased difficulty which is assuming there is already difficulty there so maybe take out increased.” -P04

Another participant commented that switching ‘or’ to ‘and’ would improve the readability of the question.

“Maybe the ‘or’ to ‘and’ because then if it would mean something different to me. It might flow better.” -P05

Recall:

Participants generally found it easy to recall times when they had experienced difficulty. This was often due to becoming self-conscious when not concentrating or maintaining focus in public, or when having a conversation.

“It’s one of those things that I am aware of. A bit self-aware that I might go off on a tangent. Sometimes I’ll go completely off subject.” -P08

Confidence:

All participants were able to answer the question easily upon the first read through. However, one participant changed their initial answer when asked further questions. This participant had initially answered no to this as they felt defensive and inclined to say things were fine when they were not.

“Um, it was purely based on defence and I needed to start to defend myself.”-P01

“The bottom line is I’m normal and I’m having to defend myself. My wife thinks I’m not normal. I will tell anyone anything and I’m less than a millimeter away from being front paper of a newspaper.”-P01

Specific probes:

As this question was designed to highlight issues with executive functioning, it was important to understand which tasks participants thought would be affected by a change to their ability to concentrate or maintain focus. Participants listed no specific daily tasks, indicating the understanding that these effect their overall ability to process understand things around them.

“I suppose working, computer work, reading maybe? I mean yeah its difficult. Um watching a program, having a serious conversation.” -P04

General Probes:

To further understand how the question can be adapted to avoid a defensive response, participant 01 was asked if there was any way the question could be reworded to seem less accusatory. It was then determined that it was not necessary an issue with the wording but served to highlight the need for further contextual information on the tool. They explained that the rationale for this should be to further reiterate the purpose of the tool.

“In an ideal world you would be presented with information and support from the start.”-P01

Question 4: Do you feel frustrated or overwhelmed when making simple decisions?

Comprehension:

The majority of participants clearly understood the question and understood the term ‘simple decisions’ as everyday decisions.

“Like what to have for dinner? What to do that day? Which way to walk?”-P04

“Well like today, we were trying to decide on if to go for a walk and I find it overwhelming. Or what are you going to have for tea? It’s overwhelming. Its everyday things.”-P05

Whilst this was the case, one participant found the term to be challenging. They explained how the term ‘simple decisions’ could imply that they are easy to make decisions, and that if there is a deficit such decisions would not be simple.

“I think simple decisions I don’t have particular difficulty. But things that others might not call complex, but I would call complex, um, and simply because it may require bringing two sources of information together.” -P02

In addition to this, participants tended to focus of the words ‘frustrated’ and ‘overwhelmed’. Often resulting in the latter part of the question not being addressed.

“I feel very frustrated at times.” -P03

“It feels like two questions in one. About the frustration and overwhelmed. Oh I’ve got it straight and I think its fine.” -P05

“I feel frustrated that I am alive.”-P01

Paraphrasing:

It was suggested that replacing the term ‘simple decisions’ with ‘everyday decisions’ would be appropriate as it removes the need to assess the difficulty of decisions, and instead highlights the more mundane, frequently faced decisions.

“Um no I think its fine as long as it’s for simple decisions. Maybe use everyday life.” -P04

It was also stated that moving terms ‘frustrated’ and ‘overwhelmed’ to the end of the question may help readability and ensure that participants understand that the question is focused on decision making.

“I’d put the simple decisions at the beginning. Because it’s at the end of the question I didn’t take it in. I didn’t read it as simple. I think if it’s at the beginning you’d be more likely to pick it up.” -P08

Recall:

Participants were able to recall how this had changed since their diagnosis.

“I just thought out how it is and how it was. You know, before the diagnosis” -P08

Confidence:

Whilst most participants were fairly confident in their answer for this, one participant who initially answered no, changed their answer when taking a further looking into the question. When asked about this, they explained that they did not know why they answered no.

“Did I? Um I look at that question and wonder how I answered no to that. But um you’re dealing with a damaged brain. Like I say, I’m surprised I answered no and I don’t know why I did.”-P02

Specific probes:

Participants were asked to give examples as to how a simple decision could make them feel frustrated or overwhelmed. One participant explained that it is frustrating to struggle with bringing together two sources of information to come to a decision.

“I wanted to buy an electric bike. And I could look at the details of one, then another and I would just, no way could I keep the details of the first in my mind. In fact I was comparing 8 different bikes. I was extremely frustrated and overwhelmed.”-P02

General probes:

To further understand why participant may have focused on ‘frustrated’ and ‘overwhelmed’, these participants were asked to expand on why they are frustrated or overwhelmed. Generally, participants expressed how they were frustrated with their overall situation. However, one participant explained how their frustration comes from the limitations now on their life due to their diagnosis rather than their functioning. They expressed that they are no longer able to make the simple decisions that they used to due to the limitations put on them due to their medication.

“Frustrated that I can’t drive or work, so its simple things and big things. I would be capable of making those discussion but I’m not being allowed to make those choices because I depend on other people because medically I’m not allowed. I’m capable but I know a lot of people aren’t.” -P04

Screening tool completion:

Overall, participants found the completion of the questions to be simple and they were mostly able to engage in the interview. One participant however, found it difficult to understand the purpose of the interview and tool, often times expressing the need for support with other symptoms and challenges to QoL including diet and social needs.

“There should be an adaptable tool, with diet, psychology, supplements, family.”- P01

No participants felt that the questions were intrusive or stated that they would be uncomfortable with answering these questions in a health care setting.

“Yes I would be happy to.”-P04

It was noted that being asked in a health care setting would actually improve how they felt about their care team.

“It would make me feel like they were actually interested.”-P05

Family facing

Question 1: Have you found any recent difficulty in understanding their thoughts, needs or opinions?

Comprehension:

Whilst both participants felt that the question was straightforward to understand, neither of them understood the question to be explicitly asking about the patient's ability to communicate, which therefore meant that issues with speech and language were not necessarily addressed upon the initial read through.

“I think it's a straight forward question and I would be able to respond to that.”- P06

Paraphrasing:

One participant explained that the patients wants should be addressed in the question and suggested adding 'wants' to the list of 'thoughts, needs or opinions'.

“I think it covers most of it. I suppose the only thing I would say is what they want is also important.”-P08

Upon a second read of the question, one participant noted that the question should put more of an emphasis on the way the patient expresses themselves.

“It’s about how he expresses himself. His language can’t express what he feels.”-P06

Recall:

Participants generally had no problem will recalling how this had changed since before diagnosis, however, if there had been improvement, they would often disregard current symptoms was they are not as bad as they have once been.

“I don’t think it’s a yes or no answer. Would I answer yes if it had happened on once in the last month or so? Well no, because it isn’t as bad.”-P06

Confidence:

Participants stated that they were confident, however, due to the interpretation of the question, both participants expressed some hesitation in trying to infer the thoughts of the patient.

“I sometimes have problems working out what’s going on in his head”-P06

Specific probes:

Specific probes for this question focused on assessing the value of listing ‘thoughts, needs or opinions’.

“It’s good because it broadens you out in your thinking. I thinks it’s good to have those there.”-P06

Participants felt that whilst examples are valuable, this this did not always prompt participants to consider how patients express themselves.

“It needs to be about how they’re expressing themselves.” -P08

General probes:

In order to address the issue of disregarding symptoms that had improved but still present, the participant who raised that was asked how the question could be changed to enable them to feel that they could answer yes. It was then suggested that it is difficult to answer as a yes or no question. They further explained how the question should specify that it is asking about minor difficulties.

“Maybe you could add a ‘no matter how minor’”-P08

Question 2: Have they shown any concerning signs of memory loss of difficulty taking in new information

Comprehension:

Participants clearly understood that the question was asking them to consider any changes to the patient’s memory or ability to process information that need addressing. The term ‘ability to take in new information’ was understood as the patient’s ability to easily process new information.

“Am I worried about his memory or does he find it difficult is he’s being told anything? I would know what you meant.” -P06

Paraphrasing:

Neither participant paraphrased the whole question. One participant highlighted that the word concerning could be removed as they believed any change should be reported.

“Do you need the word concerning? Should it not be any loss?”-P06

Recall:

As with question one, participants were able to recall how the patients functioning had changed since diagnosis. Improvement or stasis of changes were also disregarded,

with one participant explaining how the concern associated with changes decreases over time.

“Um I think it’s that concerning signs again they become less concerning as time goes on.”-P08

Confidence:

One participant expressed uncertainty with their answer, as whilst they had observed changes in the patient, they did not necessarily deem these to be concerning.

“When it all first happened I found it really concerning but as time goes on its less concerning.”-P08

It was also noted that as this can be a fairly distressing symptom, others would be enthusiastic to have the opportunity to highlight such deficit.

“99% will want the help and will be transparent. They’d be happy to, you’ll have difficulty stopping them talking.”-P08

Specific probes:

Participants were asked to give some examples of times they have noticed this to be a challenge for the patient. One said that this deficit in memory and taking in new information has completely removed the patient ability to work.

“His ability to work is off a cliff”-P06

Another stated that they find themselves having to repeat themselves more often.

“I have to answer the same questions a lot.”-P08

General probes:

As participants had mentioned that this had changed in the patient over time, participants were asked to how this had changed. Both expressed an improvement.

“If it was initially it would have been different. It was much more severe.”-P06

Question 3: Has the patient shown any recent signs of difficulty with concentrating, maintaining focus or decision making?

Comprehension:

Participants felt as though this question was straightforward and understood the question as intended. One participant understood it to be asking about how easily the patient gets distracted and understood that a difficulty in decision making can be observed as a reluctance to make decisions.

“She gets distracted and her whole focus goes and she won’t even make decisions on what she wants for dinner.”-P08

Paraphrasing:

Neither participant fully paraphrased the question, but it was suggestions that the term ‘recent’ be removed could remove ambiguity from the question.

“Um again I think the word recent um is something that could make people say no. Without recent it still makes it current but its more easy.”-P08

Recall:

Participants were able to easily remember how this has affected the patient since diagnosis.

“Yes, it’s easy to see the changes”-P06

Confidence:

Both participants were confident in their answer and neither changed their initial answers. It was also mentioned that there was no known reason as to why others would be reluctant to answer this, providing that they knew that the patient would be offered support.

“I suppose you never know but if people know it’s to get help, they’ll be very keen.”-P06

Specific Probes:

Specific probes looked at identifying the type of decisions participants thought of when reading the term 'simple decisions'. It was clear that participants understood this to mean normally easy to make every day decisions.

"Well I suppose what to eat? Do you want to wear this or that? Do you want to go here or there?"-P06

General probes:

One participant mentioned that concentrating and maintaining focus are very different to decision making.

"That's a broad question. They're quite different, those two elements"-P06

When asked if this made it difficult to answer, they explained that they would still answer yes even if the patient only had difficulty with one element, however, they felt as though it was two questions in one.

"Yes, I can distinguish it. But I would say that it could divide into two questions"-P06

Question 4: Have you noticed any recent changes in the patient's personality that affect your relationship with the patient or the patient's quality of life?

Comprehension

Patients were able to clearly understand the question as asking if the patient's personality had changed to the point where it was affecting their lives.

"I think it's clear. It's all about if they've changed as a person and if its affected our lives."-P08

Paraphrasing:

One participant said that they would not know how to rephrase the question.

"It was fine, no changes"-P08

Whilst the other stated that it feels like it is too much for a yes or no answer, suggesting that it be separated into two separate questions so that patient quality of life can be addressed as a separate issue.

“My relationship with [NAME] and his quality of life are two separate things really. They’re two big things. You could ask the patient but I don’t think they will always see it. I think it would work better as two separate questions. It’s a bit too much for a yes or no answer. It would be a bit clearer”-P06

Recall:

Participants were able to easily recall if and how the patient’s personality had changed since the completion of treatment.

“Yeah, again looking at now and before the diagnosis”-P08

Confidence:

Participants were confident in their answers for this question, however, both did highlight that this question may cause discomfort for others due to the sensitive nature of the question.

“It might be a bit sensitive for others to answer, but I’m confident.”-P08

It was also suggested that it people may be reluctant to answer honestly if the patient were to be present. It was also explained that the yes or no nature of the question is beneficial as it means that you do not need to go into detail at the time of answering.

“I think in front of my sister, she might get offended though. I think it would need to be separate.”-P08

“It might not bother people because you can just put yes and not go into it there and then.”-P06

Specific probes:

Participants were asked to give some examples as to how a change in a patient’s personality could affect their relationship. It was determined that if a patient is withdrawn, this can put a strain of communication in the relationship.

“Well if they go more into themselves, you might find it hard to keep good communication.”-P06

General probes:

As a potential for discomfort could result in other not answering honestly, participants were asked how the question could be changed to make it less challenging. Both participants expressed how it was not an issue with the wording of the question, but instead it highlights the need for people to have the opportunity to answer these questions separately from the patient.

“I think it might be difficult to ask if the patient is in the room. That would be quite difficult and could affect the answer.”-P06

Screening tool completion:

Participants found the tool easy to understand and complete. It was suggested that the tool may benefit from a short paragraph detailing the purpose of the tool and how the support that would be available should they answer yes to the questions.

“I think a paragraph beforehand explaining the purpose would be good but other than that it’s fine.”-P06

Overall there was no discomfort expressed in answering the questions, other than the points raised in question 4. Both participants would be comfortable to answer these questions in a healthcare setting.

“Yeah I’d be happy to” -P06

Screening tool edits:

The feedback obtained from phase one of cognitive interviews was used to edit the screening tool questions. Questions one, two and three of the patient-facing tool (table 12) and questions one, two and four of the family-facing tool (table 13) were changed as a result of the first phase.

Question presented	Question after editing from feedback
Have you been experiencing any recent difficulty with effectively communicating?	Do you have any difficulty with making yourself understood?
Have you had any concerning changes to your memory or ability to take in new information?	Do you have any changes to your memory or ability to take in new information?

Have you had any increased difficulty with concentrating or maintain focus?	Do you have any difficulty with concentrating or maintaining focus?
Do you feel frustrated or overwhelmed when making simple decisions?	Do you find it hard to make everyday decisions?

Table 13: Patient-facing questions before and after editing

Question presented	Question after editing from feedback
Have you found any recent difficulty in understanding their thoughts, needs or opinions?	Do they show any signs of difficulty in expressing their thoughts, needs, wants or opinions?
Have they shown any concerning signs of memory loss or difficulty taking in new information?	Do they show any signs of memory loss or difficulty taking in new information?
Has the patient shown any recent signs of difficulty with concentrating, maintaining focus or decision making?	Do they show any signs of difficulty with concentrating, maintaining focus or decision making?
Have you noticed any recent changes in the patients personality that affect your relationship with the patient or the patients quality of life?	Have you noticed any changes to their personality that affect your relationship with them?

Table 14: Family-facing questions before and after editing

5.3.3 Phase two

Participants

All participants were recruited through the Brain Tumour Charity BRIAN forum or through email lists. Potential participants were invited to contact FM directly, and were then contacted to organize a date and time most appropriate to conduct the interview.

A total of fifteen individuals offered to take part. Of these, four did not meet the inclusion criteria. One of whom, was a bereaved family member and the other three had a low-grade glioma. The eleven participants who were eligible and took part included nine patients and two family members. Patients and family members confirmed a diagnosis of grade 4 (n=9) and grade 3 (n=2) glioma. Median time since diagnosis was twenty months, ranging from five months to thirteen years.

Patient tool

Question 1: Do you have any difficulty with making yourself understood?

Comprehension

Participants understood this question to be asking about how well they are able to ensure what they say is understood by the person they are speaking to. All participants understood the term 'making yourself understood' as being in regard to verbal communication only.

"Um putting out a request or to ask for something. Or if I am having a conversation with someone, to make sure they understand my point of view."-

P10

"Well in my response there I think I was talking about a verbal response which is quite interesting. When you ask it that way I realized I didn't say anything about making myself understood in writing or texting."-P11

Paraphrasing

Some participants were unable to paraphrase the question, with most stating that they would not change it.

"I don't think it needs any different wording. I can't think of any other words."-

P13

Participants that were able to paraphrase this question all reworded it in terms of spoken communication.

"Um when talking, do you struggle to talk and express yourself and checking that the person has followed."-P15

Recall

All participants considered how their functioning had changed since their diagnosis. None of the participants expressed any difficulty with recalling how they felt since then.

"Well it's gotten worse as times gone on. But since my diagnosis."-P15

Confidence

The majority of participants felt confident in their initial answers. One participant seemed hesitant when looking through the questions again. They explained how their

confidence in their answer was affected as although they feel as though they cannot ensure that others are fully understanding what they are saying.

“8 or 9 out of 10. I think I make myself understood, but I can’t always know how others have understood.”-P20

Specific probes

Specific probes for this question focused on how a difficulty with making yourself understood could impact overall QoL. Participants mentioned how a difficulty with this could affect a person’s confidence in their abilities and therefore cause them to withdraw from activities and responsibilities.

“If I did have problems with this, I’m a mentor with the Prices’ Trust, and if I had this problem I probably wouldn’t come across as a very good mentor.”-P10

General probes

As it was seen that participants did not consider written communication when answering this question, participants were asked how this question could be worded differently to prompt this. It was suggested that this be more explicit in the wording of the question.

“Maybe change it to ‘Do you have difficulty making yourself understood through speech or writing?’”-P11

Question 2: Do you have any changes to your memory or ability to take in new information?

Comprehension

This question was understood by all participants to be addressing any detrimental changes to their memory or ability to understand visual, verbal or written information.

“It’s looking at if your memory has gotten worse”-P19

“I understood it as my ability to digest and understand, um text, reading, the news, you know, day to day bombardment of information you get. Can I still understand it without having to ask supplementary questions.”-P10

Paraphrasing

Patients often struggled to rephrase this. A few suggested the inclusion of the word ‘processing’ changing ‘taking in new information’ to ‘taking in and processing new information’ as they felt as though this was not necessarily covered.

“Um since your diagnosis have there been any changes to your memory or ability to take in and process information?”-P11

Recall

No participants expressed difficulty in recalling how they felt and all reflected on the time since their diagnosis.

“Yeah, I can think back to the diagnosis fairly well. I know when things go wrong”-P16

Confidence

Whilst no participants showed hesitancy when completing the questions, one participant said that they could not be certain due to how their life has changed since their diagnosis. They explain that as they are taking on less, it is difficult to compare to their prior situation.

“I think its possibly because I don’t have to work anymore. I don’t have to take in the same level of information.”-P10

Specific probes

Participants were asked to explain how they differentiate between memory and taking in new information. One participant expressed it was easy for them to differentiate as they have difficulty with their ability to take in new information, but not with their memory and as they are able to make this distinction, they were still able to confidently answer yes.

“It takes me longer to absorb information. I can’t take it on.”-P12

General probes

The participant who mentioned the lack of confidence in their answer was asked how the question could be reworded to make them more confident. The participant explained how they would have answered yes if they had noticed a change in their social life.

“I would say socially, I’m not aware of any changes. I was away last week and I was managing to work out routes and working out where the footpaths were. That all seemed fine. But if it wasn’t I would have said yes.”

Question 3: Do you have any difficulty with concentrating or maintaining focus?

Comprehension

Participants understood this as being able to engage and stay with a certain task. Most could not differentiate between concentration and maintaining focus, however, one participant described maintaining focus as being able to concentrate for an extended amount of time.

“It’s the period. Concentrating is the task and maintaining it is reading a chapter if you like.”-P10

Paraphrasing

The majority of participants were able to paraphrase this question whilst maintaining its intended meaning.

“Do you find it harder to concentrate or maintain focus on what you’re doing or something you’re watching?”-P20

Multiple participants emphasized the ability to focus on one or more tasks, often highlighting multitasking.

“Do you have any problems with concentrating on tasks when there’re other things going on.”-P11

“Can you give your attention to a task or multiple tasks?”-P15

Recall

There were no issues highlighted with participant recall and all participants thought of the same time frame as previous questions.

“Same as the before”-P20

Confidence

Almost all participants were confident in their answers. One expressed hesitancy as they are able to concentrate and maintain focus, but they were unsure if they should answer yes as it required more effort than it had prior to their diagnosis.

“I’m not now that I’ve thought about it. Well I find it more difficult to follow recipes. Its more energy I guess. I do have to really but in more energy.”-P14

Specific probes

Participants were asked to provide examples of activities that they believe would be affected by a difficulty with concentrating or maintaining focus. Examples given highlighted the impact such a deficit can have on most elements of daily life.

“Reading and writing. I struggle with reading. Watching tv I struggle with fiction, it’s harder to follow. You need to figure it all out.”-P15

General

As an increase of effort whilst maintaining performance was highlighted, general probes focused on how to ensure the question asked picks up on that increased effort. It was suggested that the question be worded with more emphasis on the experience of the patient rather than the outcome.

“I think as long as its clear that you want to know about how it feels rather than what they can objectively do.”-P14

Question 4: Do you find it hard to make everyday decisions?

Comprehension

All participants understood the question to be asking about common decisions that should be easy to make. Participants were able to apply the question to their own lives specifically.

“Those simple choices, do I want a cup of tea? What will I wear? Or even to those more important questions. It’s a real broad spectrum.”-P12

“It’s very broad, meals, getting dressed, about going to the toilet. It’s what you do on a daily basis”-P13

Paraphrasing

All participants that were able to paraphrase the question did so whilst retaining the intended meaning.

“Do I have any issues making normal run of the mill choices.”-P10

“Do you struggle with making simple decisions”-P15

Recall

Participants could easily remember how this had changed since their diagnosis.

“Yeah, I can tell there’s a difference from before my diagnosis”-P13

Confidence

No participants expressed any hesitancy or lack of confidence in their response. None stated any reason why others may not answer this question honestly.

“10 out of 10. Very sure”-P20

Specific probes

Although many participants gave examples of everyday decisions, specific probes were used to explore the types of decisions participants considered whilst answering this question. All participants have examples of decisions that should be easy to make and that have no serious long-term consequences.

“Do I want a cup of tea? Very simple, would you like potatoes with that?”-P15

General probes

As no issues were highlighted with the wording or understanding of this question, participants were asked if there was anything about the question they think could be changed. None of the participants had any suggested changes.

“No, I think it’s clear as is.”-P16

Screening tool completion

Overall participants found the screening tool to be easy and straightforward to complete. Whilst some participants found participation in the cognitive interview more difficult and struggled with paraphrasing, all participants were able to answer all four questions relatively quickly in the initial run through. Some participants mentioned that they were dissatisfied with the binary nature of the questions and the lack of room for expansion. However, these participants all agreed that this would be appropriate if assured of further evaluation of any present symptoms.

“I think context is needed. Like, why would you just need a yes or no answer. You need to know that it would help”-P10

None of the participants were upset or felt uncomfortable with answering the questions and all expressed that they would feel comfortable in completing these questions in a healthcare setting.

“It was good. It’s always good to have a discussion.”-P10

Family tool

Question 1: Do they show any signs of difficulty in expressing their thoughts, needs, wants or opinions?

Comprehension

Participants interpreted the question to be asking about verbal communication only. Neither were prompted to consider any deficits in methods of written communication.

“In this case it means expressing verbally. He’s still able to speak. He’s very opinionated and thoughtful. It’s all still there, but needs and want I don’t know if he always presses himself.”-P18

Paraphrasing

Both reworded the question with a distinct emphasis on verbal communication.

“Do they struggle to state what they want, what’s on their mind”-P17

Recall

Participants recalled how functioning had changed since before the patient’s diagnosis or before the onset of symptoms. Changes were also identified even if there had been noticeable improvement over time.

“Before diagnosis. 20 months ago. Its improved considerably but it’s still there.”-P17

Confidence

Both expressed confidence in their answers for this question. One participant did mention that if they were required to answer this in front of their partner, they would be inclined to answer with consideration to how their partner perceived symptoms.

“If they are with the person, they might be anxious. If you’re doing it with the partner so they would need to consider how they are feeling. It’s not always easy.”-P18

Specific Probes

For this question, participants were asked about the helpfulness of listing ‘thoughts, needs, wants or opinions. One participant did not deem them to be necessary, but that their inclusion did not remove from the readability of the question.

“Um I don’t think it was necessary. But I guess that’s just me. It does no harm I guess.”-P17

The other participant found that the list helped them answer the question and that it assisted them by prompting them to consider how a deficit in communication can affect the patient.

“Helpful to me because I put them into two categories. I know there’s no issues with his thoughts and opinions, but I’m unsure of needs and wants.”-P18

General probes

As this question aims to identify both verbal and written deficits, participants were asked how the question could be changed in order to represent this. It was determined that written communication must be plainly stated as part of the question.

“I think you need to be clear that you want people to think about written. You see, [NAME] has huge difficulty with writing now, but I wouldn’t answer yes for that.”-P17

Question 2: Do they show any signs of memory loss or difficulty taking in new information?

Comprehension

Participants generally interpreted this question as intended. It was understood that they were being asked to consider any issues that may have arisen with the patient’s memory that may need to be addressed. Whilst one participant understood the term ‘taking in new information’ to be referring to short term memory processes, the other felt as though only long-term memory was properly represented in this question.

“It about their long term or short-term memory and how they comprehend what’s going on around them”-P17

“When I read memory loss, it refers to the past. But actually, he has no memory loss of the past. He struggles with the day, holding on to the day. It’s not even taking in new information. It doesn’t quite cover that.”-P18

Paraphrasing

Paraphrasing of this question highlighted the need to change the term 'taking in new information' to emphasize the process of retaining new information in order to clearly cover short term memory.

"He definitely takes it in but he doesn't hold it. So taking in and retaining information might be better."-P18

Recall

Participants were able to clearly recall how the patient's memory had changed since their diagnosis.

"Yes, it's an easy comparison to make."-P17

Confidence

Participants were fairly confident in their answers. One was completely secure in their answer, whilst one expressed uncertainty due to the lack of clarity on short term memory.

"It would be fine if that short-term of working memory element was clear."-P18

Specific probes

Specific probes for this question were focused on how changes in patient memory are brought to their attention. Participants were asked if the patient points out that they are experiencing difficulty. It was seen that the participants will often notice the change first, but patients often play an active role in putting methods of symptom mitigation in place.

"His long-term memory is fantastic, he's actually writing a book at the moment. But the short term is not, we've set up a visual timetable and even then during the day he needs reminding."-P18

General Probes

In order to remove the doubt surrounding short term memory in this question, the participant who was unsure of their answer was asked how the question could be changed to improve confidence. It was stated that changing the wording to 'taking in and retaining new information' word serve to remove that doubt.

"If you add retaining it will solidify it."-P18

Question 3: Do they show any signs of difficulty with concentrating, maintaining focus or decision making?

Comprehension

This question was clearly understood as intended. Participants understood the question to be asking about how the patient is able to manage their concentration and process information in order to make simple decisions.

“Its being able to sustain attention and process information and make an action”-P17

Paraphrasing

Both participants rephrased the question in a way they retained the intended meaning of the question. Neither changed the word ‘decisions’

“Do they find it hard to sustain attention and make decisions”-P17

Recall

As with the previous question, participants could easily recall how this had been affected since diagnosis.

“The same as the prior two”-P17

Confidence

Neither expressed any hesitation or uncertainty in their answers.

“Totally confident in my answer, yes.”-P18

Specific Probes

Participants were asked to give some examples of the types of activities or decisions that could be affected by a deficit in this. It was seen that a deficit in concentration

and maintaining focus could make activities such as reading and watching television more difficult. It was also stated that it could have an impact on the patient's ability to maintain awareness of their surroundings. Examples of decisions were all everyday decisions that had no serious consequences.

"The day to day is harder for him. There are different elements, what would you like to eat or drink? So many differences."-P18

General Probes

Participants were asked if there was any way they would like the question to be changed to make it easier to read and answer. The similarity of the terms 'concentrating' and maintaining focus were raised, but it was not suggested as a necessary change.

"Maintaining focus and concentrating is the same thing, but it's not a big deal."-P17

Question 4: Have you noticed any changes to their personality that affect your relationship with them?

Comprehension

Both participants understood that this question was asking them to assess if the behavior or reactions of the patient have changed in a way that effects the dynamic of their relationship.

"Changes to reaction to events"-P17

"Do they seem like a different person"-P18

Paraphrasing

The intended meaning of the question was maintained in the rephrasing given by participants.

"Um are they no longer the same person they were before they had this, in such a way that you can't relate to them in the same way."-P18

Recall

Participants were able to easily recall how personality changes specifically have impacted their relationship.

"Yes, it would be very impactful so easy to recall"-P18

Confidence

Participants were confident in their answers, however, one participant mentioned that they had observed positive changes, and therefore were questioning the need to report such a change.

“Confident, maybe 4/5. I’m not sure why I need to report positive changes.”-P17

Specific probes

Specific probes for this question worked to ensure that participants were able to isolate how personality changes impact relationships. Therefore, participants were asked to give some examples of other changes to their lives that may alter their relationship. Changes in care duties and an increased sense of responsibility for the patient may cause relationship dynamics to change.

“Well there’s a shift that naturally comes with caring and having to take on more responsibility”-P17

General Probes

It was determined that the participant who reported an improvement in their relationship dynamic would not wish to answer positively to this question to avoid it being interpreted that there was a negative change.

“A positive answer could reflect poorly on the partner rather than just the patient.”-P17

Screening tool completion:

Overall, participants found the questions simple to complete and were able to engage in the interview. It was highlighted that there was some dissatisfaction with the binary nature of the questions and that a clear understanding of what answering yes to any of these questions would lead to needs to be established and stated in order for participants to feel that answering would be worthwhile.

“It’s hard to do binary responses but then ask me to think aloud. Shouldn’t patients and family members be asked why they have answered yes. What would it lead to?”-P17

No participants felt uncomfortable or upset because of the questions.

Final questions

As a result of the second phase of interviews, questions one, two and three of the patient facing questions (table 14) and questions one, two and four of the family facing questions (table 15) were edited.

Question presented	Question after editing from feedback
Do you have any difficulty with making yourself understood?	Do you find it difficult to make yourself understood verbally or through written communication?
Do you have any changes to your memory or ability to take in new information?	Do you have any difficulty with remembering things or taking in and processing new information?
Do you have any difficulty with concentrating or maintaining focus?	Do you find it difficult to concentrate or maintain focus on one or more tasks?
Do you find it hard to make everyday decisions?	Do you find it hard to make everyday decisions?

Table 15: Changes made to patient-facing questions

Question presented	Question after editing from feedback
Do they show any signs of difficulty in expressing their thoughts, needs, wants or opinions?	Do they show any signs of difficulty in expressing their thoughts, needs, wants or opinions verbally or through written communication?
Do they show any signs of memory loss or difficulty taking in new information?	Do they show any signs of memory loss or difficulty taking in and retaining new information?
Do they show any signs of difficulty with concentrating, maintaining focus or decision making?	Do they show any signs of difficulty with concentrating, maintaining focus or decision making?
Have you noticed any changes to their personality that affect your relationship with them?	Have you noticed any changes to their personality that create difficulty in your relationship with them?

Table 16: Changes made to family-facing questions

5.4 Discussion

The final version of the questions presented in tables 14 and 15 ask patients and their families if they have experienced changes to their daily lives that may be caused by a decline in their cognitive functioning. These questions are presented with consideration for the interpretation of potential tool users, ensuring that users are satisfied with the wording whilst also prompted to answer in a way that addresses the cognitive processes that the questions were designed to represent.

The two phases of cognitive interviews have highlighted both the strengths of the questions, and the ways in which the questions included in the screening tools could be misinterpreted by those they are intended for. This has enabled the questions to be edited to best suit the understanding of potential tool users whilst also maintaining their intended meaning.

A key aspect of validity is the establishment of the extent in which a measure captures what it is intended to measure [286]. Face validity is often used to describe the determination of how well an item appears to measure the characteristic or trait of interest through expert opinion, rather than assessment with participants [287]. However, it can also be used to describe the determination of if items presented are appropriate and relevant to those who would be using the measure [288]. Whilst an expert was consulted to establish whether or not the questions appeared to address areas of interest, through the use of cognitive interviewing, I have also explored participants perception of the presented questions and in doing so have been able to alter them in a way that makes them more appropriate and relevant to potential users.

One of the most notable changes made to the patient facing questions, was the rewording of questions to place an emphasis on the patients experience rather than the assessment of the outcome. This was of key importance as the main purpose of this tool is to be sensitive to the additional strain that cognitive deficits may have on patient QoL. As seen in the results of both the survey and the focus group, many patients work to mitigate their symptoms. This can result in patients maintaining the same level of outward functioning, but having to undergo additional stress and effort to do so. In contrast to this, family-facing questions had to be focused on perceptible changes from another's perspective. This was of particular importance in question 1 where it was seen that it the question must be clearly aimed at the family members

observations of changes in order to remove ambiguity with regard to issues the patient may not want to share with them.

Other changes made as a result of the interview processes focused on improving the readability and ensuring that participants were prompted to consider the intended areas of cognitive decline. This was mostly achieved by adding terms to improve clarity. Although the majority of issues and suggestions raised were directly addressed in the changing of the question, not all were.

The most commonly raised issue, was the lack of clarity as to the purpose of the tool and what a positive response would entail in terms of referral or support. It was made clear that the addition of a short paragraph before the questions detailing this would help to make potential users more comfortable and willing to answer honestly. However, this could not be included in the scope of this face validation, as it is not currently confirmed what services would be available. In addition to this, there were several instances where participants felt as though the inclusion of certain terms was not strictly necessary. In the event that its inclusion caused confusion or ambiguity, it was removed, however, in situations that they did not, and they proved useful to others they remained. A key example of this is question 3, where although some participants felt that the use of both terms 'maintain focus' and 'concentrating' was unnecessary, others expressed that they understood each term to mean different things.

There were several limitations of this study. One of the most prominent limitations seen is the proportion of participants. The majority of those who took part in this study were patients. With only two participants for the family facing tools for each phase of interviews, it is difficult to determine how representative this feedback is of the target population. One reason behind this discrepancy could be the substantial distress often experienced by family members as a result of additional care duties and acknowledgement of the disease prognosis [289]. This often leaves them with unmet needs both physically and psychologically [290] which in turn act as a barrier to their participation in research. Another factor that may have influenced this is the methods of recruitment used. Whilst both the *braintrust* and The Brain Tumour Charity are in contact and offer support to family members, it may have been of benefit to conduct more targeted recruitment. This was attempted with the social media recruitment conducted through Twitter, however, it may have been useful to seek out an organisation that was specific to family members. Although this is a limitation to the

study, it is important to note that there would likely be more patients taking part in this tool than family members. The variation of relationship dynamics between patients and their families is highlighted throughout the interviews conducted. It would be appropriate to assume that there would be patients who may object to their families having any input on their support and care. Similarly, it is understood that many patients experience social withdrawal and may have poor social support [291]. Administration of the family facing tool would need to be done so if appropriate to the individual situation. Therefore, it could be argued that the ratio of patients and family members seen in this study is representative of the potential tool users.

There were also limitations caused by conducting the interviews online. Cognitive interviewing includes observing and exploring both verbal and physical clues of uncertainty and discomfort. Therefore, it needs to be acknowledged that video calling does not offer the same seamless communication as face to face interactions. There were several instances where this was evident. These included connectivity issues meaning that segments of the interview needed to be repeated and times when participants were distracted by things around them such as email pop-ups. There was also fact that the video display does not allow for the participants hands to be seen. Therefore, subtle signs of discomfort or distress could have been missed. As this was a preempted limitation, interviews were conducted in a way that gave participants ample opportunity to express this. Furthermore, there were also benefits to the use of online interviewing. Conducting interviews online meant that those who may not have been able to take part due to logistical reason, were now able to. This meant that recruitment was able to be done nationally.

Participation in the interviews appeared to be generally fairly straightforward for participants. Paraphrasing of the questions proved to be difficult for most participants, however some patients were not able to stay engaged and on topic throughout. The more in depth questions required participants to assess the questions and look more closely into why they had answered the way they had. Due to the nature of this patient population and the symptoms being highlighted in the tool, it was already understood that this would be a challenge. Whilst it was understood prior, it was still a challenge to work through the interviews with patients with poorer cognitive functioning. This resulted in some of the interviews taking longer than intended and not yielding the outcomes needed. That being said, it was clear that even those who were not able to fully participate were able to work through the screening tool questions with no difficulty.

It is also worth noting that whilst the purpose of this study is to work towards the development of a simple cognitive screening tool, being unable to predetermine participants cognitive capabilities made it challenging to ensure a patients with a range of functioning were represented. The purpose of these interviews was to ensure that the questions were understandable to patients and their families regardless of their functioning. However, this may have led to a lack of representation of those with more severe deficit. In addition to this, as the recruitment strategy was the same as that taken in the survey and focus group, the previously mentioned bias towards younger, less impaired, computer literate is once again present. This must therefore be considered when attempting to generalise these findings to the wider HGG community.

Furthermore, several of the questions presented ask participants to consider multiple symptoms. This was done due to the grouping of deficits. The key goal of the screening tool is to detect general problems, rather than specific symptoms. Whilst this could be seen to be more difficult to comprehend, especially for those with cognitive decline, the use of the cognitive interviews did not indicate that this prove to be a challenge for participants. However, as previously discussed, the recruitment strategies used were biased towards those with better functioning, therefore this is something that will need to be considered when generalising these findings to the wider population.

This face validation has resulted in two sets of questions that are transparent and relevant to the experiences of their potential users. In order for these questions to be implemented into practice, further validation and feasibility research is required. It would be appropriate to test the ability of these questions in determining if a patient would have a positive result after undergoing more extensive batteries of neurocognitive testing.

Chapter 7: PPI

6.1 Introduction:

In this chapter, the use of Patient and Public Involvement (PPI) in this project will be explained and evaluated following the UK national standards [292]. For this purpose of this project, we will be defining PPI in accordance with the definition given by Hayes et.al (2021)[293] which is presented as “research being carried out ‘with’ or ‘by’ members of the public, rather than ‘to’, ‘about’ or ‘for’ them”. They also explain that their use of the term ‘public’ is representative of patient, potential patients, carers, and other users’ health and social care services.

The importance and value of Public and Patient Involvement (PPI) in healthcare research is clear and often required by funders, although it is not commonly seen in PhD research. Limited expectation of its inclusion, and experience of supervisory teams and students may limit motivation or confidence to implement PPI despite the benefits it could have [294]. One of the key aspects of undertaking a PhD, is to develop the skills required to become an independent researcher, therefore, students are required to learn various methodologies relevant to their field of study. It would therefore be advantageous for those students studying areas of healthcare and medicine to be encouraged and guided to implement PPI from the inception of studies. The inclusion of PPI would not only work to help familiarize students with aspects of research that they will need to carry out should they wish to continue a career in medical research, but the inclusion of PPI may help students to fully understand and appreciate the impact their work has on service users. There was some initial hesitation from the supervisory team, who have a track record in PPI innovation, to include this chapter out of concern that it might be deemed inappropriate during examination. Having sought approval from the university, and from academic peers in an ad-hoc social media survey, we feel that although PPI is a new development within PhD theses, there is broad support for it.

The importance of PPI has been increasingly understood and acknowledged for many years. Records of service users questioning the efficacy of healthcare services can be dated back to the 1950’s [295]. These challenges were the result of decisions concerning the design and delivery of such services without regard to the users’ opinions and preferences. However, with rising demand for the representation of lay perspectives in service development and research, objections against its

incorporation were also raised. Over the years, several claims have been made in objection including that those who get involved are rarely representative of 'typical' members of the public and that such input would be biased or partial [296]. On the other hand, there are key arguments that relay the importance of the implementation of PPI counter to potential objections [295] which include reasoning from several standpoints.

Firstly, it can be considered a moral requirement to implement PPI. It is a democratic right of individuals to be able to have a say in the conduct of any services that are fully or partially funded through government spending, which the public contributes to through the payment of taxes [297, 298]. Additionally, it would be seen as ethically appropriate to give members of the public the opportunity to be involved in the development and implementation of any decisions that may affect them or anything that would then be done to them. This stance mirrors that of the view presented by James Charlton in his book 'Nothing about us without us' [299]. In this, Charlton communicates that no policy or change to policy should be implemented without full representation of those affected.

There is also the argument that PPI can be used as a feedback system [300]. The implementation of PPI enables public contributors to both evaluate existing services to make sure that NHS services are meeting the needs of existing and potential patients, and to help in the development of new and altered services to make sure changes are being made with the needs of these service users in mind. Furthermore, it has also been seen that the inclusion of PPI improves the quality of health outcomes and overall patient experience [301, 302]. The inclusion of PPI in the determination of research priorities can work to identify areas that most require improvement, and therefore ensures that research conducted is relevant and representative of the needs of those affected[303].

These benefits are being increasingly acknowledged and this is mirrored in the way in which funding bodies prioritise research themes. The inclusion of PPI in a project's funding application is now often a requirement as to show that any proposed research will have a positive impact on the individuals involved [303]. A key example of this would be the priority setting study conducted by the Palliative and End of Life Care Priority Setting Partnership (PeolcPSP). The PeolcPSP asked those in end of life care, current and bereaved carers, and health and social care professionals about their unanswered questions regarding palliative and end of life care. The findings of this study has worked to highlight research priorities and is often used as a way of

allowing research funding bodies to invest their funding into research that contribute to addressing these unanswered questions [304].

This project was designed to be as pragmatic as possible. It focuses on the real-life experiences of patients and their families to identify which and how screening tool questions should be asked. The methodology undertaken has a strong focus on determining the needs of the service users, and the aim is to work towards developing a tool that is to be used to directly impact the care administered to patients. Therefore, it is paramount that the research was conducted in a way that continually prioritises the needs of the patients and their families.

Additionally, it is important to recognise the sensitive nature of the subject area. When researching any life limiting condition or illness, it is important to be considerate of the difficulties potential research participants may face when taking part in a study. As such, it is essential that any public facing documents or activities are presented with regard to specific needs (i.e., individuals with cognitive deficits may not be able to process large amounts of information in one sitting), and consideration of potential distress. The inclusion of PPI supports both a practical and ethical standpoint and has therefore formed an integral part of this project.

Due to the dearth of PPI requirements in the awarding of doctoral qualifications, this thesis makes an important contribution to doctoral scholarship and, to the best of my knowledge, is one of the first instances of integrating the UK national standards in a PhD thesis in its reporting.

Each of the six standards is detailed below. The incorporation of PPI in this project will be presented in context to how it adhered to each standard and will be explored with the prompts detailed in an audit tool designed and piloted by Nelson and Seddon in 2018[305] that was designed to highlight and describe the ways in which each standard should be met.

6.2 Standard 1: Inclusive Opportunities

This standard is in place to guide researchers to ensure that research is informed by a variety of experiences and insights. As the use of PPI is vital in ensuring research in medical science is being representative of patient needs, involvement opportunities should be available to those relevant to the research needs. The fulfilment of this standard is considered using the following indicators.

Indicator 1.1

We involve people affected by and interested in research topic/issue at the earliest stage

Both Sarah Peddle (SP) and Kathy Seddon (KS) are experienced research partners (RP) with the Wales Cancer Research Centre (WCRC). SP has expressed that her interest in cancer research stems from her own and her family's experience with different cancers. KS has direct experience with cancer that is particularly relevant to this thesis. As her late husband had a high-grade glioma (HGG), KS has first-hand experience of the challenges faced by patients and their loved ones.

The first meeting with both SP and KS in which involvement was discussed took place in January 2019. This meeting was used to consider the research plan and the specific contributions both RPs could make to the project. The first step in this study was the systematic review, to which KS contributed to the search terms used. While both KS and SP have personal experiences with regard to cancer, KS has specific experience of caring for her spouse, who had high-grade glioma (HGG). Therefore, her insight was important to ensure that all relevant terms were included. In addition to this, SP made a key suggestion for the systematic review. SP suggested that the data extraction tool used should detail whether or not included studies reported the incorporation of any PPI. This helped to highlight the lack of PPI representation in existing HGG studies.

Indicator 1.2

We identify and address barriers to taking up public involvement in research

Initially, meetings were held on a face-to-face basis where possible. Meetings were often when the RPs were already on site, however, in the event that a meeting could not be organised with consideration to this, both RPs were given the option to telephone in for meetings. Efforts were also made to conduct meetings during school hours so that SP was not required to make childcare arrangements in order to attend.

As a result of the COVID-19 pandemic, meetings moved online and were held over Zoom. SP expressed that this was more convenient for her, especially as she was home schooling her children at the time. However, due to this it was realised that meetings that lasted longer than thirty minutes were more challenging as both RPs had additional personal responsibilities. Therefore, it was identified that longer notice (at least 2 weeks) was required for such meetings.

Indicator 1.3

We make information about opportunities for public involvement available, using different methods so that we reach relevant and interested people

Both of the public contributors were drawn from the WCRC RPs. WCRC RPs are recruited from the HCRW (Health & Care Research Wales) Public Involvement Community and beyond. Opportunities for public involvement are advertised widely through websites, social media, newsletters, Twitter, and word of mouth.

Indicator 1.4

We have a fair and transparent recruitment processes for involving the public in research

The RPs that were involved with this research were recruited through the WCRC. The WCRC advertisements provide a general role description which details of different involvement opportunities. The recruitment process follows an expression of interest from a potential RP. In this RPs are asked to agree to the HCRW public involvement agreement and to register to the involvement community. Once this is completed interviews are conducted. These interviews include discussions of the role and a chance for both the panel and candidate to ask questions. The suitability of the candidate is determined on this basis and ensures candidates have a clear understanding of their role.

Indicator 1.5

We offer choice and flexibility in opportunities for public involvement in research

There are a range of projects that WCRC that RPs can get involved with. As well as being offered a range of projects, their involvement in individual studies is also determined upon their availability and individual experience. This allows RPs to contribute to areas of research that interest them, whilst considering their needs and strengths.

For this project, RPs have contributed to project meetings and have reviewed and provided feedback on all public facing documents. As previously stated, contribution to the systematic review stage was dependent on the individual expertise of the RPs. It was decided with both RPs that KS would contribute to more subject specific elements. This ensured the research conducted was designed with a patient centred focus. It was also decided that SP would contribute more in terms of ensuring that the

wording of public facing documents was appropriate and understandable. This differentiation of contribution helped to ensure that as each stage of the research developed, patient need was at the centre and that every effort was done to make the participation of patients and their families as streamlined as possible.

6.3 Standard 2: Working Together

The impact of utilising PPI is dependent on how well a research team works together. As with any working relationship, it is vital that the contributions of all involved are valued. Treating public contributors with the value they deserve allows for researchers to implement feedback truly and effectively to better the quality of the research. As well as valuing contributions, it is vital that a mutually respectful relationship is built between the researcher and RPs. A mutually respectful relationship will enable teams to work together more easily, thus resulting in a more productive environment.

Indicator 2.1

We jointly define and record the purpose of our public involvement activity

The purpose of implementing PPI in this project was discussed and minuted in the first meeting. It was agreed that SP would be mostly involved in regard to research procedures. Her role was primarily associated with the reviewing of public facing documents, ensuring that the language used was understandable and presented in a public friendly way. It was also agreed that KS would contribute to subject specific matters. This included the review of search terms for the systematic review as well as advising on participant recruitment methods and sharing key contacts.

Indicator 2.2

We develop public involvement plans and activities together

Involvement plans remained flexible to meet the needs of both RPs. Meetings were organised to suite the schedules of RPs where possible and any activities including document reviewing was discussed prior to being conducted.

Indicator 2.3

We ensure there is a shared understanding of roles, responsibilities, and expectations, which may evolve over time

WCRC RPs have a clear role description which details the responsibilities of RP's as well as the resources and support that are available to them. It is important that RPs have a clear understanding of what their role within a project is and that they have a say in what responsibilities they would like to take on.

Due to the pragmatic approach taken in this project, a concrete plan was not set from the start with regard to individual contributions. Instead, the aims of the PhD were discussed and regular meetings were held. These meetings were held to ensure that RPs were happy with how the study was progressing and also allowed us to plan how they could each contribute to the next study stage.

Indicator 2.4

We recognise individual ideas and contributions and uphold decisions together

Suggestions made by the RPs at meetings or over emails were all valued and taken into consideration. Some of which resulted in changes to the approach of the research or documentation. For example, SP suggested the importance of reporting on PPI in research which in turn resulted in the inclusion of this chapter in the thesis. In addition to this both SP and KS have had direct involvement with the formulation and presentation of this chapter, ensuring that its content is reflective of their experiences.

Overall, this standard was met through transparent and regular communication throughout the course of the project. The role and responsibilities of the research partners being discussed and agreed by both the research team and research partners themselves.

6.4 Standard 3: Support and Learning

As involvement opportunities are open to the public, it is important that public contributors are offered support and learning in areas that they may have little to no previous experience. Ensuring that RPs can expect to be supported in this way works to encourage those who otherwise may lack the confidence to take part. The purpose of this standard is to assess the way in which support, and learning is offered a promoted for PPI in research.

Indicator 3.1

We designate and monitor resources to ensure and support effective public involvement

The WCRC provides funding for RPs for ten half days (equating to thirty-five hours) on an annual basis. In addition to this RPs are able to claim travel expenses that they may incur as a result of their involvement. Due to this arrangement with the WCRC, the involvement of PPI in this project was able to take place without any additional cost. The RPs also have access to dedicated admin support from the WCRC, along with an academic lead who can provide project specific advice and support, plus pastoral support where necessary.

Indicator 3.2

We offer a range of support to address identified needs

As both SP and KS are experienced RPs, this project did not flag up any areas in which they required specific, additional support. However, as previously stated, measures were put in place to ensure involvement was as easy as possible and meetings were conducted with consideration to the RPs other responsibilities and commitments.

Indicator 3.3

We have a clearly identified point of contact for information and support

As the main point of contact for both RPs regarding this project, both RP's were given my contact details. In addition to this the contact details of two of the project supervisors, Professor Annmarie Nelson, and Dr Stephanie Sivell, were also provided, should they have any enquires that I was unable to answer.

Throughout the PhD I received support from Professor Nelson, who has a longstanding interest in PPI,[306-314] on how to implement PPI into the project. As PPI is not commonly reported in student projects, there little training offered by Cardiff University. The training that was available as a standard for PhD students was an introductory session to PPI delivered by Professor Nelson.

Indicator 3.4

We develop, deliver, and monitor learning opportunities in partnership, for all involved in research

Whilst no training programmes for RPs are currently offered through the university directly, both RPs had access to training available from the WCRC and HCRW as members of the Public Involvement community. Both groups have relevant standard operating procedures (SOPs) in place.

Indicator 3.5

We actively learn from others, we build on what we have learned and share our learning

Various aspects of the research conducted in this project have been presented at both national and international conferences, therefore work that has been impacted by the input of RPs has been shared with the wider scientific community.

In addition to this, the possibility of writing a paper focusing on PPI implementation in PhDs was discussed with SP and another PhD student in the school. Due to time restraints, this has not yet come into fruition.

A major factor contributing to the adherence of this standard is the training made available through the WCRC. With that in mind, this project ensured that any needs were identified through clearly identified points of contact, so that any issues or queries could be addressed if need be.

6.5 Standard 4: Communications

Successful communication between researchers and RPs is paramount for a successful working partnership. Therefore, it is important that methods of communication between researchers and RPs are carried out with consideration to the needs of both parties. This standard is used to help guide researchers to communicate with RPs in the most constructive way and it promotes the use of plain language for successful two-way communications as part of PPI.

Indicator 4.1

We develop and deliver a communications plan for our involvement activities

A specific plan of communication was not made as part of this project. However, given the nature of the project and the fact that only two RPs were involved throughout, it was not necessary. Having the same RPs throughout meant that methods of communication could be established from the beginning. Whilst the structure of meetings had to change as a result of COVID-19, the other main method of communication was over email.

Indicator 4.2

We are inclusive and flexible in our communication methods to meet the need of different people

Neither SP nor KS required any alternative methods of communication. However, had RPs requested written information be provided in Welsh or presented in a way that was more accessible to visually impaired individuals, Cardiff University has various services which would facilitate this, and every effort would have been made to enable this.

Indicator 4.3

We gather, offer and act on feedback, which we then share

Feedback was sought from RPs at every stage of this project. Any public facing documents were reviewed for clarity by both SP and KS and all feedback was acted upon, unless there was clear justification to do otherwise. In addition to this, opinions on subjects such as participant recruitment for the survey and cognitive interviews and the overall direction of the project was consistently sought via email and at meetings.

Methods of communication were adaptable dependent on the needs of the research partners. This led to a streamlined method of communication which was beneficial to all involved.

6.6 Standard 5: Impact

In order to promote growth and improvement of PPI in research, the impact of PPI on individual projects must be appropriately documented and evaluated. By looking at the value that PPI currently adds to research, we can work to build upon these successes. The purpose of this standard is therefore to guide researchers to capture and review any PPI implemented in their research.

Indicator 5.1

We involve the public in the assessment of public involvement in research

The RPs were asked to contribute specifically to the PPI section of this chapter using the UK Standards for Public Involvement as a structure. RPs were then asked to review the completed chapter to ensure it was representative of their experiences.

Indicator 5.2

We record our agreed purpose for public involvement and its intended outcomes

The purpose of PPI in this project was agreed and recorded at the onset of the project. Specific contributions for each study stage were determined with RPs as they were developed.

Indicator 5.3

We collect information that will help us assess the impact of public involvement in research

The UK standards along with prompts from the audit tool are used here to consolidate the information necessary to evaluate the impact PPI has had on this project. RPs were also required to keep an online diary of their involvement until this format was replaced by the use of quarterly activity reports. These reports include details of any memberships of subgroups, trials and committees and any major activities since the last quarter.

Indicator 5.4

We reflect, learn, and report the extent to which we have met our intended purpose and predicted outcomes

The purpose of this chapter is to evaluate and report the impact PPI has had on this project. Whilst the roles of the RPs are detailed in other chapters where relevant, the UK standards are utilised here to assess the way in which PPI has been conducted throughout.

Acknowledging the impact of PPI on this project has been a key aspect of this thesis. Along with the reflective activity reports completed by the research partners, the formulation of this chapter has allowed both researcher and research partners to reflect on not only the work conducted as part of this project, but also the differences between working on a student project in comparison to working with a more experienced researcher.

6.7 Standard 6: Governance

The final standard is in place to make sure that the public is involved in the governance and leadership of groups that facilitate and guide PPI. The involvement of the public is the key goal for such groups and enabling public contributors to have a say in the way these groups conduct themselves guarantees that the decisions made promote and protect public interest.

Whilst this is key in making PPI as successful as possible, this standard is not applicable to individual projects. As a result of this it is difficult to ensure this standard is met on an individual basis. However, by recruiting through the WCRC, the PPI in this study has met this standard. The WCRC incorporates PPI in the governance structure of the organisation from the Senior Leadership Group to team meetings within Themes and Work Packages[315]

6.8 Discussion:

The extent to which the adherence to each standard was dependent on the policies and practices of the WCRC was variable. The majority of the standards were met with a combination of steps taken within the project and the resources available and procedures followed by the WCRC. This is particularly relevant to standard 3, in which learning resources are available through the WCRC, but it is the responsibility of the researchers to identify any project specific needs. The only standard which no project specific steps were applicable, was standard 6, which was focused on the governance of groups that facilitate PPI. Overall, regardless of the extent to which this project was responsible, adherence to the standards presented was conducted successfully throughout this project. The adherence of these standards leads to a pleasant and productive partnership.

The inclusion of PPI in this project has added considerable value, to not only the quality of the project, but also to my personal development as a researcher. Firstly, in regard to the quality of the project. The input of the RPs has allowed me to design and conduct a piece of research that is relevant, ethical and yields the best outcomes. The consultations conducted throughout the designing of each step of the project, meant that the study was continually being developed with the overarching project aim in mind. It also meant that where appropriate, the main project aim could be refined with consideration to the patient's needs.

Ethically, the inclusion of PPI ensured that not only was the project conducted in a way that was relevant to patients, but also done so in a way that was sensitive to the

challenges that the research participants face. As well as helping with maintaining ethically appropriate practice, ensuring the comfort of participants, helped in planning more streamlined studies which in turn, helped in making sure that as much as possible was gained from each interaction. This along with maintaining relevance to the patient's needs, meant that the outcomes of the research were of the highest possible quality. This was particularly important for this research, as the outcomes were dependent on the lived experiences of patients and their families.

Whilst there were clear benefits to the inclusion of PPI in this project, there are several limitations to the way in which it was carried out. One of the key limitations faced was a lack of diversity amongst RPs. The RPs involved in this project were both Caucasian British females, of both working and retirement ages, with English as a first language. The need for diversity amongst RPs is a result of the many ways aspects such as race, nationality, gender, and class can affect peoples lived experiences. A key example of this could be what individuals prioritise in regard to overall quality of life (QoL). As one of the key underlying aims of this project is to assist in the improvement of patient QoL, having representation from a wider range of members of the public, would have been a valuable contribution. It could be argued that a lack of diversity amongst RP's does not limit the diversity of potential participants. However, the involvement of RPs that are ethnically, culturally and social diverse could work to guide the research to work in a way that targets those who otherwise would not engage with research [316].

In addition to the lack of diversity, it is also important to recognise both the benefits and limitations of involving such experienced RPs. Both RPs involved in this project have several years of involvement experience and have worked on a wide range of projects. As someone who was new to implementation of PPI, this was incredibly helpful in enabling me to become accustomed to working within such a partnership. However, when evaluating the impact of PPI on this project, such extensive experience could be seen to limit the overall representation of the general public. Through being involved with a range of research projects, RP's gain experience that, while it may assist them in understanding their roles, could be argued prevents them from truly being lay members.

With that being said, the challenges with recruitment must also be addressed. Firstly, as previously stated, the recruitment of RPs in this project was conducted through the WCRC. At the time of recruitment for this study, recruitment through such external organisations can limit the control individual researchers have on the diversity of RP's

involved in their projects. Whilst steps are taken to ensure the recruitment strategies set out by the WCRC adhere to the national standards, maintaining diversity was still an obvious issue, with a clear lack of representation of ethnic minority individuals and those from deprived communities. Therefore, the limitations faced by the governing organisation became a limitation of implementation of the PPI in this project.

Secondly, the prevalence of cognitive deficits in (HGG) must also be considered. When conducting research into such a specific aspect of a specific illness, the numbers of people with lived experience of the research area decline. In addition to this, when looking at HGG specifically, due to the prognosis that accompanies a HGG diagnosis and the symptom burden faced, it would have been incredibly challenging to engage with a patient as a RP throughout the course of the project. In addition, there are several factors that may prevent family members of patients becoming involved in research, especially if they have duties as a carer.

In addition to the limitations of how PPI has been implemented, there are also several limitations of the use of the national standards when guiding and evaluating this inclusion of PPI in this project. Even though the national standards provide clear statements on the essential aspects of good PPI, it is somewhat unclear as to who the standards are targeted towards. It can be seen that the responsibility of the fulfilment of each standard falls to different parties to varying degrees. Whilst each standard is important regardless of who is responsible, and this is by no means an argument against the use of the national standards, it could be useful to have additional and more researcher specific guidance.

The standards provide points to consider in regard to the way in which interactions between researchers and RPs are conducted and whilst they can help to ensure interactions are of a high quality, there does not seem to be any agreed standards that indicate the extent to which PPI should be implemented. As previously stated, the inclusion of PPI in health research is often a requirement for funding applications, however, a lack of comprehensive guidance may result in its inclusion being treated more as something to tick the necessary boxes rather than as an exercise to improve the efficacy of the work being done. Furthermore, the national standards do not consider how PPI may look different for different areas of research. For this PhD, the inclusion of PPI was fairly intuitive. As this is a piece of research that looks into lived experiences and utilised research methods that involved direct interaction with patients and their families, it was clear where the expertise of the RPs would be most valuable. However, this is not always the case.

Standardised expectations as to how PPI should be implemented for a range of research areas could serve to clarify how PPI can be optimally used with a range of different methodologies. Even though many areas of health research utilise 'wet lab' methods, which seldom require direct contact with patients, PPI is still an important element. Although projects such as these would not require as much hands on input from RPs, input is still required in terms of ensuring the research conducted is in line with the priorities of those it may affect. This importance has been increasingly acknowledged and in 2020, the University College London Hospitals, alongside Parkinsons UK and the Alzheimer's Society published a website aimed at offering guidance on implementing PPI in laboratory based research [317]. Currently, it appears that the extent of involvement is up to the discrepancy of research teams and funders, however, I would argue that with consideration to the ethical argument previously mentioned and the increased support available, this should be standardised.

When reflecting upon the use of PPI in this project, while the limitations must be acknowledged, it can be seen that PPI has been used in a way that has enriched the research conducted. Despite the lack of diversity, both RP's have provided a unique and valuable perspective to each element of the project. It was previously noted that the specificity of the topic area makes it challenging to recruit RPs with relevant experience, however, through the WCRC I was able to become connected with two RP's, one of which was widowed due to HGG.

From an individual point of view, whilst the use of recruitment through the WCRC limits the influence researchers have on recruitment methods, it works as a way of helping to meet the national standards without too much pressure on researchers. Looking at the time and funding restraints, along with a lack of experience, implementing PPI without the use of the WCRC would have been incredibly intimidating and could have taken away from the overall quality of the research. In addition to this, whilst the experience of the RPs included could be seen as a limitation, as a researcher who lacked any prior PPI experience, it was greatly beneficial to have that guidance from both RPs.

The overall experience of working with RPs was a pleasant and mutually beneficial one. It has helped to build a personal appreciation for the impact of PPI, as well as develop a confidence and determination to implement it in research beyond the PhD. Whilst the university provides resources and training on most methodologies and aspects of research, the lack of support available on implementing PPI was

disappointing. However, the training and support given by the supervisory team meant that PPI was conducted to a high quality which met all relevant standards.

Overall, this evaluation shows the importance in PPI in health research and displays how this can be successfully implemented in doctoral research. It also serves to highlight the gaps in guidance for researchers, as well as the lack of clear guidance available for new researchers. As doctoral research is conducted to help train researchers, and as the inclusion of PPI is increasingly becoming a standard requirement, it would be beneficial to mirror this requirement in the criteria for any doctoral research that has an impact on healthcare. However, before this becomes a standard practise for PhD students, more work needs to be done to standardise the expectations on individual researchers.

Chapter 7: General Discussion

Chapter Overview

In this final chapter, I will summarise the findings of this research evaluating how the research conducted has served to answer the research aims and how this adds new knowledge to the field of HGG research and works towards improving the quality of care available to patients. I will then be discussing of the implications for practice and future research. This will then be followed by my reflections on the limitations of this research and my experience in conducting of this PhD.

7.1 Key findings

The research conducted has provided a new insight into the nature of cognitive decline in patients with HGG and has led to the development of a face validated novel screening tool. Here I will be presenting a summary of the key findings of this PhD.

It was seen that cognitive decline is variable across patients. This was expressed both in terms of severity and nature of symptoms. It was seen that most cognitive processes are susceptible to decline, however, it is difficult to quantify due to both the complexity of symptoms and the heterogeneity of currently available assessments. Despite this, I have shown that decline can be identified through subjective experiences. Both patients and family members can provide unique insights into experienced cognitive decline. Patients are often self-aware of changes and can identify them in the increased effort they experience on a daily basis and some family members are able to observe decline through changes in the patients' personally and how they have to take on extra responsibilities as a result of the patients' cognitive decline. Through this understanding, I have been able develop two sets of face validated questions to be used to screen patients for potential cognitive decline in a primary care setting. In addition to these scientific contributions, this PhD is innovative in the way PPI has been implemented. Although the use of PPI in doctoral research is becoming more increasingly implemented [318], to the best of knowledge, this is the first to evaluate the value of, and the feasibility of incorporating PPI in doctoral research, whilst highlighting the gaps in guidance that must be refined before it is a standard requirement of healthcare related PhDs.

7.2 How were the aims addressed?

The findings presented in this thesis were the result of four study phases that were designed to answer the questions presented in chapter 1. Here I will be addressing

each of the presented questions and answer them using the research presented in this thesis.

7.2.1 Which domains of cognition are seen to decline in patients with high-grade glioma (HGG) after receiving radiotherapy?

Through the results of the systematic review (chapter 2) and survey (chapter 3) it was identified that all aspects of cognition measured in the studies presented in the systematic review are subject to decline. However, the quantification of domains was not as clear as initially hoped. The studies included in the systematic review were highly heterogeneous. They included studies with varied tumour types, interventions, and assessments. In addition to this, the assessments used often lacked specificity and many studies lacked any longitudinal data. Whilst this raised many questions regarding how to quantify domains, I was able to determine that no area of cognition was seen to be immune to decline.

Using this, the survey was conducted in a further attempt at quantifying these findings in relation to HGG patients specifically. The development of the survey was done by using situational questions derived from several existing tools aimed at assessing various areas of cognition. Through this, it was concluded that the findings of the survey mirrored those of the systematic review, and that all areas could be seen to decline.

The results of the systematic review and survey also showed that there is a great deal of variation in patient cognition. In the systematic review, this could be seen as a result of the lack of consistency in assessments used. However, the questions presented in the survey were consistent across all participants. Therefore, as the results of the survey showed the same level of variation, it can be concluded that decline is variable. However, whilst this is the case, the cognitive processes behind each of the situational questions was still unclear. As many of the daily tasks presented required a combination of several cognitive processes, I was still unable to highlight specific cognitive domains.

The variation observed could have arisen due to several causes. Even beyond the systematic review, patient data has been seen to include a wide variety of different tumour locations. Whilst a correlation between tumour location and cognitive decline was not investigated as part of this study, there is a general acceptance that differing sections of the brain can influence functioning differently[319]. The impact of tumour location on cognitive outcomes is an ongoing area of research. The idea of localised functionality is supported by the findings of Hendriks et.al (2018) who found that

tumours located predominantly in the frontal pole and the corpus callosum were associated in a decline in assessment scores for information speed [320].

In addition to this, as with many of the studies included in the systematic review, there was no follow-up data provided in this PhD. This lack of longitudinal data, and the variation of survival time of participants means that any variation in decline is not explored as part of this research. Whilst this was not an aim of this work, it should be considered that this may contribute to the variation in decline seen across patients. However, it should also be noted that whilst some of the studies presented in the systematic review reported changes in symptom severity over time, none reported symptoms to change in nature.

The complexity of cognition and the defining of cognitive domains is an ongoing area of research. However, through the pragmatic interpretation of the survey findings and further exploration into the lived experiences of patients and their families, it was subsequently highlighted that cognitive decline may lead to impairment in patient communication, memory and executive functioning. Patient communication is seen to alter through the decline of speech and language, as well as writing and typing abilities. In this, they detail how communication is effected by difficulty with both verbal and non-verbal methods. Memory was seen to be affected in regard to both memory recall and the ability to formulate new memories. Processes commonly categorized as executive functioning were also reported to be affected and described as issues surrounding attention, processing and decision making.

As a result of the absence of a standardised method of categorisation of cognitive domains, the deficits presented are best described as an insight into subjective cognitive impairment (SCI). Whilst associations between SCI and objective cognitive measures are variable between studies, associations between SCI and measures of structural brain changes are becoming increasingly consistent [321]. Additionally, SCI has been reported to be indicative of subtle decline in preclinical Alzheimer's disease [322].

The significance of SCI has also been highlighted in several brain tumour studies, including a study conducted by Prankeviciene et al (2017) [323] which found that SCI was associated with a psychological distress and may lead to an adverse impact on patient QoL. However, to the best of my knowledge, the research presented for this PhD is the first to provide an in depth exploration into SCI through the first-hand experiences of patients and family members, rather than through the use of preexisting cognitive or QoL assessments.

7.2.2 How does cognitive decline impact the QoL of patients and those around them?

Through the subjective descriptions of decline given by patients and family members, the effects on QoL were determined in the survey, focus group (chapter 4) and interview (chapter 5) findings. The descriptions given demonstrated that day-to-day activities are seen to be more challenging.

It was observed throughout, that although patients and their families may not necessarily understand the specific nature of cognitive symptoms, they are still able to identify that decline can affect most aspects of daily living. The consequence of this on the patient is both practical and psychological. Practically, it was often observed to prevent patients from maintaining their normal way of living, and led to an increased reliance on others. Psychologically, it was seen to lead to a decline in their sense of self. Being unable to keep up with existing responsibilities and having to relinquish control often resulted in feelings of frustration and upset. This is particularly pertinent as depressive symptoms have been reported to exacerbate existing medical conditions and result in an increase in functional disability and cognitive impairment [324]. Whilst studies have been conducted into the understanding the emotional well-being of patients with HGG (refs), this research is the first present first hand descriptions of depressive symptoms that patients believe are caused by cognitive decline.

It was also identified that more generalised issues were reported to be more detrimental to QoL than specific deficits. An example of this would be numerical calculation. It was agreed in the focus group, that of all the tasks listed, a difficulty with this would be the least detrimental. This was because a challenge as specific as this was seen to be easier to mitigate. However, the prolonged use of mitigation strategies was also seen to exacerbate fatigue. Additionally, fatigue was also reported throughout the survey and focus group to be an exacerbator of cognitive difficulties. This has previously been seen to be the case in patients with multiple sclerosis, where patients reported that fatigue impaired their cognitive capabilities [325]. This is further supported by a 2022 study conducted by van Coevorden-van Loon. It is reported that fatigue may be associated with cognitive difficulty in patients with LGG [326]. As high levels of fatigue reported in patients with HGG [327], it can therefore be assumed that those with HGG experience this same difficulty. The effect fatigue has on patients could then be seen as another factor that contributes to the findings presented in the cognitive interviews (chapter 5), that the focus of the screening tool questions should be on the increase in effort of dealing with decline rather than the outcome.

The accumulation of this was seen to have a potentially negative affect on the patients relationships with those around them. In the survey, it was seen that family members may notice a negative change in the patients personality. The idea that personality may alter with the progression of cognitive decline has been reported in studies of patients with multiple sclerosis. It was reported that those who were experiencing cognitive decline were associated with both lower extraversion and conscientiousness [328]. Both of which were reported in this research. Lower extraversion was reported as patients retreating from activities and social interactions and lower conscientiousness was described as patients being less considerate of the needs of those around them.

These perceived personality changes, as well as a potential increase of patient reliance on their family, may shift the dynamic of the relationship. This can in turn, result in family members feeling overwhelmed and resentful. This detrimental impact was also reported by Rohde et al. (2019), in their study of the psychological wellbeing of family caregivers of stroke survivors. They found that those caring for stroke survivors with cognitive deficits were more likely to exhibit symptoms of anxiety and depression [329]. This was mainly seen in the results of the survey, and was not as fully developed as an outcome in the focus group. This could be caused by the smaller number of participants in the focus group versus the survey. Therefore, the results of the focus group may not have been able to capture the variation of family experiences. However, it should also be acknowledged that family member participants may have been hesitant to candidly speak in a group that included patients, as a reluctance in reporting deficits in the presence of the patient was express both during the focus group and reiterated throughout the cognitive interviews.

Although it is commonly understood that cognitive decline has a negative impact on QoL, this research is, to my knowledge, the first to provide an in depth exploration as to how decline impacts the day to day lives of HGG patients and those around them. It works to further our understanding of the overall burden faced by patients and the strain this may put of their families, and thus highlights the requirement for further support.

7.2.3 How can decline be best detected in patients without the use of extensive neurocognitive assessments?

In answering the previous two questions, it was identified that a potential screening tool would work best if focused on the impact decline had on QoL. By looking more into the effects on QoL, this removes the need for domain specific questions or tasks. Therefore, the methods of detection selected for this screening tool were designed to focus on the overall impact of decline, rather than specific mechanisms. In addition to this, as family members may be able to offer a unique perspective, it is important that they are given the opportunity to report their observations. However, as the presence of the patient has been seen to influence the level of information given by family members, it was necessary to develop a separate family-facing tool.

The findings of this research have indicated that most patients and their families are keen to be asked about the effect decline has on their QoL, especially if this will lead to an improvement in the care and support received. Whilst this was the case, this research has also served to highlight the barriers to reporting decline faced by patients and their families. It was commonly seen that a lack of information on cognitive symptoms could contribute to the perceived stigma around a decline in functioning. Those who were not informed of how their/ the patients' cognition could decline often felt as though their experience was isolated, or feeling as though these symptoms did not need addressing. This led to a general acceptance that support was not available and that these struggles were just a part of their new reality.

This acceptance was also highlighted by the number of participants throughout this research that reported the use of coping mechanisms. In developing an understanding surrounding the coping mechanisms used, I was able to determine that patients may not report decline if asked about the outcome of tasks. An example of this can be seen in the cognitive interviews (chapter 5). The initial questions presented asked participants to evaluate the overall outcomes of deficits associated with communication, memory and executive functioning. However, it was seen that the use of coping mechanisms often meant that patients could maintain these abilities. This then provided the rationale for wording questions in a way that asked patients about the effort associated with reaching these outcomes.

In this research, it was also found that both patients and family members can provide unique insights into experienced cognitive decline. This study presents findings that show that some family members notice changes in the patients' personally and have to take on extra responsibilities as a result of the patients' cognitive decline. This has highlighted the value in allowing family members of patients the opportunity to report

decline. The impact that an individual's condition may have on the lives of those closest to them is widely recognised across many other illnesses and disabilities, but is often regarded as an unmet need [330]. In addition, it has also been previously seen that this may impact various areas of family life as a whole [331]. However, this is the first study that I know of that has actively explored how family members perceive cognitive decline in patients with HGG.

Using this information, I was able to draft two sets of questions. One to be presented to patients and the other for family members. These questions were then face validated with potential tool users to ensure that they were interpreted as intended and representative of their lived experiences. Although there are preexisting methods of assessing SCI, including the Background Questionnaire – Adult [58], these are usually lengthy, and therefore not practical for a primary care setting, and not specific and sensitive to the needs of patients with HGG. The questions presented in this PhD are the first to be designed specifically for addressing SCI in patients with HGG. As a result of the severe symptom burden and poor prognosis associated with HGG, the cognitive symptoms faced must be considered in the wider context of their lived experiences. Therefore, it was important that any questions developed were done so with this at the centre. In addition to this, each set of questions presented in this research consist of only 4 questions and do not require specialist delivery, meaning that they are feasible for a primary care setting.

. Furthermore, the face validation led to the questions being presented in a way that attempt to bypass some of the barriers to reporting. Overall, the findings of this PhD indicate that the best way of detecting cognitive decline in patients is to allow them, and those around them, the opportunity to report decline by directly asking questions that are broad enough to capture their subjective experiences. To the best of my knowledge, this research is the first to suggest this in favour of administering a generalised tool such as the MMSE. As discussed in the systematic review, the MMSE is a widely used tool designed to easily detect cognitive impairment. However, the results presented throughout this thesis show that there is no clear cut or consistent classification for cognitive domains and the behaviors associated with them. Therefore, the design of available assessments somewhat subject to the authors interpretation of cognition. This includes those assessments adapted for the survey. Therefore, for the purpose of developing a screening tool, it was necessary

that the key focus was the experiences of the patient and those around them, rather than remaining focused on underlying cognitive processes.

On the basis of this, it was surmised that a screening tool for cognitive deficits that alter QoL should be developed with regard to SCI. Therefore, a separate tool that is representative of this is needed, rather than working to adapt an existing screening tool which would either be clouded by the interpretation of the author or be designed with regard to the needs of a different patient population. The latter of which would be inevitable, as there is currently no cognitive screening tools that have been developed specifically for patient with HGG. This is the first research that has been conducted into developing, a simple screening tool for cognitive decline in patients with HGG, which prioritises the lived experiences of those who would be using it.

7.3 Implications for practice and research

The rationale behind this research was to aid in bridging the gaps in current care for patient with HGG. I have presented evidence to support the understanding that patients' cognitive needs are poorly addressed by HCP. This PhD presents a face-validated method of determining if patients could be experiencing cognitive decline which is negatively impacting the QoL of them and those around them. However, further work is needed to have this fully validated, implemented and accessible to patients. Following this study, I am left with several questions surrounding the validity and practicality of this tool. I will now present the opportunities for practice a discussion of the further research that is needed for this to come to fruition.

7.3.1 Cognitive screening in a primary care setting

For patients diagnosed with HGG, treatment is rarely administered with curative intent. Instead, treatment is conducted with the goal of extending survival and preserving QoL. A diagnosis of HGG is often accompanied by a progressive decline of cognitive functioning. While the exact cause is still somewhat unclear, it is understood that this is caused by an accumulation of tumour symptoms and treatment side effect. Ideally, patients would be presented with information regarding this from the offset, and have access to ongoing support for these deficits. This is a key aspect in the NICE guidelines for brain tumour patients, so it is clear that the benefit of this is already widely recognised [67]. However, as this is not always the case, and as highlighted in this research, patients and their families are often left with unmet needs that negatively impact QoL.

Cognitive decline leads to both unmet practical and psychological challenges. This study has identified that both patients and their families would benefit from help

beyond what is currently available to them. Through the cognitive interviews, and survey responses, it was expressed that even the opportunity to discuss these symptoms and have them acknowledged would have psychological benefits. As previously stated, following the completion of treatment, patients are often reliant on primary care services for support. The tool presented has been designed with regard to the limitations of such services, and would therefore be suitable for administration in this setting.

When trying to design a screening tool that is accommodating to the limits of primary care services, it is important to consider both restraints on time and resources. The length of the questions presented would enable screening to be conducted within the time restraints of most primary care services. As well as this, the simplicity of the questions means that it would not be necessary for them to be completed in the presence of a cognitive specialist.

Before this is possible, research is needed in order to address the practicality of incorporating, or implementing, it into practice. Research into implementation is conducted with the aim of answering the questions that arise regarding implementing new procedures into practice. This covers a broad spectrum of factors, including those that affect implementation, the processes of implementation, and the results of implementation [332].

This research has presented evidence to suggest that there is variability across patients regarding the availability of care and resources. Therefore, in order to make a suggestion as to how the tool should be administered, we would need to have a more clear understanding of the support available in a primary care setting. Once this is established, it would be possible to suggest a method of tool administration that would be accessible to all. Moreover, the determination of who would be administering the tool would be dependent on the method of administration and the services available.

As well as the need to research the practicality of implementing the presented tool, more work is needed to ensure its validity. Although the presented tool is validated with regard to the experiences of participants, it is important to ensure all key aspects of cognition have been addressed. Confirmation that the intended aspects were represented was received from a neuropsychologist who works directly with glioma patients, however, due to the lack of HCP input, it would be beneficial to seek further content validity from a larger group of topic experts.

Attaining a consensus on which cognitive domains are presented by which question could serve to highlight if any additional questions are needed. I would therefore propose that a Delphi survey and consensus event be held in order to achieve this.

As this tool is presented as a method of simply detecting which patients would benefit from more in depth cognitive assessment, criterion validity is required. This could be done by assessing how the results of this tool may correlate to the results of more extensive tests. As I have already discussed throughout this thesis, there is a notable issue with the consistency of assessment use. Therefore, it may be beneficial to include discussion on assessments used in the afore mentioned consensus event. This event would then not only contribute to the content validity, but also aid in the planning of research to acquire criterion validity.

7.3.2 Access to support

As previously stated, it is recognised by NICE that patients would benefit from further support for their cognitive symptoms, including access to neuropsychological rehabilitation. The designing of the proposed screening tool, means that those who would benefit from this can be easily identified, thus hastening this referral process. With consideration to the typical disease trajectory faced by patients, ensuring the efficiency of referral is incredibly important.

In a review conducted by Coomans et al (2019) [333] it was seen that there was a lack of evidence available to support the use of pharmacological intervention for the treatment of cognitive decline. However, they did find that there is evidence to support the use of neurorehabilitation methodologies. They found that whilst this is the case, there is a lack of consensus as to the timing in which neurorehabilitation is administered. However, it was acknowledged by several of the studies that early intervention is more successful in retaining function. Therefore, if the tool proposed is further validated, it may work to not just grant access to support, but also enable fast identification of those with cognitive decline, and therefore improve clinical outcomes of neurorehabilitation.

As mentioned in chapter 1, it is also suggested that the patients and caregivers be referred to national and community resources such as support groups and respite care. The findings of this thesis indicate that the QoL of family members of patients with HGG may be affected by a decline in patient cognition. Therefore, it may be appropriate to further investigate the value that respite care could have with regard to HGG. Use of the proposed tool, could help to not just facilitate access to such

resources, but also serve to highlight a need for better support for family members of patients.

The results of this research provide a valuable insight into the complexity of the relationships between patients and those closest to them. I have presented evidence that the increase of patient reliance on family often results in a notable shift in the relationship dynamic. The added responsibilities faced by the family member, along with the psychological impact of trying to accept the HGG diagnosis leads to increased distress and a reduced QoL [290]. Family members should therefore, be offered additional support on how to adjust to these changes. This is a finding of other studies that look into support for families of those with neurodegenerative diseases. In a study of family caregivers of patients in the later stages of dementia, the benefits of professional support for family members was acknowledged, yet there is still a lack of support in place [334].

Throughout this thesis, I have presented findings that draw attention to the varying experiences of patients and their families. This variation is not just caused by varying symptoms, but also discrepancies in the quality of care received. This was often seen to be determined by the frequency of contact with HCP's. While all patients received quarterly follow ups with their oncology team, these appointments are mainly focused on determining if there is any tumour progression. Therefore, the discrepancies described in this study are likely to be mostly resultant of accessibility issues. There is evidence of this being the case from the focus group data, where access to support, even through primary care services, was described as a "postcode lottery". Therefore, more needs to be done to standardise this access to care. This could be achieved with the by providing patients access to palliative support from a much earlier stage in their illness. However, an evidence review conducted by Byrne et al. (2022) concluded that there has not been enough research conducted into early palliative interventions to fully understand the impact this has on patient and family QoL[335].

While it is suggested that a positive result of the presented screening tool be followed up with further in-depth assessments, there is still a lack of understanding as to the services that are available to administer these. Furthermore, once criterion validity is established, it may be that in-depth assessment of all positive results is not practical. For this reason, the question as to what other methods would serve to support patients and their families must be addressed.

Being able to answer this question, is arguably the most important aspect of implementing a new screening tool. The results presented in the face validation of the

tool indicated that a key motivator of answering questions honestly and openly was that it would lead them to getting better support. We must therefore, research into what specialist support services are available. This is not only important for understanding what is available, but also the feasibility of getting access to these services for patients with HGG.

From the evidence identifying the variation of support access, it can be concluded that patients may need to travel in order to access specialist support. With consideration to the debilitating symptom burden experienced by patients, they may not see this as beneficial. Therefore, once available resources and support routes have been established, it will need to be determined whether or administration of the screening tool should be accessible to all, or just those in areas with readily available services.

7.4 Limitations of the research

In evaluating the impact of this research and its implications, it is important to acknowledge its limitations. This study has several limitations. One of which being the pragmatic decision to recruit outside of NHS settings. Cardiff University School of Medicine ethical approval was obtained for the survey, focus group and cognitive interviews conducted. The decision to not recruit participants from NHS settings resulted in several limitations. Most notably was the lack of HCP participation. In both the survey and focus group, there is a distinct lack of HCP representation. Had NHS R&D approval to recruit been granted, I would have been able to access HCP's through NHS recruitment pathways and not had to rely on HCP's taking part in their free time. Although this study has been conducted with priority to patient and family experience, having that additional insight from HCP's may have aided in further understanding how a tool could be practically implemented. This would have helped in determining how a potential tool could be administered. Additionally, having a larger contribution from topic experts could have worked towards ensuring the content validity of the proposed questions. However, throughout the PhD I presented and discussed the progress of the PhD with two neuropsychologists, one of which reviewed the initial draft of the screening tool.

As well as the reliance on public recruitment strategies impacting HCP representation, it also influenced the representation of patients and family members. All participants across the survey, focus group and cognitive interviews were recruited through known brain tumour charities or social media. Had NHS ethical approval been granted, participants could have been recruited in clinic. This would have enabled us to access

those who were not active in online HGG communities. While online recruitment was seen to be efficient throughout the research, its use may provide less demographic diversity [242]. On the one hand, it could be argued that those seeking out online support networks and advice may be experiencing enhanced difficulty, especially if they are experiencing symptoms that their healthcare team has not been explicit about. However, when considering the effect cognitive decline has on daily functioning, the use of online recruitment may be unintentionally excluding those with worse functioning. This is likely as it is already understood that social media recruitment is bias towards younger people and those who regularly use the internet [336].

This study was conducted with a pragmatic approach. As such, this research was conducted in several stages, with the design of each being dependent on the results of the previous. Therefore, it was decided that separate applications for ethical approval would be sought for each stage, rather than attempt to preempt the specifics of each methodology ahead of time. Furthermore, as the survey was being developed, it was clear that as a result of the COVID-19 pandemic, and the prioritisation of COVID related research, the time it would have taken to obtain NHS ethics would have overstretched the timescale available for the PhD. Therefore, it was not practical for this to be done.

A limitation faced throughout this PhD was the challenge around generalising the findings to the wider HGG population. The recruitment strategies used throughout had a heavy emphasis on social media. Whilst this proved to be effective with recruitment of patients and family members, this meant that difficulties with internet accessibility were not mitigated, and therefore may have led to the exclusion of those with more advanced illness. In addition to this, it is worth noting that even if recruitment of a sample representative of a wide range of functioning, the subjective nature of cognition makes it challenging to generalise the experiences of a select sample to all those with HGG. It can be said that the questions presented in this thesis are designed with regard to the needs and preferences of the participants of this study. However, in continuing this research with the aim of it being implemented into practice, this will need to remain a consideration. Once further validation of the tool items has been established, a feasibility study will need to evaluate how patients with worse functioning interact with the tool. Another limitation of this project was the absence of in person research. As with online recruitment, online research limits research to those who are able to access the internet. This may result in those with advanced illness being excluded from taking part. However, in person research was

simply not feasible due to the government imposed COVID restrictions. Although this meant that research methods were fairly limited, it has given me the opportunity to learn how to utilise online applications for research. The advantages to online research were clear throughout this project as it often served to reduce costs and enabled the participation of those who may not have been able to due to logistical reasons [336].

7.5 Reflections

As stated in the survey (chapter 3), it was important for me to consider any personal bias I may have when conducting this research. In doing this, I have been able to truly expand my understanding of the challenges faced by patients and their families. Whilst it is impossible to ever truly know the reality of the burden of HGG without experiencing it first hand, the information provided from those who took the time to participate in this study has not just allowed me complete my PhD, but also appreciate the importance of patient focused care.

This was reinforced through my learning of PPI and how to incorporate it into research. Prior to this, although I have conducted research focused on individuals with cognitive dysfunction caused by neurodegenerative diseases, the lived experiences of those involved was not a key outcome. It has made me aware that although research is most certainly needed surrounding cognitive mechanisms and curative treatments, it is still necessary to ensure that patients have access to the best care possible.

This PhD has given me the opportunity to learn research methods which allow for current understanding to be built upon and used in a pragmatic way to benefit the lives of patients.

7.6 Conclusion

This study was conducted with the purpose of working towards developing a screening tool to detect cognitive symptoms in patients with HGG who had completed radiotherapy. At the start of this research, I had planned to try to somewhat quantify the domains of cognition seen to decline. However, as time went on and I was given the opportunity to meet and talk to those who were living with this reality or had been beside those who had, it was increasingly obvious that understanding their lived experience held more value. It has shown me that cognitive decline should not just be defined by what a person can and cannot do, but should also encapsulate the additional effort it may take to do it.

In establishing this understanding, I have been able to design and face validate two sets of questions which ask patients and their families key questions to identify SCI. In doing this, it is hoped that in the future, this will provide patients with the opportunity to access support or further in depth cognitive assessment.

Patient need has been at the forefront of each of the stages of this study. The pragmatic approach taken throughout this study has meant that each step was conducted to make the best use of the step before and was developed with input from PPI research partners. Therefore, I feel that this research not only contributes to the improvement of care, but does so in a way that is truly representative of the needs of those effected.

Overall, although more work is required in order for the benefits of the new screening tool to be seen, I believe that this work has been successful in beginning that process.

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Supplementary Appendix A: Data Extraction Form

Data Extraction Form adapted from the Cochrane Collaboration

Title of the systematic review: *What are the cognitive deficits observed in adults with brain cancer after receiving radiotherapy or combined chemo-radiotherapy?*

This form has been developed by adopting and customizing the “Data collection form for intervention review – RCTs and non-RCTs” of The Cochrane Collaboration. Some new sections have been added into this tool and the irrelevant sections have been removed from the original form. Information included on this form should be comprehensive, and may be used in the text of the review.

Notes on using this data extraction form:

- Be consistent in the order and style you use to describe the information for each included study
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.
- Include any instructions and decision rules on the Data Extraction Form, or in an accompanying document. It is important to practice using the form and give training to any other authors using the form.
- We will protect the document in order to use the form fields (Tools / Protect document)

General Information

1. Date form completed <i>(dd/mm/yyyy)</i>	
2. Name/ID of person extracting data	
3. Report title <i>(title of paper/ abstract/ report that data are extracted from)</i>	
4. Report contact details of person extracting data	
5. Publication type <i>(e.g. full report, abstract, letter)</i>	
6. Study ID <i>(e.g. 01 plus surname of first author and year first full report of study was published e.g. Smith 2001)</i>	

7. Country in which the study conducted	
9. Study funding source (including role of funders)	
10. Possible conflicts of interest (for study authors e.g. not reported)	
11. Notes:	

Eligibility

Study Characteristics	Review Inclusion Criteria <i>(Insert inclusion criteria for each characteristic as defined in the Protocol e.g. cross-sectional, cohort or case-control)</i>	Location in text <i>(page#/fig/table)</i>
12. Type of study		
13. Population description		
14. Type of cancer <i>(Brain Metastasis, High grade glioma, low grade glioma or meningioma) (If metastatic, what is the primary?)</i>		
15. Types of outcome measures <i>(Cognitive tests (i.e MMSE), patient reports of cognition, carer/professional observations regarding cognition.)</i>		
16. Decision <i>(with reasons for either inclusion or exclusion)</i>		
17. Notes:		

DO NOT PROCEED IF STUDY IS EXCLUDED FROM REVIEW

Population and setting

	Description	Location in text <i>(page#/fig/table)</i>
18. Population description <i>(from which study participants are drawn)</i>		
20. Method/s of recruitment of participants		
21. Notes:		

Methods

	Descriptions as stated in report/paper	Location in text <i>(page#/fig/table)</i>
22. Aim of study		
23. Design <i>(e.g. cross-sectional study, cohort study, case-control study)</i>		
24. Sampling technique <i>(e.g. random or convenience)</i>		
25. Assessment frequency <i>(i.e; every 1 month post RT)</i>		
26. Notes:		

Intervention

	Descriptions as stated in report/paper	Location in text <i>(page#/fig/table)</i>
27: Radiation protocol <i>(WBRT, STRT, Proton beam, brachytherapy or Gamma knife radiosurgery)</i>		

28: Dosage/Fractionation		
29. Was chemotherapy also part of the patients' treatment? If so detail type and dosage.		
30. Did patients undergo resection?		
31. Notes:		

Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text <i>(page#/fig/table)</i>
32. Total number of participants/Sample size		
33. Age group		
34. Notes:		

Outcomes

How outcomes measured	Description as stated in report/paper	Location in text <i>(page#/fig/table)</i>
35. Outcome type <i>(detected by examination/observation: who examined/observed?)</i>		
36. Self-reported reported outcomes <i>(detected by questionnaire: validated or non-validated?)</i>		

Cognitive decline (Note: Not detail here under outcome. Detail should be reported in results section)	Description as stated in report/paper	Location in text <i>(page#/fig/table)</i>
37. Outcome measurements names <i>(ie. MMSE,HVLT-R)</i>		
38. Time points reported		
39. Type of measurement <i>(Percentage/Odds ratio/Risk ratio)</i>		
40. Is outcome/tool validated? <i>(Yes/No/Unclear/Not mentioned)</i>		
41. Notes:		

Results and findings

Outcome : Cognitive decline (Note: detail here)	Description as stated in report/paper	Location in text <i>(page#/fig/table)</i>
43. Results		
44. Response/non-response rate		
45. Any other results reported		
46. Unit of analysis (e.g. by individuals)		
47. Statistical methods used and appropriateness of these methods (e.g. proportion/%s, RR/OR)		
48. Whether results weighted? (e.g. Yes/No)		

49. Notes:

Limitation and mitigation strategy

	Description as stated in report/paper	Location in text(<i>page# /fig/table</i>)
50. Strength		
51. Limitation		
52. Strategies to overcome the limitation		
53. Notes:		

Conclusion and other information

	Description as stated in report/paper	Location in text <i>(page#/fig /table)</i>
54. Key conclusions of study authors		
55. Notes:		

How is everyday memory and processing altered in patients with high-grade glioma after radiotherapy?

Participant information

You are being invited to take part in a study that is looking into the everyday memory and processing of patients receiving radiotherapy for high-grade glioma.

Background:

As stated in the World Health Organisation (WHO) definition, early identification of problems is a key aspect of patient care. For patients with high-grade glioma there are no consistent ways to detect memory and processing problems following radiation.

Early detection of these problems could trigger timely referral to a specialist and access to rehabilitation programs. The rehabilitation may work to improve memory and processing function, reduce symptom burden, and benefit overall quality of life.

Purpose:

This survey is being conducted as part of a doctoral degree project looking at developing a screening tool for the memory and processing changes experienced by high-grade glioma patients after receiving radiotherapy.

In order to design a screening tool that is specific to the needs of patients with high-grade glioma, it is important to gain a better understanding of how patients experience changes in memory and processing on a day to day basis. The aim of this survey is to gain that understanding.

Who can take part?

Patients and their families and friends are invited to share their experiences and how they have been altered since undergoing radiotherapy.

Healthcare professionals are also invited to give an insight into their observations of the challenges faced by patients after receiving radiotherapy.

How long it will take:

The survey should take around **10 minutes** to complete

Data protection

Before you agree to take part in the survey, we would like to ask you to take your time to read the following information.

Data protection and usage:

All data collected in this survey will be held securely by the survey software provider Jisc (www.jisc.ac.uk; previously BOS) under contract and then retained by the Marie Curie Palliative Care Research Centre at Cardiff University (MCPCRC) in accordance with the General Data Protection Regulations (GDPR; EU 2016/679) and the Data Protection Act 2018 (DPA 2018). For more information on data protection, please follow the link: [General Data Protection Regulation \(GDPR; EU 2016/679\)](#). Cookies, personal data stored by your web browser, are not used in this survey.

Cardiff University is the Data Controller and is committed to respecting and protecting your personal data in accordance with your expectations and Data Protection legislation. The University has a Data Protection Officer who can be contacted at inforequest@cardiff.ac.uk. Further information about Data Protection, including your rights and details about how to contact the Information Commissioner's Office should you wish to complain, can be found at the following: <https://www.cardiff.ac.uk/publicinformation/policies-and-procedures/data-protection>

Privacy

Your participation is confidential. This means no one will be told you are taking part and participation will not affect your treatment or care. Responses will be anonymised so that any identifiable information provided will not be used in the report and while direct quotations may be used in the report, any identifiable information will be removed.

Data Handling

All research data will be handled according to the principles of the regulation. Data will be stored on a password-protected computer with appropriate backup. Data transfer will be closely monitored and made available to members of the research team only. All data will be retained for at least 5 years post-study closure. Only members of the research team will have access to this anonymous data.

Participation

Please note that participation is completely voluntary and you may withdraw at any time.

However, please note that once the survey has been submitted, your data will be used as part of the study.

If you do not wish to take part, you need do nothing further. Please take any time you may need to discuss the opportunity to take part with family and friends before making your decision.

By participating in this survey you are consenting to the use of your survey responses for research purposes. This includes future reports, journal publications, future research, conference presentations, and educational purposes.

Contact information

If you have any concerns or questions regarding the survey, please feel free to contact Francesca Mazzaschi at mazzaschifi@cardiff.ac.uk

I have read and understood the information provided and I consent to take part in this survey * *Required*

yes

Participant identification

Who is taking part in this survey? * Required

- A patient who has received radiotherapy for treatment for high grade glioma
- A friend or family member of a patient who has received radiotherapy for treatment for high grade glioma
- A healthcare professional with direct and regular contact with patients who have received radiotherapy for treatment for high grade glioma
- None of the above

Please confirm that you are aged 18 or over * Required

- I am 18 years of age or over

Thank you

You do not match the requirements for participation in this survey. We would like to thank you for your attention and time.

If you are in need of further information regarding cancer care and support, please do not hesitate to contact the following:

Marie Curie

online at: <http://www.mariecurie.org.uk/help/support>

by phone: 08000902309 (*Mon-Fri: 8am-6pm sat-sun: 11am-5pm*)

Macmillian Cancer Support

online at: <http://macmillan.org.uk>

by phone: 08088080000 (*Mon-Sun: 8am-8pm*)

Survey Instructions

For the following questions please answer how often you have found yourself experiencing the following situations in comparison to before you underwent radiotherapy.

Each question has a free text box. Please feel free to add further details if you would like to explain your answers further

Patient experience

Q1.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Having to double-check that you have done something (i.e. locking the door)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q2.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Being unable to recall events in the order that they occurred	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q3.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Being unable to recall something you were told in the last week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q4.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Getting halfway through reading something before realising you have already read it	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q5.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Having to re-read something to fully understand the meaning	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q6.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Getting the feeling that a word is 'on the tip of your tongue'	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q7.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often

Forgetting to do something you had planned and wanted to do	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Any further information:

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Q8.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Having difficulty remembering details of what happened the day before	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

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Q9.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often

Losing your train of thought whilst speaking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Any further information:

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Q10.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Being unable to stay engaged when listening to someone talking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

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Patient experience (cont.)

Q11.

	Much less often	Slightly less often	The same a before	Slightly more often	Much more often
Finding yourself getting details of what someone has told you mixed up or confused	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q12.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Realising that you have repeated yourself or asking the same questions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q13.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Misplacing items around the home	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q14.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Not knowing 'where to start' when undertaking a task	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q15.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
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Being unable to efficiently multitask	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Any further information:

Q16.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Finding it difficult to write by hand or draw	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q17.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Having difficulty typing on a computer or phone keyboard	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q18.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Being unable to solve addition or subtraction calculations	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q19.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Being unable to solve multistep calculations (i.e. percentages)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

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Do you have any further comments about any changes you have experienced in your memory and processing?

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About you

Age

Gender

Approximate date of diagnosis

Tumour location

Approximate radiotherapy end date

Did you complete the full course of radiotherapy?

yes no

If you selected 'no', approximately how much was completed?

How did you find out about this survey?

Survey Instructions

For the following questions please answer how often you have noticed the patient experiencing the following situations in comparison to before they underwent radiotherapy.

Each question has a free text box. Please feel free to add further details if you would like to explain your answers further

Family and friend observations

Q1.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Having to double-check that they have done something (i.e. locking the door)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q2.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Seeming unable to recall events in the order that they occurred	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q3.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Being unable to recall something they were told in the last week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q4.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Forgetting that they had read something	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q5.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
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Having to re-read a piece of text to fully understand the meaning	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Any further information:

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Q6.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Getting the feeling that a word is 'on the tip of their tongue'	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

--	--

Q7.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often

Forgetting to do something they had planned and wanted to do	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Any further information:

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Q8.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Having difficulty remembering details of what happened the day before	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

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Q9.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often

Losing their train of thought whilst speaking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Any further information:

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Q10.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Being unable to stay engaged when listening to someone talking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

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Family and friend observations (cont.)

Q11.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Finding that they get details of what someone has told them mixed up or confused	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q12.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Realising that they have repeated themselves or asked the same questions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q13.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Misplacing items around the home	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q14.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Not knowing 'where to start' when undertaking a task	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q15.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often

Being unable to efficiently multitask	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Any further information:

Q16.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Finding it difficult to write by hand or draw	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q17.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Having difficulty typing on a computer or phone keyboard	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

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Q18.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Being unable to solve addition or subtraction calculations	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

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Q19.

	Much less often	Slightly less often	The same as before	Slightly more often	Much more often
Being unable to solve multistep calculations (i.e. percentages)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

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Do you have any further comments about the changes you have observed in memory and processing in your loved one/ friend?

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About you and the patient

What is your relationship to the patient?

Age of patient

Gender of patient

Approximate date of patient diagnosis

Tumour location

Approximate end date of radiotherapy

Was the full course of radiotherapy completed by the patient?

- yes
- no

If you selected 'no', approximately how much was completed?

How did you find out about this survey?

Survey Instructions

For these questions please answer how often you observe, or patients and family members report, the following situations.

Each question has a free text box. Please feel free to add further details if you would like to explain your answers further

Professional observation

Q1.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Having to double-check that they have done something that they should have (i.e. locking the door)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q2.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Being unable to recall events in the order that they occurred	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q3.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Being unable to recall something they were told in the last week without prompt	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q4.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Forgetting that they had read something	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q5.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Having to re-read a piece of text to fully understand the meaning	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q6.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Getting the feeling that a word is 'on the tip of their tongue'	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q7.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Forgetting to do something they had planned and wanted to do	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q8.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Having difficulty remembering details of what happened the day before	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q9.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Losing their train of thought whilst speaking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Q10.

Please don't select more than 1 answer(s) per row.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Being unable to stay engaged when listening to someone talking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

Professional observation (cont.)

Q11.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Finding that they get details of what someone has told them mixed up or confused	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q12.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Realising that they have repeated themselves or asked the same questions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

--	--

Q13.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Misplacing items around the home	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

--	--

Q14.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Not knowing 'where to start' when undertaking a task	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

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Q15.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Being unable to efficiently multitask	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

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Q16.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Finding it a challenge to write by hand or draw	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

--	--

Q17.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Having difficulty typing on a computer or phone keyboard	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q18.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Being unable to solve addition or subtraction calculations	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Q19.

	Never	Rarely	Occasionally	Frequently	Very Frequently
Being unable to solve multistep calculations (i.e. percentages)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any further information:

<input type="text"/>	
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Do you have any further comments about memory and processing in patients?

<input type="text"/>	
----------------------	--

About you

Which is your primary profession?

- Neuro-oncology Doctor
- Other specialised doctor (Please specify)
- General practitioner
- Oncology nurse
- Other specialised nurse (Please specify)
- Nurse
- Care home, or home care staff
- Clinical researcher (Please specify research area)
- Occupational Therapist
- Speech and language therapist
- Physiotherapist
- Clinical neuro-psychologist
- Other (Please specify)
- Prefer not to say

Please specify:

How did you find out about this survey?

Thank you

Thank you for your participation.

If you would like any further information regarding this study, please feel free to contact Francesca Mazzaschi at mazzaschifi@cardiff.ac.uk

In addition, if you are in need of further information regarding cancer care and support, please do not hesitate to contact the following:

Marie Curie

online at: <http://www.mariecurie.org.uk/help/support>

by phone: 08000902309 (*Mon-Fri: 8am-6pm sat-sun: 11am-5pm*)

Macmillian Cancer Support

online at: <http://macmillan.org.uk>

by phone: 08088080000 (*Mon-Sun: 8am-8pm*)

Key for selection options

24 - Age

18-25

26-35

36-45

46-55

56-65

66-74

75+

25 - Gender

Male

Female

Other

Prefer not to say

27 - Tumour location

Frontal lobe
Parietal lobe
Occipital lobe
Temporal lobe
Cerebellum
Brain stem
Unknown

52 - Age of patient

18-25
26-35
36-45
46-55
56-65
66-74
75+

53 - Gender of patient

Male
Female
Other
Prefer not to say

55 - Tumour location

Frontal lobe
Parietal lobe
Occipital lobe
Temporal lobe
Cerebellum
Brain stem
Unknown

Supplementary Appendix C: Participant Information Sheet (Focus Group)



PARTICIPANT INFORMATION SHEET

Stakeholder meeting to aid the development of a screening tool for the cognitive deficits experienced by patients with high-grade glioma after receiving radiotherapy.

You are being invited to take part in a stakeholder meeting. Before you decide whether or not to take part, it is important for you to understand why the research is being undertaken and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish.

Thank you for reading this.

1. What is the purpose of this research project?

This meeting is taking place as part of a doctoral project that is looking at developing a screening tool for the cognitive changes experienced by patients with high-grade glioma after receiving radiotherapy.

Following a review of the literature surrounding cognitive changes reported in patients with brain tumours after receiving radiotherapy, we conducted a public survey to establish an understanding of how high-grade glioma patients experience the highlighted changes in their day-to-day lives. The survey was aimed to ask patients, family members, carers, and healthcare professionals to share their experiences of day-to-day mental tasks and how they have changed since undergoing radiotherapy.

As with the review, we found that patient cognition is affected in a variety of ways. Due to this variation, it is necessary to highlight which changes are the most detrimental to patient quality of life. This is required to ensure that the use of any potential screening tool has the maximum effect on preserving quality of life.

The aim of this event is to prioritise the results of the review and survey. This will work to form an outline of the key components needed to develop a simple screening tool.

Why have I been invited to take part?

You have been invited because of your experience as:

- A patient diagnosed with high-grade glioma
- A family member or friend of a patient with high-grade glioma
- A healthcare professional with direct interactions with high-grade glioma patients (i.e Neuro-oncologist or Neuro-oncology nurse)
- A healthcare professional that would be involved in the referral process (i.e GP, Neuropsychologist, or nurse)

2. Do I have to take part?

No, your participation in this meeting is entirely voluntary and it is up to you to decide whether or not to take part. If you decide to take part, we ask that you to sign a consent form. If you decide not to take part, you do not have to explain your reasons and it will not affect your legal rights

You are free to withdraw your consent to participate in the research project at any time, without giving a reason, even after signing the consent form.

3. What will taking part involve?

Taking part will involve attending one meeting via zoom where you will be asked to share your opinions on the results of the previously mentioned survey. We will discuss how cognitive changes effect patient quality of life and how these changes could be best identified. As an aid to the discussions, we will be using an application called Mentimeter. This is a simple to use application that will allow you to vote on different topics and ensures that everyone will have the opportunity to share their thoughts.

The reason we ask you to fill out a consent form is so that we know you agree and are aware to the meeting will be recorded and the analysis of Mentimeter responses as part of our work to develop the screening tool.

4. Will I be paid for taking part?

No. You should understand that any suggestions you give will be as a gift and you will not benefit financially in the future should this research project lead to the development of a new screening tool.

5. What are the possible benefits of taking part?

There will be no direct advantages or benefits to you from taking part, but your contribution will help us in making sure that the screening tool we are working towards developing provides the maximum benefit to patients and their loved ones.

6. What are the possible risks of taking part?

Due to the sensitivity of the topic, we understand that some participants may find subject matters addressed in this study to be distressing. For this reason, we would like to remind you that you may leave the meeting at any time.

7. Will my taking part in this research project be kept confidential?

All information collected from you during the research project will be kept confidential and any personal information you provide will be managed in accordance with data protection legislation. Please see ‘What will happen to my Personal Data?’ (below) for further information.

8. What will happen to my Personal Data?

Cardiff University is the Data Controller and is committed to respecting and protecting your personal data in accordance with your expectations and Data Protection legislation. Further information about Data Protection, including:

- your rights
- the legal basis under which Cardiff University processes your personal data for research
- Cardiff University’s Data Protection Policy

- how to contact the Cardiff University Data Protection Officer
- how to contact the Information Commissioner's Office

may be found at <https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection>

Any personal data obtained will remain confidential in line with the Data Protection Act (2018) and GDPR (2016). No identifiable information will be included in the data that is to be reported. For example, people's names, addresses, hospital details will be removed from any direct quotes used.

Individual details such as diagnosis, treatment, and occupation details will not be included in the report and data will be stored in a secure folder on the Cardiff University Network, only available to the research team.

We would like to once again remind you that you are free to withdraw at any time prior to or during the meeting, however any responses recorded prior to withdrawal cannot be withdrawn and will be analysed and reported.

Anonymous data will be retained for five years.

9. What will happen to the data collected at the meeting?

The video/audio recording will be used to help summarise the matters discussed. If any direct quotes are used in any reports, they will be completely anonymised.

Your responses on any polls or word clouds will be analysed in order to develop an outline of key components. This data will also be anonymised.

10. What if there is a problem?

If you wish to complain or have grounds for concerns about any aspect of the manner in which you have been approached or treated during the course of this research, please contact Francesca Mazzaschi at mazzaschifi@cardiff.ac.uk . If your complaint is not managed to your satisfaction, please contact the Cardiff University Postgraduate Medic team at pgrmedic@cardiff.ac.uk

11. Who is organising and funding this research project?

The research is organised by Francesca Mazzaschi at the Marie Curie Palliative Care Research Centre at Cardiff University under the supervision of Professor Annmarie Nelson and Professor Anthony Byrne.

The research is currently funded as a Marie Curie studentship.

12. Who has reviewed this research project?

This research project has been reviewed and given a favourable opinion by the Cardiff University School of Medicine Ethics Committee.

13. Further information and contact details

Should you have any questions relating to this research project, you may contact us during normal working hours:

Francesca Mazzaschi PhD Research Student
Division of Population Medicine
Tel: 02922511096

Email: mazzaschifi@cardiff.ac.uk

Thank you for considering to take part in this research project.

Supplementary Appendix D: Consent form (Focus Group)



CONSENT FORM

	Please initial box
I confirm that I have read the information sheet dated 13.1.21 version 2 for the above research project.	
I confirm that I have understood the information sheet dated 13.1.21 version 2 for the above research project and that I have had the opportunity to ask questions and that these have been answered satisfactorily.	
I understand that my participation is voluntary, and I am free to withdraw at any time without giving a reason and without any adverse consequences (e.g. to medical care or legal rights, if relevant). I understand that if I withdraw at any point throughout the meeting, information about me that has already been obtained may be kept by Cardiff University.	
I understand that data collected during the meeting may be looked at by individuals from Cardiff University or from regulatory authorities, where it is relevant to my taking part in the research project. I give permission for these individuals to have access to my data.	
I consent to the processing of any personal information I may give during the meeting for the purposes explained to me. I understand that such information will be held in accordance with all applicable data protection legislation and in strict confidence, unless disclosure is required by law or professional obligation.	
I understand who will have access to personal information provided, how the data will be stored and what will happen to the data at the end of the research project.	
I consent to the meeting being recorded for the purposes of the research project and I understand how it will be used in the research.	
I understand that anonymised excerpts and/or verbatim quotes from the meeting may be used as part of the research publication.	
I consent for my responses on Mentimeter to be analysed for the purpose of the project.	

I understand how the findings and results of the research project will be written up and published.	
I agree to take part in this research project.	

Title of research project: Stakeholder meeting to aid the development of a screening tool for the cognitive deficits experienced by patients with high-grade glioma after receiving radiotherapy.

SREC reference and committee: SMREC 20/115

Name of Chief/Principal Investigator: Professor Annmarie Nelson

Name of participant (print)

Date

THANK YOU FOR PARTICIPATING IN OUR RESEARCH

PLEASE KEEP A COPY OF THIS FORM

Supplementary Appendix E: Invitation Email (Focus Group)

Invitation email:

Dear (Participant name)

Thank you for showing interest in taking part in our stakeholder event.

This event will take place on the **2nd of February 2021 at 13:00 GMT until 15:30 GMT.**

This event will require the use of a Zoom enabled device and additional access to the internet to use interactive software throughout the meeting.

We kindly ask you to take a few minutes to read through the attached information sheet and return the attached consent form before joining the meeting.

Please click the link below to join the meeting: (Meeting link to go here)

If you have any further questions, please do not hesitate to get in touch.

Kind regards,

Francesca Mazzaschi

Supplementary Appendix F: Thank you email (Focus Group)

Thank you email:

Dear (Participant name here)

I would like to thank you for taking part in our recent stakeholder event on the 2nd of February.

Your contributions are greatly appreciated, and I hope you found the event to be of value.

If you, or your loved one are in need of further information regarding cancer care and support, please do not hesitate to contact the following:

Marie Curie

online at: <http://www.mariecurie.org.uk/help/support>

by phone: 08000902309 (*Mon-Fri: 8am-6pm sat-sun: 11am-5pm*)

brainstrust

online at: <https://brainstrust.org.uk/>

by phone: 01983 292 405

Macmillian Cancer Support

online at: <http://macmillan.org.uk>

by phone: 08088080000 (*Mon-Sun: 8am-8pm*)

Kind regards,

Francesca Mazzaschi

Supplementary Appendix G: Participant Information Sheet (Cognitive Interviews)



PARTICIPANT INFORMATION SHEET (V1)

Face validation of a potential screening tool for cognitive deficits experienced by patients with high-grade glioma after receiving radiotherapy.

You are being invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being undertaken and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish.

Thank you for reading this.

14. What is the purpose of this research project?

This study is taking place as part of a doctoral project that is looking at developing an easy to use set of questions (a screening tool) which would help to pick up cognitive (e.g thinking and memory) changes experienced by patients with high-grade glioma after receiving radiotherapy.

We have already conducted a review of the literature describing cognitive changes, followed by a public survey and focus group with patients who have had radiotherapy. From this work, we have been able to establish an understanding of how patients experience cognitive changes as well as how their close family members perceive them.

Using the data collected, we have drafted some questions that are designed to identify when a patient may be suffering with cognitive difficulties following the completion of their treatment. If by using these questions as a screening tool doctors and nurses can more easily identify patients with these problems, then they are more likely to be referred for further support.

The aim of this study is to trial these questions with potential tool users. We hope to apply your feedback to help refine the tool, to ensure it is suitable for users to complete.

Why have I been invited to take part?

You have been invited because of your experience as:

- A patient diagnosed with high-grade glioma
- A family member a patient with high-grade glioma

15. Do I have to take part?

No, your participation in this meeting is entirely voluntary and it is up to you to decide whether to take part. If you decide to take part, we will organise a time and date to suit

you to carry out the interview and we ask that you to sign the consent form that has been sent to you. If you decide not to take part, you do not have to explain your reasons and it will not affect your legal rights.

You are free to withdraw your consent to participate in the research project at any time, without giving a reason, even after giving consent.

16. What will taking part involve?

Taking part will involve attending a single one-to-one meeting via zoom. This meeting will involve you reading through the drafted tool questions followed by a short interview with a member of the research team. In this interview you will be asked various questions about the wording of the tool, whether you found any words or sentences were unclear and to give your overall opinion on the questions as they are currently set out.

17. Will I be paid for taking part?

No. You should understand that any feedback you give will be voluntary and you will not benefit financially in the future should this research project lead to the development of a new screening tool.

18. What are the possible benefits of taking part?

There will be no direct advantages or benefits to you from taking part, but your contribution will help us develop the screening tool to the maximum benefit to patients and their loved ones.

19. What are the possible risks of taking part?

Due to the sensitivity of the topic, you may find some of the conversation to be distressing. For this reason, we would like to remind you that you may leave the meeting at any time.

If you need further information regarding cancer care and support, please do not hesitate to contact the following:

Marie Curie

online at: <http://www.mariecurie.org.uk/help/support>

by phone: 08000902309 (*Mon-Fri: 8am-6pm sat-sun: 11am-5pm*)

brainstrust

online at: <https://brainstrust.org.uk/>

by phone: 01983 292 405

Macmillian Cancer Support

online at: <http://macmillan.org.uk>

by phone: 08088080000 (*Mon-Sun: 8am-8pm*)

20. Will my taking part in this research project be kept confidential?

All information collected from you during the research project will be kept confidential and any personal information you provide will be managed in accordance

with data protection legislation. Please see ‘What will happen to my Personal Data?’ (below) for further information.

21. What will happen to my Personal Data?

Cardiff University is the Data Controller and is committed to respecting and protecting your personal data in accordance with your expectations and Data Protection legislation. Further information about Data Protection, including:

- your rights
- the legal basis under which Cardiff University processes your personal data for research
- Cardiff University’s Data Protection Policy
- how to contact the Cardiff University Data Protection Officer
- how to contact the Information Commissioner’s Office

may be found at <https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection>

Any personal data obtained will remain confidential in line with the Data Protection Act (2018) and GDPR (2016). No identifiable information will be included in the data that is to be reported. For example, people’s names, addresses, hospital details will be removed from any direct quotes used.

Individual details such as diagnosis, treatment, and occupation details will not be included in the report and data will be stored in a secure folder on the Cardiff University Network, only available to the research team.

We would like to once again remind you that you are free to withdraw at any time prior to or during the meeting, however any responses recorded prior to withdrawal cannot be withdrawn and will be analysed and reported.

Anonymous data will be retained for five years after which it will be deleted.

22. What will happen to the data collected at the meeting?

The video/audio recording will be used to help summarise the matters discussed. The video recording will not be included in the data analysis. If any of your recorded quotes are used in any reports, they will be completely anonymised.

23. What if there is a problem?

If you wish to complain or have grounds for concerns about any aspect of the manner in which you have been approached or treated during the course of this research, please contact Professor Annmarie Nelson at nelsona9@cardiff.ac.uk. If your complaint is not managed to your satisfaction, please contact the Cardiff University Postgraduate Medic team at pgrmedic@cardiff.ac.uk

24. Who is organising and funding this research project?

The research is organised by Francesca Mazzaschi at the Marie Curie Palliative Care Research Centre at Cardiff University under the supervision of Professor Annmarie Nelson, Professor Anthony Byrne, Dr Stephanie Sivelle, Professor Katherine Brain and Dr James Powell.

The research is currently funded as a Marie Curie studentship.

25. Who has reviewed this research project?

This research project has been reviewed and given a favourable opinion by the Cardiff University School of Medicine Ethics Committee.

26. Further information and contact details

Should you have any questions relating to this research project, you may contact us during normal working hours:

Francesca Mazzaschi PhD Research Student
Division of Population Medicine
Email: mazzaschifi@cardiff.ac.uk

Thank you for considering taking part in this research project.

Supplementary Appendix H: Consent Form (Cognitive Interviews)



CONSENT FORM

Title of research project: Face validation of a potential screening tool for cognitive deficits experienced by patients with high-grade glioma after receiving radiotherapy.

SREC reference and committee:

Name of Chief/Principal Investigator: Professor Annmarie Nelson

	Please initial box
I confirm that I have read the information sheet dated 7.5.21 version 1 for the above research project.	
I confirm that I have understood the information sheet dated 7.5.21 version 1 for the above research project and that I have had the opportunity to ask questions and that these have been answered satisfactorily.	
I understand that my participation is voluntary, and I am free to withdraw at any time without giving a reason and without any adverse consequences (e.g. to medical care or legal rights, if relevant). I understand that if I withdraw at any point throughout the meeting, information about me that has already been obtained may be kept by Cardiff University.	
I understand that data collected during the meeting may be looked at by individuals from Cardiff University or from regulatory authorities, where it is relevant to my taking part in the research project. I give permission for these individuals to have access to my data.	
I consent to the processing of any personal information I may give during the meeting for the purposes explained to me. I understand that such information will be held in accordance with all applicable data protection legislation and in strict confidence, unless disclosure is required by law or professional obligation.	
I understand who will have access to personal information provided, how the data will be stored and what will happen to the data at the end of the research project.	
I consent to the meeting being recorded for the purposes of the research project and I understand how it will be used in the research.	

I understand that anonymised excerpts and/or verbatim quotes from the meeting may be used as part of the research publication.	
I understand how the findings and results of the research project will be written up and published.	
I agree to take part in this research project.	

Name of participant (print)

Date

THANK YOU FOR PARTICIPATING IN OUR RESEARCH

PLEASE KEEP A COPY OF THIS FORM

Supplementary Appendix I: Thank you email (cognitive Interviews)

Thank you email:

Dear (Participant name here)

I would like to thank you for helping to evaluate our screening tool.

Your contributions are greatly appreciated, and I hope you found the meeting to be of value.

If you, or your loved one are in need of further information regarding cancer care and support, please do not hesitate to contact the following:

Marie Curie

online at: <http://www.mariecurie.org.uk/help/support>

by phone: 08000902309 (*Mon-Fri: 8am-6pm sat-sun: 11am-5pm*)

brainstrust

online at: <https://brainstrust.org.uk/>

by phone: 01983 292 405

Macmillian Cancer Support

online at: <http://macmillan.org.uk>

by phone: 08088080000 (*Mon-Sun: 8am-8pm*)

Kind regards,

Francesca Mazzaschi

Supplementary Appendix J: Accepted abstracts

(Cardiff University PGR MEDIC conference) presented as a 5 minute thesis (2019)

Developing a screening tool for the late effects of treatment for brain cancers

Francesca Mazzaschi^{1,2}

Supervisors: Professor Annmarie Nelson^{1,2}, Professor Anthony Byrne^{1,2}, Professor Kate Brain² and Dr Stephanie Sivell^{1,2}

1 Marie Curie Palliative Care Research Centre, Cardiff UK, 2 Division of Population Medicine, School of Medicine, Cardiff University, Cardiff UK.

Funding: Marie Curie PhD studentship

In the UK approximately 9,000 people are diagnosed with primary brain tumours each year. Around half of which are malignant. The most common type of malignant brain tumour are gliomas. High-grade glioma is particularly aggressive and accompanied by an array of debilitating symptoms. These can range from physical, psychological and cognitive deficits. Symptom burden is heightened by the substantial effects of radiotherapy or chemo-radiotherapy which cause both acute and late-delayed side effects. This accumulation of symptoms, especially those of a cognitive and psychological nature, can alter the patient's relationships with those around them. Whilst neuro-rehabilitation and supportive interventions are emerging in the UK, there are currently no nationally agreed referral criteria. It is therefore necessary to establish a standardised screening tool that is easily administered in a non-specialised environment. The overall aim of this project will be to develop a readily accessible and clinically applicable screening tool designed to detect the neurocognitive effects of brain irradiation and combined chemo-radiotherapy. Methods will include; (1) a complete a systematic review of the current literature and on-going trials (2) presentation of the results of the systematic review for an expert consensus to determine the symptoms of interest and treatment options available (3) design a screening tool to be tested with patients and carers with cognitive interviews. This will lead to the implementation of an easily accessible, clinically applicable screening tool. This will enable patients receiving high doses of brain radiotherapy to access neurocognitive therapy that may lessen their symptom burden.

Key words: High grade glioma, Radiotherapy, Chemo-radiotherapy, Cognitive side effects, Neuro-rehabilitation.

(European Association of Palliative Care Annual Conference) presented as a poster (2020)

What are the cognitive deficits observed in adults with brain cancer after receiving radiotherapy or combined chemo-radiotherapy? A systematic review.

Background: Between 2014 and 2016, 11,725 people were diagnosed with brain tumours. Standard treatment consists of surgery, radiotherapy and chemotherapy. Treatment of high-grade gliomas, which account for 70-80% of primary brain tumours, is conducted with palliative intent. High-grade glioma is accompanied by an array of debilitating symptoms. Symptom burden is heightened by the effects of radiotherapy or chemoradiotherapy. The symptoms faced by the patient, especially those of a cognitive and psychological nature,

can alter the patient's relationships with those around them and is in turn detrimental to quality of life. Aims: Identifying cognitive deficits as early as possible is essential to support the patient, and to help those around them emotionally adjust. It also provides a more in depth understanding of the patient's needs, and possibly allow access to appropriate neurorehabilitation. This systematic review will work to identify the cognitive deficits associated with brain irradiation. Methods: A formal search of Medline, Cumulative Index to Nursing and Allied Health Literature, EMBase, PsychINFO, Web of Science, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov and World Health Organisation International Clinical Trials Registry Platform was conducted. Studies were reviewed and critically appraised independently by two reviewers. As included studies are heterogeneous, a narrative synthesis was conducted. Results: 4027 papers were identified in the initial search. Screening resulted in 49 papers being included in the final report. The most commonly used method of cognitive assessment reported was the Mini Mental State Examination (MMSE). Deficit was most commonly reported in areas of Recall and Attention. Conclusion: Whilst many studies reported a decline in cognition, the lack of sensitivity of the MMSE may have resulted some areas of cognition being overlooked. This highlights the need for a more sensitive standardised screening tool.

(European Association of Palliative Care Annual Conference) presented as a poster (2020)

Everyday memory and processing alteration in patients with high-grade glioma after radiotherapy: A mixed method, public survey.

Mazzaschi F, Sivell S, Byrne A, Brain K, Powell J & Nelson A

Background: Symptoms experienced due to high-grade glioma (HGG) and its subsequent treatment can negatively affect patient quality of life. Cognitive changes can be particularly difficult for the patient and those around them to understand due to their subjective nature. Aims: Primary: to better understand the areas of cognition that are altered in patients with HGG after receiving radiotherapy (RT). Secondary: To establish an understanding of how patients and their families may perceive changes. Methods: A mixed method, public survey of stakeholder experiences of everyday cognitive functioning. Patients, their family and friends, and healthcare professionals (HCPs) were asked how often they experience/observe difficulty with daily mental tasks since undergoing RT. Likert scale questions identified frequency of experiencing specific deficits using descriptive statistics. Free text data regarding participants' experiences were analysed thematically. Results: 143 participants completed the survey comprising patients (n=91), family and friends (n=46) and HCPs (n=6) Patients and family and friends reported an average increase in difficulty with daily tasks. HCPs indicated that they had observed difficulty in all daily tasks. Free text responses indicate that whilst decline in cognition was observed by family and friends at a similar frequency to the experiences of patients and both acknowledge the strain on daily living, there is a distinction between how these changes are described. Conclusion: Decline in patients with HGG is variable between patients and can be experienced across all domains of cognition. Decline has an obvious negative impact on the quality of life of both patients and those around them. For an accurate insight into an

individual's cognitive needs, it is important to address both the experiences of the patient, but also the observations and experiences of those around them. This may offer insight into the overall impact that is not reported by patients.

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Cognitive alteration in patients with high-grade glioma after radiotherapy

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Background: Symptoms experienced due to high-grade glioma (HGG) and its treatments can negatively affect patient quality of life. Cognitive changes can be especially difficult to understand as they are more challenging to quantify and describe. Aims: Primary: to better understand the areas of cognition altered in patients with HGG after radiotherapy (RT). Secondary: to establish an understanding of how patients and their families may perceive changes. Methods: A mixed method, public survey of stakeholder experiences of everyday cognitive functioning, asking patients, their family and friends (FF), and healthcare professionals (HCP) how often they experience/observe difficulty with daily mental tasks after RT. Likert scales were coded 1 to 5. For patients and FF, 1 represented 'much less often' and 5 'much more often'. For HCP 1 represented 'never' and 5 'very frequently'. Responses were descriptively analysed. Open-ended questions were thematically analysed. Results: 143/148 participants (97%) completed the survey (patients n=91; FF n=46; HCP n=6). Many situations received responses ranging 1 to 5. Patients, and FF, reported mean responses to be above 3 (same as before) for all questions, ranging from 3.4 to 4.3. HCPs reported observing patient difficulty in all daily tasks. Free text responses show that patients and FF acknowledged a strain on daily living, with recurrent themes including patient reliance on others and a decline of emotional wellbeing of patients. Distinctions between responses show FF focus more on patient personality changes and how patient-family interactions are negatively affected. Patients describe changes first-hand, with emphasis on coping mechanisms. Conclusion: Decline may be experienced across all cognitive domains. This negatively impacts both patients and those around them. Whilst both express this, both give unique insight as to how this is experienced. Both perspectives should be accounted for when assessing a patient's cognitive state.

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Incorporation and evaluation of the Patient and Public Involvement national standards within doctoral research focussed on the improvement of quality of life of patients with high-grade glioma

Introduction:

The benefits of including patient and public involvement (PPI) are increasingly acknowledged by both researchers and funding bodies. However, it is not usually a required aspect of doctoral research and no specific guidelines for students wishing to incorporate PPI. PPI was integrated throughout a PhD project working towards the development of a screening tool for cognitive deficits experienced by patients with high-grade glioma (HGG), adhering to the UK national standards as much as possible.

Aims:

To incorporate and evaluate the extent to which PPI adhered to the UK national standards and the value it added to this PhD project overall.

Methods:

PPI activities, and input to this project, were evaluated against the national standards and explored with prompts presented in an audit tool developed by Nelson and colleagues.

Result:

It was challenging as a new researcher, to implement PPI by following the standards alone. As the standards are dependent on the policies of the institutional host (Wales Cancer Research Centre (WCRC)) in various ways, this led to some confusion as to the responsibilities of the researcher. Therefore, more project specific guidelines could be beneficial. That being said, the standards were met with a combination of steps taken within the project, the resources available and the procedures followed by the WCRC. Adhering to these ensured that the research was relevant for HGG patients and conducted with their needs in mind.

Conclusion:

This evaluation shows the importance of PPI in health research and demonstrates how it can be successfully implemented in doctoral research. It also serves to highlight the gaps in guidance for researchers, as well as the lack of clear guidance available for new researchers.

Impact:

This evaluation highlights both the value of organisations such as the WCRC and the need for more project specific guidelines.