A Systematic Review of the Effectiveness of Interventions (Pharmaceutical and Psychosocial) for Cognitive and Learning Impairments in Children Diagnosed with a Brain Tumour

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The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

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Finally I would like to dedicate this thesis to my late father and mother, who never saw my dream become a reality.
ABSTRACT

Tumours of the brain and the central nervous system (CNS) account for a quarter of all childhood cancers. Despite being a rare condition, it is the most frequent cause of death from disease in children aged 1-14 years, and accounts for just under a fifth of all bereavements in childhood. Recent medical advancements together with improvements in neurosurgery, radiation therapy and chemotherapy have facilitated earlier diagnosis. This has resulted in an increase in the aggregated survival rates of children diagnosed with brain tumours. As a result, children are living longer with greater neurocognitive morbidity. Statistics indicate that 40-100% of long-term survivors of a brain tumour will demonstrate some degree of cognitive dysfunction. Hence, the National Health Service (NHS) and other international health care providers are increasingly focusing on the rehabilitation needs and quality of survivorship of this population.

The objectives of this thesis are to identify and evaluate the effectiveness of interventions (pharmaceutical and psychosocial) for cognitive and learning impairment within a paediatric neurooncology population. This will be addressed via a systematic review of all current research using a selection of Electronic Databases. The result of which will hope to provide a guide for appropriate service provision to address long-term neuro-rehabilitation and psychological needs in the future.

A limited number of studies were retrieved in this systematic review; only three studies met the inclusion criteria. Thus, a narrative review resulted in limited conclusion about the effectiveness of psychosocial and pharmaceutical interventions on neurocognitive and learning impairments in a paediatric brain tumour population. Of the studies retrieved, all demonstrated promising results for the future of paediatric rehabilitation. However, it is the limited number of studies retrieved that is of most interest, highlighting a very small
evidence base and potentially problematic research design. Solutions to these difficulties are suggested.
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<td>CNS:</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>NHS:</td>
<td>National Health Service</td>
</tr>
<tr>
<td>IQ:</td>
<td>Intelligence Quotient</td>
</tr>
<tr>
<td>QOS:</td>
<td>Quality of Survival</td>
</tr>
<tr>
<td>MPH:</td>
<td>Methylphenidate Hydrochloride</td>
</tr>
<tr>
<td>ADHD:</td>
<td>Attention Deficit Hyperactivity Disorder</td>
</tr>
<tr>
<td>MTA:</td>
<td>Multimodal Treatment Study</td>
</tr>
<tr>
<td>PRISMA:</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
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CHAPTER ONE: INTRODUCTION

The detection and management of paediatric brain tumours have developed significantly with recent advancements in science (Moore, 2005; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004). The result of this is most clearly illustrated by an increase in survival rates from 31% (1966-1970) to 71% (2001-2005) (Childhood Cancer Statistics, 2010). However, as survival rates increase, the impact of brain tumours and their treatment regimens (neurosurgery, radiotherapy and chemotherapy) have become of greater concern to clinicians and researchers. Research demonstrates that many children will experience neurocognitive deficits as a consequence of both their brain tumour and the medical interventions used in their treatment, the results of which have a significant impact on children’s cognitive development and learning outcomes (Mulhern et al, 2004). With the decrease in the mortality rate, research has established that children diagnosed with a brain tumour are now living longer with greater morbidity; consequently there needs to be further interventions to minimise the impact of acquired cognitive and learning deficits (Sands, 2009). Hence, it is important for practitioners to gain a better understanding of the pharmaceutical and psychosocial interventions used to facilitate neurocognitive recovery, after the acute phase of treatment, for children surviving a brain tumour. Consequently, this understanding will facilitate the development of recommendations for education systems and the progression of the child’s transition into adult services later in their life.

The aim of this thesis is to systematically review the literature on the effectiveness of interventions (pharmaceutical and psychosocial) aimed at alleviating cognitive and learning impairments within a paediatric brain tumour population.
1.1 Neurocognitive and Learning Deficits

To understand the aim of this review it is important to be aware of the outcomes of routine assessment in clinical neuropsychology and cognitive research. These include the long-term neurocognitive (for example deficits in memory, attention, executive functioning) and learning consequences (for the purposes of this thesis this is defined as difficulties in the acquisition of new information and/or impaired academic attainment) of brain tumours in a paediatric population. It is important to note that neurocognitive consequence impact on learning. Thus these deficits are reflected in assessments of cognitive functioning, academic attainment and intelligence quotient (IQ). Deficits in visual and motor difficulties, sensory impairments and auditory processing can result in difficulties with attention and speed of processing, which consequently can impact on academic attainment, particularly the learning of new information.

1.1.1 Cognitive Functioning

A brain tumour can have a profound impact since the development of a space occupying lesion, mass effect and its location can have implications for a patient’s neurocognitive profile (Iuvone et al, 2011). Additional secondary factors such as neurosurgery, chemotherapy and radiation therapy may also have an adverse effect on developing CNS and neurocognitive functioning (Moore, 2005). The prevalent neurocognitive impairments, which are routinely assessed in clinical neuropsychology and cognitive research include: altered processing speed, attention, executive functioning, memory, episodic and working memory (auditory and spatial) (Copeland, Moore, & Ater, 1999; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008; Mulhern et al, 2001; Mulhern, et al 2004b). Table 1 outlines areas of clinical importance and impairments experienced by individuals as a consequence of paediatric brain tumours. Although the table examines each deficit individually, it is not
**Table 1.** Key aspects of cognitive functioning identified in routine clinical neuropsychology assessment and cognitive research of paediatric brain tumours population.

<table>
<thead>
<tr>
<th>Cognitive Functions</th>
<th>Definition</th>
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<tr>
<td>Executive Functioning</td>
<td>Executive functioning is a complex aspect of cognitive processing, which requires the co-ordination of several sub processes to achieve a particular goal. Examples include task switching and planning (Elliott, 2003).</td>
</tr>
<tr>
<td>Memory</td>
<td>Memory involves the structures and processes involved in the storage and subsequent retrieval of information. Memory is involved in processing of information. This information takes many different forms, e.g. images, sounds or meaning. Memory can be separated into three separate stages: sensory, short-term, and long-term (Matlin, 2005).</td>
</tr>
<tr>
<td>Working Memory</td>
<td>Working memory is a temporary storage and workspace in the brain. It is a system, which holds and processes moment-to-moment information before storing new knowledge in the long-term memory. It is important in higher order thinking, learning, and achievement. It is also important for cognitive flexibility and planning ability, as well as learning and the ability to self-monitor (Eysenck &amp; Keane, 2005; Just &amp; Carpenter, 1992).</td>
</tr>
<tr>
<td>Attention</td>
<td>Attention is considered the foundation of most cognitive and neuropsychological functions. It is the selectivity of processing: how we actively process specific information presented to us in our environment (Cooley &amp; Morris, 1990; Eysenck &amp; Keane, 2005).</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>The speed at which cognitive processes can be carried out (Bull &amp; Johnston, 1997).</td>
</tr>
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</table>
the intention to suggest that each component is neuropsychologically distinct from the others.

1.1.2 Academic Attainment

The learning consequences of paediatric brain tumours are often described in relation to academic attainment. These children may experience problems with handwriting, spelling, reading, vocabulary, mathematics, attention, ability to complete tasks on time, planning, organisation and problem-solving, with literacy and numeracy being the most common academic difficulties (Upton & Eiser, 2006). The term learning outcomes has to be treated with caution as the learning of new information is not just related to academic attainment, but will also affect IQ. In comparison to their healthy peers, the paediatric brain tumour population incur secondary consequences such as IQ loss and sub-optimal academic achievement (Mulhern & Butler, 2004). It is hypothesised that learning impairments experienced by the paediatric brain tumour population are also closely associated with neurocognitive impairments (Mulhern & Butler, 2004).

1.1.3 IQ

Neurocognitive outcomes in many studies have been conceptualised primarily in terms of a measurement of the patient’s overall cognitive ability. This is presented as previously noted in an individual’s academic attainment and also in their IQ (Mulhern et al, 2004). Subsequently IQ loss has been demonstrated among this population (Mulhern & Butler, 2004). A number of studies, which are discussed in this introduction, have used IQ and academic achievement as identifiers for neurocognitive impairment, but it is important to note no causal relationships have been identified. Thus Dennis, Hetherington, and Spiegler
(1998) advocate an investigation of the impact on the “acquisition of knowledge” or the process by which children learn and acquire information over time, in addition to assessing “knowledge availability” in children. The authors suggest that cognitive deficits may be related to deficiencies in the basic processes by which knowledge is acquired. Levisohn, Cronin-Golomb, and Schmahmann (2000) suggest that numerous aspects of cognition, including attention and working memory, may underlie changes in IQ and academic performance. This is supported by Fry and Hale (2000) whose research using a healthy population found that almost half of developmental increases in IQ can be attributed to age related improvements in working memory and processing speed. They attribute the other to alternative forms of maturation, such as the changes in the frontal cortex during childhood and adolescence. Thus deficits in areas such as attention and memory may result in difficulties acquiring new information; the consequences of which are reflected in IQ and academic achievement. Hence, studies need to focus on how brain tumours and their treatment affect cognitive components, which are utilised in the acquisition of knowledge. Although the distinctions between these factors are important they remain outside of the scope of this thesis.

1.2 Tumour Type and Known Deficits

As already noted, the degree and type of impairment is dependent upon various factors including the type, location, size, invasiveness and treatment performed (Nejat, El Khashab, & Rutka, 2008). For example, Figure 1 demonstrates the varied presentations of patients depending upon only the type and location of the brain tumour. Image A illustrates a child with a diagnosis of a medulloblastoma who presented with a brief history of nausea, vomiting and headaches; this is also associated with memory and attention deficits (Crawford, MacDonald, & Packer, 2007). Image B presents a craniopharyngioma (midline suprasellar mass lesion with invagination into the third ventricle); this patient presented with
progressive visual loss and headaches. The neurocognitive deficits associated with this tumour include processing speed and memory (Carpentieri et al, 2001; Thompson, Phipps, & Hayward, 2005). Image C presents an ependymoblastoma. This patient had a brief history of seizures, leg weakness and cognitive impairments to attention and memory (Maksoud, Hahn, & Engelhard, 2002). Finally, Image D demonstrates a third ventricular pineoblastoma, symptoms included a history of vomiting and headaches and non-specified cognitive deficits (Jakacki et al, 1995; Nejat et al., 2008).

**Figure 1.** Sagittal magnetic resonance images of paediatric brain tumours in different brain regions (Nejat et al, 2008) reproduced with permission.
Most paediatric tumours are located within the posterior fossa, particularly in patients diagnosed under the age of ten years (Muzumdar, Mahore, Balasubramaniam, & Goel, 2009). The posterior fossa is a small space located near the brain steam and the cerebellum, as demonstrated in Figure 2. This area is mainly concerned with the maintenance of consciousness, respiration, pulse, blood pressure, facial expression and sensations, hearing and swallowing mechanisms (Muzumdar et al, 2009). Tumours in this area are at risk of blocking the flow of spinal fluid, resulting in increased pressure on the brain and the spinal cord due to limited space (Muzumdar et al, 2009). There are also increasing concerns about tumours in the posterior fossa and damage to the cerebellum, which has been noted to modulate mental and social functions (Riva & Giorgi, 2000; Schmahmann, 2013). Tumours in the posterior fossa can have implications for severe disability in the areas of hemiparesis, speech disorders and facial or ocular muscle palsies, and can lead to hydrocephalus and mortality (Muzumdar et al, 2009).

Figure 2. Posterior fossa ependymoma in an 11-month-old female infant (Vázquez et al, 2011) reproduced with permission.
Brain tumours can occur in different locations, in addition to this there are different types of brain tumours. The World Health Organisation has published a classification system for tumours of the central nervous system according to their location and histology (Louis et al, 2007). The most common tumours are supratentorial low-grade tumours, medulloblastoma, brain stem glioma, cerebellar astrocytomas, supratentorial high-grade tumours, and craniopharyngioma (Strother et al, 2002). However, the most frequent diagnosed malignant brain tumour among paediatric patients is that of a medulloblastoma, these account for 10-20% of all paediatric brain tumours (Dhall, 2009; Whelan, Krouwer, Schmidt, Reichert, & Kovnar, 1998). The most prevalent brain tumours and their deficits are displayed in Table 2.

Table 2 demonstrates that each type of tumour can result in a variety of neurocognitive, psychological and learning deficits. Furthermore, it illustrates the difficulties in determining which factors (location, type and treatment) may account for neurocognitive and learning deficits. Evidence suggests that other factors in addition to tumour type (moderating factors) may also account for the deficits; these additional factors will be discussed later in this introduction.

Although it can be difficult to identify the origin of a deficit, the literature suggests that deficits may be a consequence of damage to the cortical and subcortical white matter (Moore, 2005; Mulhern et al, 2004b). To further understand the neurocognitive consequences of brain tumours, it is important to understand how the brain develops and the possible impact that the treatment of paediatric tumours may have on the brain.
<table>
<thead>
<tr>
<th>Tumour</th>
<th>Location in the brain</th>
<th>Frequency in Paediatric Population</th>
<th>Interventions</th>
<th>Deficits</th>
<th>References</th>
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<td>Medulloblastoma</td>
<td>Infratentorial compartment. Tend to be invasive of normal cerebellar tissue.</td>
<td>15-25% of paediatric brain tumours most frequently occur between 3 and 4 years and 8 and 9 years.</td>
<td>Surgical resection and radiotherapy are an essential part of treatment (radiotherapy is either delayed or not given to children under the age of three). Chemotherapy is used selectively.</td>
<td>Attention, memory, particularly relating to visual and sustained attention, verbal/spatial memory, nonverbal abstract thinking, verbal abstract thinking, processing speed, executive functioning and language deficits. Impact on quality of life. Lower academic achievement scores, lower IQ.</td>
<td>(Crawford et al, 2007; Edelstein, Spiegler, Fung, Panzarella, Mabbott, Jewitt, D'Agostino, Mason, Bouffet, &amp; Tabori, 2011; Modha et al, 2000; Mulhern &amp; Butler, 2004; Mulhern et al, 2001; Nejat et al, 2008; Ribi et al, 2005; Ruika &amp; Kuo, 2004; Whelan et al, 1998).</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Infratentorial compartment. 70% occur in the posterior fossa. 2.9% of central nervous system tumours in this age category. Peak incident from birth to 4 years.</td>
<td>Surgical resection identified as the best cure. However, only 30-50% can be completely resected. Usually require radiotherapy. Chemotherapy is given to younger children as a substitute for radiotherapy.</td>
<td>Memory recall decreased manual dexterity, spatial working memory, processing speed, language processing and verbal memory deficits.</td>
<td>Attention and visuospatial memory impairments. Modest declines in reading, significantly lower IQs, lower nonverbal intellectual functioning, lower academic skills in writing and math, and impairments in visual–motor abilities.</td>
<td>(Di Pinto, Conklin, Li, Xiong, &amp; Merchant, 2010; Figarella-Branger et al, 2000; Maksoud et al, 2002; Nejat et al, 2008)</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>Supratentorial. Usually occur in the Suprasellar region from epithelial remnants of the Rathke’s pouch. Most common intracranial tumour of childhood (2.5 -9 %). Peak incident 5-9 years.</td>
<td>Managed with a single shunting system in conjunction with endoscopic fenestration of the septum pellucidum. Resection of the tumour can be undertaken after the ventricles have been decompressed and the patient has been stabilized. However, the resection must be fully cognizant of the critical location of the tumour adjacent to the optic apparatus, pituitary gland and stalk, hypothalamus, and vessels of the circle of Willis. Stereotactic radiosurgery and fractionated radiotherapy are increasingly being used.</td>
<td>Memory recall decreased manual dexterity, spatial working memory, processing speed, language processing and verbal memory deficits.</td>
<td></td>
<td>(Carpentieri et al, 2001; Cavazzuti, Fischer, Welch, Belli, &amp; Winston, 1983; Kalapurakal, 2005; Nejat et al, 2008; Thompson et al., 2005; Waber et al, 2006)</td>
</tr>
</tbody>
</table>
The process of neurodevelopment starts soon after conception (DeAngelis, 2000). The brain develops sequentially, with the more primitive areas of the brain developing before the more sophisticated sections (Perry, 2000). The first areas of the brain to fully develop are the brainstem and midbrain, which govern the bodily functions necessary for life. At birth, the lower portions of the CNS are very well developed, whereas the higher regions (the limbic system and cerebral cortex) are still rather primitive (Perry, 2000). The major structures of the brain are well formed by the time of birth, but development continues for at least twenty years (Chamley, Carson, Randal, & Sandwell, 2005). From birth to five years the cerebral cortex develops rapidly. Throughout this period the volume of the brain changes, grey matter volume decreases (grey matter processes information involved in muscle control, sensory perception such as seeing and hearing, memory, emotions, and speech) and white matter increases (i.e. myelination) (Toga, Thompson, & Sowell, In press). Myelination occurs rapidly during the first two years of life, particularly in the prefrontal cortex; it then continues slowly until adolescence (Casey, Giedd, & Thomas, 2000; Chamley et al, 2005).

White matter has an important function: it facilitates speed and transmission of information throughout the brain, thus the structural integrity and maturity of white matter pathways are important for enabling a smooth flow of information (Paus, 2005) – see Figure 3. The frontal and prefrontal lobes are the last areas of the brain to finish myelination. These areas are used for a variety of functions, most particularly, executive functioning, which involves the planning and organisation of behaviour, as well as the allocation of attention (Paus, 2005). O’Sullivan et al. (2001) has demonstrated diffusion-related changes in normal white matter that correlate with executive functioning. Damage to this area could explain deficits relating to attention, as identified in the research literature (Steinlin et al, 2003).
Myelin (the protective nerve coating around nerve axons) degradation hinders the flow of information within the brain and between the brain and body. (Figure 3 from Image © 2009 RelayHealth and/or its affiliates is reproduced with permission.)

It is postulated that the long-term effects of treatment on white matter result in cognitive deficits, as treatment diminishes an individual’s ability to acquire new information, rather than a loss of previously learnt information (Palmer et al, 2001). This may be secondary to other cognitive processing impairments, including deficits in attention, short-term memory, speed of processing, visual-motor coordination and sequencing abilities, all of which are supported by white matter tracks (Reddick et al, 2003). Reddick et al. (2003) Highlight the importance and implications that a reduction in white matter has on neurocognitive functioning. A further model developmental model (Figure 4) by Reddick et al. (2003) also highlights the relationship between a decreasing normal-appearing white matter volume and deficits in attention, which are reflected in intelligence scores and below average academic achievement.
**Figure 4.** Proposed developmental model of the relationship between normal-appearing white matter (NAWM), attention, memory, intelligence (Full Scale IQ (FSIQ) and academic achievement (Reddick et al, 2003) reproduced with permission

1.3.1 **Plasticity and the Early Vulnerability Hypothesis**

Evidence for the importance of early development in the brain emphasises the potential hazard for children with a space-occupying lesion who receive neurosurgery, chemotherapy and radiotherapy interventions to the brain. However, research has identified that the brain may be able to adjust to the potential damage from a tumour or treatment for a brain tumour and continue functioning appropriately (Davis, 2010). Two competing theories of age-based plasticity and the early vulnerability hypothesis present competing perspectives which may explain the cognitive presentations of children with a brain tumour in comparison to adults who have similar pathological conditions but have severe cognitive dysfunction (Davis, 2010; Dennis, 2000).

**1.3.1.1 Early Vulnerability Hypothesis**

Current paediatric neurooncology literature suggests that patients who are of a younger age when they start treatment will have poorer outcomes than those who are treated later in their childhood, due to the vulnerability of the brain during the early stages of
development (Dennis, 2000; Mulhern, Hancock, Fairclough, & Kun, 1992). Thus treatment can be potentially detrimental to the brain’s development. The early vulnerability hypothesis suggests that cognitive development is dependent on the integrity of a particular cerebral structure at specific stages of development. Therefore, if a specific cerebral region is damaged at a critical stage of development it may have adverse consequences for cognitive development (Luciana, 2003).

1.3.1.2 Age-Based Plasticity

Further literature indicates that children with an CNS lesion who are given treatment at an earlier age will perform better on neuropsychological tasks than those who receive treatment later in life (age-based plasticity) (Dennis, 2000). Neuroplasticity suggests that the brain can adapt to impairment, as a young brain is immature and less susceptible to the impact of cerebral damage. Plasticity is thought to be at a prime stage during early development when the central nervous system is less rigidly specialised and synapses and dendritic connections remain unspecified (Huttenlocher & Dabholkar, 1997). Similarly in a traumatic brain injury population, Anderson et al. (2009) hypothesise that in a the flexibility of the brain enables functions to be reorganised and transferred from damaged brain tissue to healthy brain tissue. Traumatic brain injury, an injury to the brain caused by an external force after birth and acquired brain injury, which include all types of traumatic brain injuries and also brain injuries caused after birth by cerebral vascular accidents. These are often areas of greater research and can help to inform neurooncology findings due to the similarities in presentation and deficits.

The patient’s age/stage of development at the time of treatment is an important factor; it has shown to be a moderating factor in the development of cognitive and learning deficits not only in relation to the age-based plasticity and early vulnerability hypothesis. Research has also shown that neurocognitive impairments may manifest in later life
rather than in childhood (Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004). The impact of the time since treatment will be discussed later in this review.

1.4 Primary Interventions

Alternative hypotheses such as hippocampal neurogenesis (Monje et al, 2007 & Monje et al 2012) can be considered as a causative factor in cognitive impairments in a brain tumour population. The literature on brain development identifies white matter degradation as a key factor in the development of neurocognitive and learning deficits.

Therefore, it is essential that potential origins of white matter degradation, such as the interventions for paediatric brain tumours be considered. The armamentarium currently used to treat tumours of the CNS include: neurosurgery, chemotherapy and radiotherapy; these can be used independently or in combination. Only a small proportion of tumours are treated with surgery alone (Iuvone et al, 2011). The extent, quantity and types of these interventions are dependent upon the progression, location and type of tumour (Moore, 2005).

The development of effective interventions at the acute phase of treatment for paediatric brain tumours is not without problems as clinicians attempt to maintain a balance between the effectiveness of interventions and acceptable toxicity. For example, high doses of chemotherapy, radiotherapy and less conservative neurosurgery have been associated with reduced cancer progression, but with severe morbidity due to changes in white matter volume (Moore, 2005).
1.4.1 Neurosurgery

The presence of a brain tumour can potentially have a significant impact on a patient's functioning and can be the principle determinant of cognitive deficits, particularly those located in the cortex (Iuvone et al, 2011). The resection of a tumour without any additional interventions has been demonstrated to have a significant impact on processing speed, attention, memory and visual-constructive copying (Steinlin et al, 2003).

Recent evidence suggests the site of the tumour appears to be the best predictor of cognitive deficits. Iuvone et al. (2011) Identified patients with tumours in the supratentorial hemisphere to be at greater risk; this contradicts other studies which propose there is greater risk to those with hemispheric tumours (Mulhern & Butler, 2004). As well as finding the site of the tumour to be an appropriate predictor of risk, Iuvone et al. (2011) found that the dimension of the tumour and tumour related factors (perilesional oedema, compartment/localized hypertension, and hydrocephalus) had a greater impact on IQ impairment than tumour location.

Patients can undergo numerous surgical resections during the course of their treatment; this indicates the potential for further damage. In a study by Young and Johnston (2004) exploring the treatment of eighteen patients for paediatric brain tumours, surgical resection was attempted in all patients, second-look surgery in four patients and ventriculoperitoneal shunts were inserted in two patients. Within this study a total of twenty-four operations were performed, illustrating the extensive use of surgery in this population.

A limited number of tumours (low-grade) require only neurosurgery. Therefore this poses a challenge in identifying the implications of neurosurgery alone on cognition and
learning. Iuvone et al. (2011) Suggests that initial screening for pre-existing neurocognitive impairments should not be neglected, as prior assessment could help to provide a baseline for assessing the true neurological impact of surgery and other interventions. However, in clinical settings this is not always possible due to resources, time and the patients’ presentation, which may preclude initial screening. Hence, services have to rely on clinical interviews, which emphasise premorbid presentation.

1.4.2 Radiotherapy

Radiotherapy is an integral part of treatment for many paediatric brain tumours. The method by which radiotherapy is delivered varies. Differences include changes in the dose of radiation, the size and shape of the radiation beams and the number of treatment sessions given to the patient. With advancements in imaging and computing, different forms of radiotherapy are becoming available; photon and proton beam radiotherapy are currently being used in the paediatric brain tumour population (Yock & Tarbell, 2004).

1.4.2.1 Armamentarium of Radiotherapy

The most common forms of radiotherapy include: conventional x-ray radiation (photon), intensity-modulated radiation therapy, stereotactic radiosurgery (gamma knife) and proton therapy (Taylor & Maughan, 2010).

Conventional two-dimensional x-ray radiation (photon) is the most common form of radiotherapy. External photon beams are directed at the tumour using a medical linear accelerator, delivering beams from different angles, which converge on the tumour (Taylor & Maughan, 2010). The area around the tumour is also treated to ensure the whole tumour is irradiated. However, due to the application of this method, doses are kept at a lower level ensuring minimal exposure for healthy tissue surrounding the
tumour (Taylor & Maughan, 2010). The superiority of dose distributions has resulted in reduced neurocognitive implications (Taylor & Maughan, 2010; Yock & Tarbell, 2004).

Intensity-modulated radiation therapy enables clinicians to shape the radiation beams to the three-dimensional shape of the tumour. The radiation is delivered from different angles, allowing the dose of radiotherapy to be variable dependent upon more metabolically active parts of the tumour. This results in a more precise form of radiotherapy, which can deliver a stronger more effective intervention with greater protection of surrounding healthy tissue (Taylor & Maughan, 2010).

Stereotactic radiosurgery (gamma knife) is a tool, which focuses thousands of high intensity gamma radiations directly onto the tumour without affecting the healthy tissue around the tumour. Individually, each radiation beam is too weak to damage healthy tissue but when focused precisely on the tumour, the beams intersect and the combined radiation is sufficient to treat the targeted area (Taylor & Maughan, 2010).

Proton therapy uses a three-dimensional approach to precisely target tumour cells (Taylor & Maughan, 2010). Protons are different from photons because they travel in a straight line until the energy is deposited at an end target (Merchant et al, 2008). This results in a radiation scatter, which significantly reduces side effects and complications. Consequently, this reduces the incidence of late mortality and reduces the risk of secondary malignancies from the radiation treatment itself (Merchant et al, 2008).

With the exception of photon radiotherapy each type represents advanced and precise forms of radiotherapy which attempt to focus more directly on the tumour with minimal affect to surrounding healthy tissue (Taylor & Maughan, 2010). In comparison to
photons, proton beam radiotherapy, a newer and not widely available intervention, aims to improve outcomes (Yock & Tarbell, 2004).

1.4.2.2 Limitations of Radiotherapy

Despite these advancements and the advantages of proton beam radiotherapy, it will take years of follow-up research into children who have been treated with protons to confirm the benefits of this modality (Merchant et al, 2008). Daw and Mahajan (2013) Concur that clinical trials with long-term follow-up are needed to confirm effectiveness of proton therapy. It is also important to note that a systematic review of the clinical effectiveness of proton therapy has demonstrated that the evidence for the clinical efficacy of this treatment relies on non-control studies (Olsen, Bruland, Frykholm, & Norderhaug, 2007). For paediatric neurooncology populations, all of the studies evidenced were case series and offered no comparison to other treatment strategies (Olsen et al, 2007). Therefore, results should be interpreted with caution in regard to the effectiveness of this treatment (Brada, Pijls-Johannesma, & De Ruyscher, 2007).

Further limitations of radiotherapy include a risk of secondary malignancies, particularly in children (Yock & Tarbell, 2004). Evidence also supports radiation therapy as a contributing factor to neurocognitive impairment; deficits include impaired short-term memory, working memory, attention span and processing speed (Hoffman & Yock, 2009; Mabbott et al, 2008; Ris & Noll, 1994; Ullrich, 2009).

In general, the long-term effects of radiation therapy are found to be age-dependent: the younger the child is at the time of radiation therapy, the greater the cognitive deficits (Prados & Russo, 1998). This may be a consequence of brain immaturity and on-going development during the early formative years of a child’s life, when areas of the cortex
associated with cognitive functions remain vulnerable to neurotoxins (Moore, 2005). Recognising these consequences, children under three years of age pose a challenge to treat, as craniospinal irradiation is typically not administered due to the increased risk of neurocognitive deficits (Gottardo & Gajjar, 2008). Clinicians in Europe are reluctant to irradiate the brain prior to 36 months of age in order to allow for further brain development, with the aim of reducing neurocognitive impairment (Davis, 2010). However, clinicians in the United States of America offer radiation therapy prior to 36 months, despite evidence of cognitive dysfunction (Davis, 2010). Mulhern et al. (2004b) have emphasised that longitudinal studies consistently demonstrate significant declines in IQ over time in patients treated with craniospinal radiotherapy for a medulloblastoma, compared to other forms of intervention, which demonstrate less severe deficits in IQ. For example, individuals treated for low-grade astrocytoma by surgery alone demonstrated less severe deficits in IQ. Significant declines in IQ should be investigated, as a healthy child’s IQ is not expected to change significantly over time; changes in IQ may possibly indicate cognitive impairment (Meadows et al, 1981; Mulhern et al, 2004).

The main cognitive processes, which underlie IQ, consist of processing speed, working memory, executive functioning and attention. Declines in IQ can be associated with cognitive impairment. Indicators of this can be difficulties with numerical ability/arithmetic, comprehension, memory and processing (Mulhern et al, 2004). Other possible factors for declines in IQ can include socioeconomic factors, lack of schooling and other medical conditions such as hydrocephalus.

It has been hypothesised that a decline in neurocognitive functioning and IQ may be linked to the loss of cerebral white matter and a failure to develop white matter at an adequate rate in relation to the child’s development (Mulhern et al, 2004). As previously
noted, one of the functions of white matter is to increase axonal conduction velocity, which facilitates information flow through the brain. Moore, Copeland, Ried, and Kopecky (1992) suggested that radiation therapy may impede neuronal transmission speed, resulting in slower and disorganised cognitive processing. Including neuropsychological toxicity, other serious complications are recognised in the literature, such as hormone deficiencies, growth retardation and secondary malignancies (Butler & Mulhern, 2005).

However, it is important to note that in the majority of studies exploring cognitive and learning impairments post radiotherapy, neuropsychological testing was limited to IQ measurements; hence, this may have obscured the possible presence of specific deficits of cognitive functions. Iuvone et al. (2011) Evaluation of different cognitive functions pre-surgery, demonstrate that cognitive deficits can be found in patients with normal IQs; therefore, other assessments should be conducted to control for this possibility. Moreover, it is important to be mindful that other factors can be attributed to a decline in IQ, such as hydrocephalus (Mulhern et al, 2004).

1.4.3 Chemotherapy

Chemotherapy is a form or combination of medication, which interrupts the chemical process of cell division by damaging the genes inside the nucleus of the cells (Childhood Cancer Statistics, 2014). Historically brain tumours were treated by neurosurgery, followed by radiotherapy (Prados & Russo, 1998). However, because of the vulnerability of the brain both of these interventions are limited and researchers have sought methods to delay irradiation to allow for further brain development (Kedar, 1997). Chemotherapy remains an important part of treatment in the paediatric brain tumour population. It allows for a reduction or absence of radiotherapy in patients and has been found to increase the disease-free survival in primitive neuroectodermal
tumour/medulloblastoma patients (Kedar, 1997). In comparison to radiotherapy, chemotherapy is not typically associated with the same levels of toxicity; this is particularly important for the treatment of younger children as delaying radiotherapy can potentially limit neurocognitive and learning impairments in the developing brain (Duffner et al, 1993).

Table 3 demonstrates the varied forms of chemotherapy interventions for paediatric brain tumours and the combinations in which they are used to increase disease-free survival in patients.

However, it is important to recognise the benefit of using chemotherapy in conjunction with other forms of treatment, including neurosurgery and radiotherapy. For example, in the results reported in the Medulloblastoma section of Table 3, the patients were given adjuvant chemotherapy (following craniospinal irradiation) which facilitated a reduced-dose radiotherapy (Gottardo & Gajjar, 2008). Table 3 and additional studies also demonstrate achievements in the outcomes of studies into children treated for Medulloblastoma, however these achievements have been offset by a lack of progress in those treated for high-grade glioma (Gottardo & Gajjar, 2008). Furthermore, some forms of this intervention still struggle to conquer the challenges faced from neurotoxicity (Grill & Bhangoo, 2007). A strong relationship between neurocognitive deficits and the types of chemotherapy, for example, the use of intrathecal (method of delivery) methotrexate particularly in conjunction with whole brain radiation therapy, has been reported to correlate with neurocognitive deficits (Ris & Noll, 1994).
**Table 3.** Chemotherapy Interventions for Paediatric Brain Tumour Populations (Kedar, 1997; Prados & Russo, 1998).

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Type of chemotherapy</th>
<th>Results of previous studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymoma</td>
<td>Combination (Cyclophosphamide &amp; vincristine)</td>
<td>Significant response to chemotherapy in the paediatric studies</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>A combination of Cisplatin, Etoposide, Vincristine, Cyclophosphamide, Carboplatin and Methotrexate.</td>
<td>Medulloblastoma is one of the most chemosensitive childhood brain tumours. Standard care for Medulloblastoma.</td>
</tr>
<tr>
<td>High-grade Glioma</td>
<td>Combination (1-(2-chlorethyl-3-cyclohexyl-1-nitrosourea (CCNU), Vincristine &amp; Prednisone), (CCNU &amp; Vincristine) and Procarbazine or Topotecan.</td>
<td>Some sensitivity to chemotherapy</td>
</tr>
<tr>
<td>Brainstem Glioma</td>
<td>Vincristine, Carboplatin, Cyclophosphamide and combination (Cyclophosphamide &amp; Thiotepa)</td>
<td>A minority of patients with a brainstem glioma respond to chemotherapy</td>
</tr>
<tr>
<td>Low-Grade Glioma</td>
<td>Combination (Actinomycin-D &amp; Vincristine), (6-thioguanine, Procarbazine, Dibromodulcitol, BCNU &amp; Vincristine) and (Carboplatin &amp; Vincristine)</td>
<td>Subset of low-grade glioma that respond well to chemotherapy</td>
</tr>
</tbody>
</table>

Due to the toxic nature of chemotherapy, not only are malignant cells affected, but it can also have adverse effects on healthy tissue. The degree of damage depends upon the cumulative dose. Common side-effects include alopecia, anaemia, thrombocytopenia, granulocytopenia, nausea, vomiting, gastrointestinal side-effects, hypersensitivity reactions, organ damage and neurocognitive effects (Kedar, 1997). Common neurocognitive effects include deficits in working memory and processing speed.
(Mabbott et al, 2008). For example, Edelstein, Spiegler, Fung, Panzarella, Mabbott, Jewitt, D'Agostino, Mason, Bouffet, Tabori, et al. (2011) explored the neurocognitive effects on patients treated for medulloblastoma as a child. The results of this study indicate an association between age at diagnosis and poorer IQ and academic achievement scores, the youngest being the worst affected. Furthermore, a decline in working memory regardless of age at diagnosis was noted. This longitudinal study identified the significant later life impairments chemotherapy had on educational and occupational attainment. A criticism of much of the literature based on both chemotherapy and radiation therapy studies, is that they fail to account for any evaluations of pre-treatment neurocognitive deficits; as previously noted, this makes it difficult to exclude any prior neurological effects.

Despite the evidence for neurocognitive deficits, chemotherapy has shown to be an effective intervention which can delay or prevent the use of radiation therapy for some brain tumours, sparing the developing brain from further neurotoxicity; as previously noted, damage to cortical and subcortical white matter has been identified as a precursor to neurocognitive dysfunction in this population (Paus, 2005). Figure 5 demonstrates a decline in white matter and the deficits associated with this decline post-chemotherapy in an individual being treated for a primary central nervous system lymphoma (Drappatz, Schiff, Kesari, Norden, & Wen, 2007). The left image shows normal white matter and the right image, white matter three months later, after six doses of high-dose methotrexate. This highlights the development of confluent abnormal T2 hyperintensity in the subcortical and periventricular white matter, extending into the internal capsules bilaterally with preservation of the corpus callosum. The patient was symptomatic with memory loss, inattention, and word-finding difficulties.
Figure 5. Highlights a decline in white matter pre and post chemotherapy. (Figure 5 from Drappatz et al. (2007) reproduced with permission.)

1.5 Survivorship and Wellbeing

Evidence for the neurocognitive and learning consequences of paediatric brain tumours indicates that these deficits may also have further negative implications. Neurocognitive deficits and learning impairments have been found to impact on both individual functioning and quality of survival (QOS), which has consequences for an individual’s psychological wellbeing. A continuum of psychological problems has been observed, these include: behavioural problems, maladjustment, depressive and anxiety symptoms, and poor self-conception of significant emotional dysregulation and severe mental illness, including short-term or long-term personality disturbance and psychosis (Turner et al, 2009). Turner et al. (2009) highlight the implications of developmental factors as patients fail to adapt to developmental challenges, which can emerge when children perform increasingly complex tasks at an independent level. This is supported by research that suggests a negative association between time since diagnosis and overall adjustment (Mulhern, Kovnar, Kun, Crisco, & Williams, 1988; Seaver et al, 1994). However, a study by Lannering, Marky, Lundberg, and Olsson (1990), exploring long-
term survivors of paediatric brain tumours, found self-reported QOS was not related to the degree of disability. Those who reported psychological/emotional dysfunction (14%) also evaluated their QOS lower than patients with other aspects of long-term sequence, which included cognitive, hormonal, motor and visual dysfunction. Although these psychological factors are of importance, this thesis will focus only on neurocognitive and learning consequences of paediatric brain tumours.

1.6 Moderators

A variety of other factors have also been associated with neuropsychological consequences of children undergoing treatment for brain tumours, for example tumour location, the gender of the patient, and neurological complications. The most prominent literature is associated with the factors of age and time since treatment.

1.6.1 Age

More pronounced cognitive deficits have been associated with younger neurooncology patients. Literature suggests that there is an inverse relationship between younger children and neuropsychological and neurobiological severities (Moore, 2005). Younger children have been associated with lower cognitive scores in comparison to children who were older at the time of treatment (Aarsen et al, 2009; Mulhern & Butler, 2004). Mulhern et al. (2001) found significant associations between age and neurocognitive performance among survivors of childhood medulloblastoma. They identified that the younger the patient’s age at the time of therapy, and the longer the duration since craniospinal irradiation, resulted in further neurocognitive impairment. In comparison, Levisohn et al. (2000) identified that younger age is associated with a more favourable cognitive outcome which may reflect the neural plasticity of the brain, analogous to the recovery of language following left-hemispherectomy. However, there are a limited
number of studies demonstrating this result in comparison to more impaired cognitive outcomes.

Research indicates that six years of age is a sensitive period for determining neuropsychological outcome during radiotherapy (George et al, 2003; Palmer et al., 2003; Palmer et al, 2001). However, Steinlin et al. (2003) suggest five to ten years as a more vulnerable age range for those at risk of neurocognitive sequelae, and Iuvone et al. (2011) conclude that it is unclear if young age is a main risk factor for cognitive deficits at diagnosis. Levisohn et al. (2000) suggest that these findings may be a consequence of tumour type, as the diagnosis of a medulloblastoma is uncommon in younger children and would reflect greater impairment. It is important to note that this may have been a representation of Levisohn et al. (2000) patient sample, as other research suggests it is the most common malignant tumour in a paediatric population with The frequency peak is under five years of age (Miller 1968). The findings may also reflect a lack of sensitivity of neuropsychological testing or that the functional domains in which older children experience difficulty (initiation and organisation of speech and visual-spatial organisation skills) do not make large developmental gains between the ages of seven and eleven years (Levisohn et al, 2000).

With regard to possible explanations of age being a contributing factor to neurocognitive deficit; Mulhern et al. (2001) hypothesised that the impact of age during treatment may be associated with normal appearing white matter. As previously noted a reduction in white matter may result in cognitive deficits, as it diminishes an individual’s ability to acquire new information rather than a loss of previously learnt information (Palmer et al, 2001). Therefore patients who are younger when they receive treatment may struggle to acquire new information in comparison to older children. However, Mulhern et al. (2001) research does not support Reddick et al. (2003) developmental model of a relationship between normal appearing white matter and attention, memory, intelligence
and academic achievement (Figure 4). Mulhern et al. (2001) findings could not be attributed to memory and attention, only factual information, verbal abstract thinking and non-verbal abstract thinking.

1.6.2 Time since Treatment

Both longitudinal and cross-sectional studies have identified that cognitive functioning declines with increasing time since treatment, suggesting that injury may have an effect on on-going development with increasing deficits emerging as childhood progresses (Mulhern et al, 2004; Mulhern et al, 2001; Spiegler et al, 2004). This has been termed in a traumatic brain injury population as ‘growing into deficit’ (Middleton, 2001). Similarly in neurooncology populations Spiegler et al. (2004) suggest that intellect, processing speed and visual memory decline as time from diagnosis increases, in patients treated for posterior fossa tumours. In support of this, Hoffman and Yock (2009) note that IQ continues to decline for a number of years after the completion of treatment. Typically, the adverse effects of an intervention have been noted for around one to two years post-therapy in neurooncology patients (Butler & Mulhern, 2005). However, further studies have demonstrated these effects continue for up to ten years post-intervention (Edelstein, Spiegler, Fung, Panzarella, Mabbott, Jewitt, D'Agostino, Mason, Bouffet, Tabori, et al, 2011; Hoppe-Hirsch et al, 1995).

It is hypothesised that these long-term effects are the result of changes to the structure of the brain, in particular the white matter, vasculature and cortical thickness. This can adversely effect a child’s ability to acquire skills at the same rate as their peers (Edelstein, Spiegler, Fung, Panzarella, Mabbott, Jewitt, D'Agostino, Mason, Bouffet, Tabori, et al, 2011). Hoffman and Yock (2009) warn that the impairment of tissue growth, development and function are not the only consequences and they suggest that over time radiation therapy can also induce secondary cancers.
1.6.3 Resilience

In addition to moderating factors that explain risk and vulnerability, there are also factors of resilience that account for results that do not conform to likely trends for neurocognitive morbidity.

1.6.3.1 Cognitive Reserve

A reserve against impairment originates from the idea that there does not appear to be a direct link between the degree of brain pathology and the clinical manifestation of that damage (Stern, 2002). Literature regarding cognitive reserve focuses on two concepts, passive and active models. Although these models are described in relation to aspects of the patient which can be protective against the effect of biological risk, it is also important to state that they can also enhance biological risk (Dennis, 2000).

1.6.3.2 Passive Models

Passive models such as brain reserve, threshold and neuronal, are defined in terms of the amount of damage that can be sustained before reaching a threshold for clinical expression (Stern, 2002). The threshold model recognises the construct of brain reserve capacity. It believes that once individual limits of clinical threshold have been attained, and brain reserve capacity is depleted past this threshold, specific clinical or functional deficits emerge (Satz, 1993). Therefore greater brain reserve capacity may be seen as a protective factor, since an individual may not experience cognitive deficits because their capacity has not been exceeded in comparison to an individual with the same tumour whose brain reserve capacity has been exceeded.

However, it is important to note that the passive models do not account for individual differences in how the brain processes cognitive tasks after impairment. They also do not address potential qualitative differences between the consequences of different types
of brain tumours (Stern, 2002). This suggests the model alone does not explain all aspects of reserve.

### 1.6.3.3 Active Models

Stern (2002) suggests that there are two types of active models that explain how the brain actively attempts to compensate for neurological damage, these are cognitive reserve and compensation models. Cognitive reserve proposes that the brain utilises brain networks that are less susceptible to disruption, processing tasks in a more efficient manner. The cognitive reserve model also does not assume that patients with the same tumour type and location will have similar presentations. Because of individual variability in how they cope with the tumour, the same amount of damage will have different effects on different people. In comparison, the second model is the compensation model, which suggests that patients learn to use brain networks that are not normally used by individuals with intact brains, in order to compensate for brain damage (Stern, 2002).

#### 1.7 Aims and Objectives of the Systematic Review

In consideration of the evidence for neurocognitive and learning deficits described above, a systematic review of the effectiveness of interventions (pharmaceutical and psychosocial) for cognitive and learning impairment, within a paediatric population following the diagnosis of a brain tumour, will be undertaken. This will be addressed via a systematic review and meta-analysis (if it is appropriate to integrate the data statistically) methodology. Additionally, the implications of this literature on clinical and research practice will be addressed in the discussion:
• Research Question 1: How effective are interventions (pharmaceutical and psychosocial) for cognitive and learning impairment of paediatric patients with brain tumours?

• Research Question 2: What are the implications of the literature for clinical and research practice?
CHAPTER TWO: SCOPING

The Armstrong, Hall, Doyle & Waters (2011) paper has been used as a guide to inform the development of this systematic review.

2.1 Identifying the Research Question

The objectives of this project were to:

Question 1) Systematically review the literature (no restrictions were applied to the study design of the literature), to identify the neurocognitive and learning consequences of paediatric brain tumours.

Question 2) Systematically review the literature (no restrictions were applied to the study design of the literature), to determine evidence for the effectiveness of interventions (pharmaceutical and psychosocial) for cognitive and learning impairments within a paediatric brain tumour population.

It is hypothesised that conducting a systematic review on both of the above questions could be beyond the scope of this thesis.

After the development of the search terms, a trial search was conducted for questions one and two. The retrievals from the search for question one were deemed too large to be included in this study. An initial search conducted in Medline only in July 2012 retrieved 6,173 papers.
The search was refined to explore the neurocognitive and learning consequences of either Ependymoma or Medulloblastoma paediatric brain tumours. The two most prevalent malignant paediatric brain tumours were selected in the hope that one of them would generate a suitable number of retrievals to be included in the study (Dhall, 2009). Furthermore MESH headings of ‘treatments’ and ‘Cognitive Outcomes’ were used in the search to broadly identify neurocognitive outcomes and interventions used to treat these tumour types.

The results of both searches were considered too extensive for the first section of this project (Table 5) in addition to the second section (question two), which retrieved a total of 2,513 for both pharmaceutical and psychosocial intervention searches.

1) Children AND Ependymoma AND Treatments AND Cognitive Outcomes

2) Children AND Medulloblastoma AND Treatments AND Cognitive Outcomes

A systematic review of literature, to identify the neurocognitive and learning consequences of paediatric brain tumours will not conducted. Therefore it is important to consider the current literature and possible gaps in this area of research.
### Table 4. Search results for independent tumours

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Electronic database</th>
<th>Papers retrieved</th>
<th>Total number of papers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymoma</td>
<td>AMED</td>
<td>2</td>
<td>753</td>
</tr>
<tr>
<td></td>
<td>CINAHL</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cochrane Library</td>
<td>11</td>
<td></td>
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<td></td>
<td>EMBASE</td>
<td>412</td>
<td></td>
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<td></td>
<td>Medline</td>
<td>310</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PsycINFO</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>AMED</td>
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<td>1378</td>
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<td>CINAHL</td>
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<tr>
<td></td>
<td>PsycINFO</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

#### 2.2 Identifying Relevant Studies

The current armamentarium in the post-acute recovery period used for the rehabilitation of the paediatric brain tumour population addresses physical, learning, visual, motor and cognitive impairments (Limond & Leeke, 2005). The impact of cognitive and learning deficits in paediatric brain tumours are evident from the reviewed literature and are becoming more significant as survival rates increase due to scientific advancements and high quality health outcomes. Therefore, it is important that evidence for effective
interventions directed at restoring areas of deficit or implementing compensatory activities are explored. For the purposes of this introduction, a review of the most prevalent psychosocial and pharmaceutical interventions administered after the acute recovery phase, for paediatric patients with a brain tumour, will be conducted. Additional interventions will be identified and explored in the results and discussion section of this review.

2.2.1 Rehabilitation and Outcome Measures

Various methods of treatment, both psychosocial and pharmacological are utilised in the rehabilitation of children with a brain tumor. Wilson (1997) focuses on four different aspects of cognitive rehabilitation for brain injury. First, rehabilitation via drills and exercises, Secondly, the use of theoretical models of cognitive psychology to identify the impairment and thus remediate the deficit. Thirdly, an approach driven by the patient, and uses a combination of learning theory, cognitive psychology and neuropsychology to identify and inform the intervention. The final approach is holistic, which assumes cognitive functions are interlinked and cannot be separated from emotion, motivation and non-cognitive functions. Thus all need to be addressed by rehabilitation programs. Although Wilson (1997) categories four aspects of rehabilitation this thesis recognises that these approaches often overlap and thus will explore three approaches: remediation, compensation and a holistic approach.

Although the presentation of patients often reveals potential cognitive deficits, methods of assessment are equally as important and outcomes measures need to be utilized throughout rehabilitation to monitor the progress of the deficit and the impact of the intervention.
2.2.2 Remediation

Remediation, specifically cognitive remediation is a method of teaching that targets areas of deficit involved in learning and basic day-to-day functioning that may be impaired. The primary aims of remediation are to reinforce specific cognitive deficits.

Remediation is a psychosocial intervention which uses a systematic approach, utilising different strategies such as: behavioural interventions, cognitive behavioural therapy, instruction in metacognitive strategies, social skills training, traditional brain injury techniques such as drills, massed practice (a continuous practice of different cognitive drills), and supportive and dynamic psychotherapeutic approaches aiming to improve cognitive functioning (Butler & Mulhern, 2005). Outcome measures such as standardised tests of working memory and attention function to assess the deficit and identify potential progress or decline.

Remediation is based on the principle that the brain can adapt after injury and thus reorganise its structural pathways (Luria, 1963). This has important links to neuroplasticity and the reorganisation of the brain for functional recovery. Thus Luria suggest that by separating cognitive deficits into individual components, which are then practiced and over learned on tasks similar to the nature of the component deficit (Butler & Mulhern, 2005). Consequently remediation has demonstrated relationships among dendrite growth, structured environmental stimulation and the recovery of lost functions (Sohlberg & Mateer, 2001).

An important development in remediation is Butler et al. (2008) Cognitive remediation programme, which uses techniques from a variety of different disciplines, these include: Clinical Psychology, brain injury rehabilitation and special education/educational
psychology, to develop a tripartite model. It is a team approach which consists of the child, therapist, parent and teachers. First, principles of massed practice taken from brain injury rehabilitation interventions are used to help develop attention processes (Sohlberg & Mateer, 1996). The focus of these interventions is to exercise attention processes in the areas of sustained, selective, divided and executive attention control. This is a manual approach, during which the child is engaged in a 15 minute learning based activity, which is then alternated with more intrinsically interesting activities such as board games or computer games (Butler et al, 2008). This process helps the child sustain their attention over 20 two-hour sessions. To ensure the task is set at an appropriate level for the child, a 50-80% rule of correct responding is followed. If the child falls below a 50% correct response rate the task is changed to a more suitable basic task. Once the child has achieved 80% accuracy, the task will be moved up to the next level of difficulty. If the child did not achieve 80% they would repeat the task (Butler et al, 2008).

The second part of the tripartite model is the use of metacognitive strategies, which are based on techniques used in special education and educational psychology. Strategies are taught to each child and as their performance improves, the strategies become part of the child’s repertoire and help the child to monitor their own thinking. Each of the strategies is idiosyncratic to the participant and as the child progresses over the course of the remediation they frequently acquire new and innovative strategies (Butler et al, 2008). Strategies are categorised into: task preparedness, on-task performance, and post-task strategies. Within each of these categories are numerous strategies such as ‘hints’. This strategy suggests that if a child is struggling, they should be encouraged and taught to seek assistance or a hint (Butler et al, 2008). Participants are assigned an individual therapist who will monitor their performance whilst participating in the drills. Research indicates that techniques such as metacognitive strategies, which teach individuals to
monitor their own thinking, have been used to improve attention processes in brain injured children (Butler & Mulhern, 2005).

Thirdly, a cognitive-behavioural approach based on the work of Meichenbaum (1977), taken from the discipline of Clinical Psychology, completes the tripartite model. A cognitive-behaviour approach attempts to: reframe cognitive struggles, provide psychotherapeutic support, acknowledge weaknesses and roadblocks to improvement, acknowledge learning strengths, monitor their own internal dialogue, stress inoculation and encourage the patients to become their own ‘best friend’ rather than ‘worst enemy’, ensuring a realistic, positive, and optimistic learning environment (Butler & Mulhern, 2005). This intervention is directed at developing the participant’s ability to withstand distraction and maintain their attention thereby allowing them to improve their verbal mediation skills and thus their self-control. The therapist initially models how to self-talk through a distraction experience. The participant then practices this with the therapist serving as a distracter. Once the dialogue has been successfully incorporated, the child is then coached to internalise the dialogue and use it covertly (Butler et al, 2008).

The majority of cognitive remediation research has been conducted in the field of paediatric acquired brain injury. Butler et al (2008) have been at the forefront of developing and applying these principles to a paediatric population with neurocognitive deficits as a result of interventions for cancer. They have noticed that the techniques used in the rehabilitation of a traumatic brain injury population appear to have relevance for a paediatric neurooncology population, as they both exhibit similar neuropsychological disturbances.
In 2002 twenty-one individuals treated for a CNS related malignancy completed a
cognitive remediation pilot study. The aim of this pilot was to develop an innovative,
psychologically based outpatient rehabilitation program that would improve
dysfunctional attention processes and associated neuropsychological deficits (Butler &
Copeland, 2002). The results identified a statistically significant improvement in all
attention measures, in comparison to the control group which did not manifest any
significant changes (Butler & Copeland, 2002). However, it should be noted that neither
of the groups demonstrated any statistical significance on the arithmetic achievement
test. Furthermore, the methodology of the study was compromised in that the groups
used in the study consisted of an unequal sample size and non-random assignment of the
treatment condition took place. Although limited reviews of the cognitive remediation
programme have taken place within a paediatric neurooncology population, significant
support for the programme can be found in brain injury literature (Ben-Yishay & Diller,
1993; Carney et al, 1999).

Despite the positive results some aspects of functioning, particularly episodic and
semantic memory/new learning are generally not considered to be amenable to
remediation and therefore compensatory approaches are recommended (Mateer &

2.2.3 Compensation

Compensatory interventions involve the use of strategies and tools designed to enable
the patient to cope with the impairment. Compensatory methods typically focus on
activities of daily living and can be provided through the use of assistive technology or
physical aids (such as a diary) or it can be a strategy (e.g. mnemonics or structured
templates for following a process). The aim of a compensatory intervention is to
improve the individual's functioning in the real world and outcome measures are
therefore based on goals or improvements in a specific skill (e.g. how many words can be read, or whether the knowledge of how to complete long multiplication has been learnt).

Compensatory interventions predominantly rely on the accommodation within the school setting and the use of assistive technology to help patients to compensate for their deficits (Armstrong & Briery, 2004). This approach utilises the individual’s abilities, such as memory or processing speed, which have remained unaffected by rehabilitation approaches. Accommodation techniques and technologies then work around the patients’ areas of deficit and continue to build on their strengths (Armstrong et al, 1999). The compensatory model focuses largely on language-based learning and performance, with minimal emphasis on visual, motor learning and performance (Armstrong & Briery, 2004; Brown, 2004). The primary components consist of: extended time limits for school examinations, the use of true/false and multiple-choice formats in testing, rather than essay examinations, written hand outs in order to decrease demand for copying from the blackboard, voice recognition technology and equipment to tape record classroom lectures, which may help to minimise the impact of the child’s deficit (Brown, 2004; Butler & Mulhern, 2005). They can also provide school reintegration programmes, special education support, environmental modification and assistive technology (Brown, 2004). School based intervention can involve a number of activities which are idiosyncratic to the needs of the child, the aim being to socialise and facilitate the children back into education and to address their emotional needs (Brown, 2004).

Limited studies have been conducted to demonstrate the effectiveness of these interventions (Brown, 2004). However, studies which are often based on feedback from teachers and parents report that the techniques are of benefit to the patients (Armstrong et al, 1999; Armstrong & Briery, 2004; Brown, 2004).
For example Kerns and Thomson (1998) utilised a memory device to improve neuropsychological functioning in those who have severely impaired memory, secondary to a brain tumour and treatment. The participant involved in the compensatory memory system was provided with a notebook with several sections. These sections included: a memory log, in which to make notes to assist their episodic memory; a calendar section, which allowed them to keep a record of activities and keep track of the passage of time; a ‘things to do section’ which enabled participant to log all of their upcoming assignments; an orientation section, which contained important personal information, for example, names of teachers, classroom numbers and their counsellor’s name; and a transportation section, which contained their bus schedule and a map of the school. Training within this method involves three stages; acquisition, application and adaptation. To support the participant, parents were also trained in how to use the memory book. Furthermore, role-plays and teacher assistance were used to ensure adequate knowledge and the use of the memory book. The participant was instructed to use the notebook on a daily basis and was also supplied with a daily checklist to supplement the memory notebook.

Although the Kerns and Thomson (1998) study, as a compensatory intervention, is not expected to significantly improve memory impairment, it was of benefit to the participant. For example academic achievement increased slightly when the raw scores were evaluated and participant continued to use the memory system after the trial had finished. Furthermore, teachers reported that after the study was completed none of the participant had trouble with class attendance or the completion and submission of assignments on time, demonstrating a benefit to their daily living (Kerns & Thomson, 1998). Likewise encouraging results for memory deficits utilising a compensatory diary and remediation approach have been demonstrated in acquired brain injury studies (Ownsworth & McFarland, 1999).
When evaluating the extent of the compensatory interventions needed to aid the patient, conventional evaluations can be redundant, as they are often based on static concepts of learning disabilities (Armstrong, Blumberg, & Toledano, 1999; Brown, 2004). Ecological intervention may need to be intermittently reviewed as the child develops. Armstrong et al. (1999) suggest that evaluation should be considered a process, with re-assessment every 18-24 months or as clinically needed.

Furthermore, the evaluation of compensatory methods via outcome measures also needs to be addressed. Compensatory interventions such as the Kerns & Thompson (1998) memory aid often utilise measures such as the Wechsler Intelligence Scale for Children (WISC) to demonstrate the impact on broader deficits, consequently these studies will demonstrate limited changer thus limited general recovery of function, which can hinder the perceived effectiveness of the intervention. However, some measures such as achievement measures (Wechsler individual achievement test (WIAT) and wide range achievement test (WRAT)) can be used to measure change brought about by the compensatory intervention as they are attainment measures (i.e. as they are looking at current level of academic attainment rather than an underlying cognitive function).

Compensatory interventions are often linked with pharmacological interventions and cognitive rehabilitation as part of an efficient rehabilitation package. The cognitive interventions are indicative of those associated with the aforementioned cognitive remediation; pharmacological interventions will be addressed later in this thesis.
2.2.4 Holistic

A holistic approach to rehabilitation can be defined as dynamically interlinking cognitive, emotional and behavioral aspects of rehabilitation, which is undertaken by addressing rehabilitation in an integrated interdisciplinary team approach (Clare, Wilson, Carter, Roth & Hodges, 2004). Wilson describes this model of rehabilitation as a “partnership” incorporating the medical team, the patient and systemic factors such as the individual’s family, friends and significant others from educational/vocational settings (Wilson & Gracey, 2005). This approach incorporates elements of exercises such as massed practice with goal setting from remediation and compensation approaches. A holistic approach to rehabilitation appreciates the need to address cognitive, emotional, behavioural and social consequences of the brain injury (Wilson 2008).

A holistic approach is mindful of the important factors involved in the rehabilitation of paediatric neurooncology patients, such as the influence of their environment and significant others. Butler and Mulhern (2005) believe it is of great important to educate significant others in the patient’s life about their deficits and the specific needs associated with their treatment. Rehabilitation literature, such as Butler and Mulhern (2005) also suggests that neurooncology patients may require specific provisions and support.

Butler and Mulhern (2005) support the notion of combining cognitive remediation with ecological interventions to maximise therapeutic gains, however noting that children cannot be expected to return to a baseline, pre-insult status. They specify that to maximise therapeutic gains, changes in environmental demands combined with additional rehabilitation may benefit the patient. Additionally, they highlight the
importance of remaining mindful of changes in the child’s presentation. As previously noted, cognitive functioning declines with increasing time since treatment, therefore the patient may develop further deficits as they age (Mulhern, Khan, et al, 2004; Mulhern et al, 2001; Spiegler et al, 2004).

A holistic approach to rehabilitation has the largest evidence base in adult brain injury; along with memory aids (SIGN, 2013). These methods are not only accessed via outcome measures that are typically goal-based, and questionnaires (self and significant others), but also a range of standardised neuropsychological tests to ensure there has not been general recovery. Measures look at variables hypothesised to be improved directly by remediation, or the improvement of underlying skills developed in long-term studies. Again academic attainment/achievement measures may also be used.

2.2.5 Pharmacological Interventions

Neurooncology literature also indicates the need to consider pharmacological interventions in addition to psychosocial interventions to manage neurocognitive difficulties; specifically attention and working memory which underlie global cognitive declines following a paediatric brain tumour (Clark, Baker, Gardner, Pompa, & Tait, 1990; Whyte et al, 2004). Therefore, in addition to the psychosocial interventions, the use of pharmacological interventions will also need to be addressed; the most prevalent and researched intervention is Methylphenidate hydrochloride (MPH), a generic form of Ritalin (Conklin et al, 2007; Conklin et al, 2010a; Mulhern et al, 2004 & Thompson et al, 2001).
2.2.6 Methylphenidate Hydrochloride

The MPH is a piperidine derived stimulant, namely, methyl-alpha-phenyl 2-piperidineacetaten hydrochloride (Gagnon, Low, & Schreier, 2005). MPH is thought to enhance the functioning of the frontostriatal (anterior) attention network (Rubia et al, 2011). This is an important function as the frontostriatal systems have been shown to play a role in cognition (Chudasama & Robbins, 2003).

Children with brain tumours often present with attention deficits and impulsivity (Riddick et al, 2003). MPH works to increase dopamine levels in the brain, dopamine is a neurotransmitter associated with attention. The therapeutic effect of stimulants is achieved by slow and steady increases of dopamine, which are similar to the way dopamine is naturally produced in the brain (Meyers, Weitzner, Valentine & Levin, 1998).

Results have demonstrated significant improvements in cognitive functioning, specifically visual-motor speed, verbal memory, expressive speech function, executive function (ability to switch mental set and divide attention), and fine-motor coordination. Attention and behavioural improvements among children with brain tumours and other cancers of the CNS, specifically in areas of sustained attention and processing speed have been noted in previous research (Conklin et al, 2010b).

2.2.7 Methylphenidate and Attention Deficit Hyperactivity Disorder

MPH is synonymous with treatments for attention deficit hyperactivity disorder (ADHD) and other diagnoses which result in ADHD type behaviours, such as acquired brain injury. The effectiveness of MPH, a stimulant medication, in improving cognitive
performance, has been demonstrated within these populations (Murray et al, 2008; Whyte et al, 1997; Whyte et al, 2004; Willmott & Ponsford, 2009).

Results from the Multimodal Treatment Study of Children with ADHD (MTA), a fourteen month, large and comprehensive treatment study of ADHD, which included 579 children diagnosed with ADHD, aged from 7 to 9.9 years of age, from six different sites across the United States of America, established that a combined treatment of intensive behavioural treatment and intensive medication management were significantly superior to intensive behavioural treatment alone and to routine community care, in reducing ADHD symptoms (MTA Cooperative Group, 1999). The combination treatment also allowed children to be treated with lower doses of medication (Carey, 2000). On average, medical management also proved to be more effective than intensive behavioural intervention.

However, in a commentary review Carey (2000) notes that the patients receiving just medication were also provided with support, encouragement and practical advice; this was not deemed to be a behavioural treatment. Moreover readings from an approved list and eight additional sessions were also provided for medical emergencies. Although it does not define this as behavioural support, the research also does not define what support was provided in these sessions or what support the reading list gave. Furthermore Carey (2000) suggests the study does not establish that MPH is a specific remedy for children with a diagnosis of ADHD. There was minimal reporting of the response of the behavioural management programme and the results were varied dependent upon the patient’s clinical problems. More importantly, Carey (2000) critiques the study for the fact that the diagnostic criterion for ADHD was vague, which made it challenging to identify who was included in the study population.
The MPH trials were also critiqued by Pappadopulos et al. (2009), who indicated that in clinical settings poor adherence and early termination of MPH would impact on the effectiveness of the treatment. In the MPH trial they identified a discrepancy between parental verbal reports of medication adherence and physiological adherence measures. Nearly half of the parents were inaccurate informants of their child’s ADHD medication adherence and that they often overestimated actual adherence.

These concerns may address why six to eight years later a study by Molina et al. (2009) suggests that the type or intensity of a fourteen-month treatment for ADHD did not predict functioning. Despite initial symptom improvement, which was maintained post-treatment, there was still a significant impairment in adolescence. Thus additional interventions are still needed to target specific deficits.

### 2.2.8 Methylphenidate and Paediatric Neurooncology

In addition to the evidence for the use of MPH in ADHD and brain injury populations, there is increasingly reported evidence in favour of the use of MPH with paediatric neurooncology populations (Conklin et al, 2010a). As previously noted, children with malignant brain tumours may incur damage to cortical and subcortical white matter particularly within the frontal and prefrontal lobes (Moore, 2005; Mulhern & Butler, 2004). These areas have been found to be used in executive functioning which involves the planning and organisation of behaviour, as well as the allocation of attention; this may therefore account for attention difficulties (Paus, 2005). Thus MPH may be of benefit for attention problems in a paediatric neurooncology patient.

Research exploring the use of MPH in children with brain tumours has demonstrated a benefit for neurocognitive problems, as demonstrated in Table 4. Table 4 demonstrates the use of MPH treatment on neurocognitive impairments; additionally MPH has been
found to be of benefit for social deficits (Mulhern et al, 2004b). Although Mulhern et al. (2004b) results demonstrated improvement in social behaviours and academic competence, there were limited improvements in neuropsychological functioning and academic achievement.

Table 5. The Effects of MPH on Neurocognitive Deficits

<table>
<thead>
<tr>
<th>Neurocognitive Deficit</th>
<th>Evidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Significantly greater improvement with MPH than a placebo in a patient’s sustained attention as well as in an overall index of attention problems. Improvements in attention observed in both the classroom and the participant’s home. Also significant benefits for the long-term use of MPH.</td>
<td>(Conklin et al, 2010a; Conklin et al, 2007; Conklin et al, 2010b; Mulhern et al, 2004a; Mulhern et al, 2004b)</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>Significant benefits for the long-term use of MPH.</td>
<td>(Conklin et al, 2007; Conklin et al, 2010b)</td>
</tr>
</tbody>
</table>

In contrast to the improvements in attention and processing speed, the administration of MPH has not resulted in a statistically significant and consistent improvement in associative learning, verbal memory, IQ and academic skills (Conklin et al, 2010b; Thompson et al, 2001). A further limitation of MPH has been linked to the pharmacokinetics of MPH. MPH has shown to have a half-life of 4 hours and reaches its bioavailability within 90 minutes, suggesting it does not have a lasting effect (Brown et al, 1997). In the Mulhern et al. (2004b) literature, there was a trend for teachers to perceive more benefits than the parents due to the timing of the lunchtime dose.
Despite encouraging literature, Butler and Mulhern (2005) conclude that it is yet unknown if MPH ultimately facilitates academic achievement among survivors of paediatric brain tumours with attention problems. The majority of these studies have relied on either or both parental and teacher reporting, therefore it is important to consider the potential for reporting error and bias (Conklin et al, 2010a; Mulhern et al, 2004b). It was also difficult to differentiate the results between those who had a diagnosis of a brain tumour and those who had a diagnosis of leukaemia (Conklin et al, 2010a; Mulhern et al, 2004b).

2.2.9 Paediatric Rehabilitation

It is important to remember that methods of rehabilitation in paediatric populations are often limited and the literature is not extensive in either adult or paediatric populations; although an adult population is an area of greater research. Thus alternative diagnoses such as brain injury and ADHD, where rehabilitation has been established are drawn upon.

Further complications are the context under which major studies have been undertaken. In the United States of America a single national outcome study was undertaken, with a standard protocol, which incorporated all children with cognitive impairments associated with cancer or its treatment. Thus a large majority of research includes other cancer diagnoses, which may provide complications when identifying the effects of interventions on neurooncology populations.

Considering above research a PICO process was used to frame the clinical question considering the research discussed in the introduction chapter. Thus the focus of the project will be a systematic review of the literature to determine evidence for the
effectiveness of interventions (pharmaceutical and psychosocial) on cognitive and learning impairments within paediatric patients with brain tumours.

2.3 Literature Search of Relevant Studies

Based on this literature an initial search was constructed on a limited number of data bases (Medline), to identify potential relevant studies, with guidance from the Health Faculty Team Librarian at the University of Leeds. Also a variety of databases and hand journal searches were conducted to identify further resources such as reference lists for the final searches. Studies which did not meet the minimum inclusion criteria such as oncology were divided into irrelevant studies and potentially irrelevant studies. The potentially irrelevant studies allowed for the identification of articles, which yielded appropriate references for secondary searches (hand searching). Secondary searches included articles such as Butler and Mulhern (2005), which reviewed interventions for the neuropsychological late effects associated with the treatment of acute lymphoblastic leukaemia and malignant brain tumours, yet were not included in the results, as the focus in the paper was a review not an assessment of an intervention.

2.4 Study Selection

Exclusion and inclusion criteria’s were considered, with the support and guidance of Consultant Paediatric Oncologists, Consultant Paediatric Neurologist and Consultant Child and Adolescent Psychiatrist, Leeds Community Healthcare NHS Trust. Particular emphasis was placed during the scoping process on the population inclusion and exclusion criteria by narrowing the population to allow for the removal of potentially irrelevant papers, this included different diagnosis and the separation of adult and child populations.
Furthermore, guidance for the development of the population search terms were taken from Boluyt, Tjosvold, Lefebvre, Klassen, and Offringa (2008), which aimed to assess the usefulness of existing search filters in finding child health search terms. However, it is important to note that the search terms of Boluyt et al. (2008) were based on a ‘sensitive child filter’, which was developed by the Cochrane Child Health Field. Although, Boluyt et al. (2008) conclude that the sensitivity of the child health search terms were 98% (380/378; 95% confidence interval, 96%-99%). The search terms appear limited in that they failed to identify studies which use hyphenated key words, these include: Neo-nat*, Post-nat*, Pre-school and Pre-pubescent.

Furthermore, the study contained an error in including the search term Paediatric twice and did not identify studies that used alternative spellings of Paediatrics. For example, a review of the Neonatal search terms, conducted on 9 March 2012, using Ovid SP databases (AMED, EMBASE, MEDLINE, PsycINFO and Web of Science), highlighted a further 952 studies which may be of relevance to the review, which were found in the Neo-nat* search and not in Neonat*, highlighting the importance of using both hyphenated and non-hyphenated words.

2.5 Charting the Data

A database was constructed to identify and consider the population sample utilised in this review, specifically the range of diagnosis of the patients retrieved in the initial searches. Articles were screened using this basic inclusion and exclusion criteria.

The information extracted from the data screening process for relevant studies was placed onto an Access database to ensure accurate recording and transparency to allow for conclusions to be drawn about the population/diagnostic criteria in the final review.
2.6 Collating, Summarising and Reporting the Results

After collating evidence from initial searches based on the effectiveness of psychosocial and pharmaceutical secondary interventions it was apparent that the dominant methodology reported was the single case. This has implications for the methodological quality and the reliability of the results discussed in this thesis. The quality assessment of the papers will be discussed in the methodology section of this thesis as some argue quality assessment is not an essential aspect of a scoping chapter (Armstrong, 2011).

Furthermore the potential implications of the literature relating to participants with an alternative CNS diagnosis such as leukaemia or a co-morbid diagnosis being grouped together in the final results section of the studies. For example, mental health problems or an epilepsy, will need to addressed in the final systematic review because the presence of such diagnoses are significantly associated with neuropsychological impairments and may have an adverse impact on the results (Iuvone et al, 2011).

2.7 Optional Consultation

Consultation was sought from professional in the disciplines noted above during the scoping review. It was important to utilise their knowledge and expertise in areas of anatomy and current interventions. The development of the extensive search strategies was also supported by research assistants who initially developed a basic set of search terms for an additional research project.
CHAPTER THREE: METHODOLOGY

This chapter describes the methodology of the systematic review, outlining the procedure for data extraction and the proposed method of data analysis. This chapter also reviews the development of the study by describing the methods used to inform searching, data extraction, synthesis and analysis. An outline of the review process can be found in Figure 6.

3.1 Research Design

A survey of empirical studies comparing psychosocial and pharmaceutical interventions, for learning and cognitive outcomes, in a paediatric brain tumour population was undertaken. This research design allowed for a rigorous, but objective procedure, for the collection and compilation of data to provide evidence-based answers. It also provided a transparent analysis, appraisal and synthesis of the best available evidence, whilst reducing the potential for subjectivity or bias in the findings. This design allowed for a review of research from different disciplines, whilst also considering the impact of the interventions.

Clinical decisions are often made based on multidisciplinary team working, thus research should also accommodate varied perspective. By combining the evidence-based outcome of this review with professional judgement, it will enable clinicians to make informed decisions about future policy and intervention within services. Consideration was also given to the limitations of this design, including the ability generalise the findings and the potential problems of research that utilises small sample sizes.
3.2 Development of the Study

The development of the search terms, data coding and data synthesis were informed by the Centre for Reviews and Dissemination (CRD) (Centre for Reviews & Dissemination, 2009), and the Cochrane Handbook for Systematic Reviews of Interventions (CHSRI) (The Cochrane Collaboration, 2011). Further guidance was received from Dr Matthew Morrall (Consultant Paediatric Neuropsychologist and Field Supervisor) and Professor Stephen Morley (Programme Director at The University of Leeds and Academic Supervisor). Supervisory meetings provided opportunities to reflect on the progress of this thesis and discuss difficulties and limitations that could hinder the development of the thesis.

A protocol was developed as part of the transfer viva exam in September 2012. The protocol outlined the proposed question, which was determined as a result of the scoping progress; it gave detailed information regarding the inclusion and exclusion criteria, (which are listed below) and described how the review process would be conducted with regards to critical appraisal and data analysis. The transfer viva provided an opportunity for external clinicians to comment on the protocol. Thus aiding the progress of the study and limiting potential bias by providing a clear hypothesis and method without prior knowledge of the results. Although the transfer viva was a challenging process it shaped the methodology of the thesis, particularly the critical appraisal section. The examiners offered guidance and prepared me for the challenges and frustrations of reporting the results of studies within a CNS population.
3.3 Search Strategy for Identification of Studies

3.3.1 Criteria for Study Inclusion

The studies to be included in the review were required to meet the following criteria. This criterion was determined through the course of discussions with supervisors named above and specialists in paediatric and neurooncology fields.

- Population: Paediatric neurooncology patients, under the age of eighteen years.
- Context: Neurocognitive (Impairment in cognitive domains, including: attention, executive functioning, speed of processing, working memory and other aspects of memory.)
- Interventions: The key interventions of interest include both pharmaceutical and psychosocial interventions for neurocognitive consequences of paediatric brain tumours.
- Outcomes: Impact on functioning (specific focus cognitive and learning aspects of functioning)
- Study Design: No limits.

3.3.2 Exclusion Criteria

Literature concerning participants diagnosed with brain tumours at the age of eighteen years or over was excluded from this study as was, literature relating to participants with a co-morbid diagnosis. Non-English language reports were also excluded. It is acknowledged that this might introduce bias (DeAngelis, 2000), but resources for
translation were not available. It was hypothesised that this limitation would not impede the review, as the majority of paediatric neurooncology studies are published in English.

3.3.3 Development of Search Strategies

To try and eliminate forms of biases such as database, publication bias and source selection bias and to increase the yield of relevant studies retrieved; the development of search strategies, terms and selection of databases, were informed by a variety of different sources. These included: the research aims and the guidance of CHSRI, Miss Janet Morton - Arts and Social Science Faculties Team Librarian, Miss Elizabeth Neilly – Health Faculty Team Librarian, Drs Picton, Wilkins and Elliott - Consultant Paediatric Oncologists, Dr Livingston - Consultant Paediatric Neurologist at The Leeds Teaching Hospitals NHS Trust, Dr Stanley - Consultant Child and Adolescent Psychiatrist, Leeds Community Healthcare NHS Trust and Miss Helen Stocks and Miss Kate Ablett - former Research Assistants at The Leeds Teaching Hospitals NHS Trust (The Cochrane Collaboration, 2011). This was a challenging process and it took considerable time to source appropriate individuals. However, consultation with these individuals resulted in a list of extensive search terms and databases/journals. The final search terms used in the systematic review are shown in Appendix I.
Figure 6: The Process of Systematic Review

1. Citations identified from the primary search (electronic search) of selected databases
2. Retrieved abstracts from the primary search are reviewed in accordance with inclusion and exclusion criteria (Screening form)
3. Hard copies of relevant and potentially relevant citations obtained
4. Non-relevant citations were discarded
5. Secondary search (hand search) of the abstracts of additional citations missed in the primary search
6. Full review of relevant studies from both primary and secondary searches with the data extraction form
7. Included Studies
8. Excluded Studies
3.4 Searches: Electronic Databases

The databases utilised in the search included:

- The Allied and Complementary Medicine Database (AMED)
- Applied Social Sciences Index and Abstracts (ASSIA)
- Australian Education Index
- British Education Index
- British Education Internet Resource Catalogue
- Current Educational Research in the UK (CERUK)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- Cochrane Library
- CSA Neurosciences Abstracts
- Digital Education Research Archive
- Education-line
- Education Literature Datasets
- EMBASE
- Education Resources Information Center (ERIC)
- Google Scholar
- Index to these accepted for higher degrees by the universities of Great Britain and Ireland
- MEDLINE
- PsycINFO
- Scopus
- Social services abstracts
- Social Sciences Citation Index
- Sociological abstracts
As previously noted a diverse range of professionals from a variety of different academic fields, education, neurooncology and neuropsychology, were consulted to confirm that all appropriate search engines had been accessed in the primary search.

In addition to the primary electronic searches, a secondary hand search of reference lists from the relevant or potentially relevant articles retrieved in the primary searches were undertaken to ascertain any further research that had not been identified in the electronic searches. Key author searches such as ‘Mulhern’ were undertaken using Google Scholar. Further explanation of this process is given in the data extraction section of the methodology. The outcomes of primary and secondary searches are recorded in the results section.

The final searches using the above databases were conducted six months prior to the completion of the systematic review, in January 2013. The searches were calibrated to receive an automatic alert of all new literature that met the search criteria for the review. Studies, which were retrieved by the automatic alert between January 2013 and June 2013, are noted in the discussion, but have not been included in the review.

A detailed search log was kept to ensure the search process could be replicated. The log included a record of the detail of how searching was undertaken, for example which websites, journals were searched, when and how many time. This also included the list of search terms and MESH terms used.
3.5 Searches: Hand Searches

In addition hand searches of relevant non-electronic reviews and journals were considered, but no relevant sources were identified during consultation. Due to time constraints key authors were not contacted to identify further studies and potential sources of information. This may have limited the identification of further papers, authors and search terms.

3.6 Dates Used in the Search Criteria

The criteria for the search dates used in the review of the empirical literature were set in accordance with the first issue of the journals used in the thesis and January 2013 (the final search). However, it was noted that studies of importance were often retrieved from a later date (post 2000). It is hypothesised that these dates coincide with advancements in the field of paediatric neurooncology, a growing awareness of the impact of neurocognitive morbidity and its management. Nevertheless, to ensure the searches yielded an appropriate retrieval, the search dates were set idiosyncratically, in accordance with the start of each journal.

3.7 Data Extraction

After all of the retrievals from the search strategies had been extracted and assembled in EndNote X5, an initial review of all the retrievals was conducted using a data extraction form. The first section involved a data screening process (Appendix II), which involved a review of the title and available abstract of each article. Articles were systematically screened using the inclusion and exclusion criteria.
The information extracted from the data screening process for relevant studies was placed onto an Access database to ensure accurate recording and transparency for data synthesis. All irrelevant papers from the searches were documented, stating why they had failed to meet the inclusion criteria. This information is available on request in electronic format, due to the size of the document. Relevant and potentially relevant papers and their references were used in the secondary searches and hand searching. All relevant papers, which met the inclusion criteria, were retrieved in full.

The data extraction form (Appendix II) used to systematically elicit data was designed with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and CRD (Centre for Reviews & Dissemination, 2009; Liberati et al, 2009). The form was designed to be explicit, record relevant details and reduce potential errors of judgement and bias. The data extraction form was assessed for its ability to extract appropriate studies and information, by two individuals via a pilot study.

3.7.1 Methodological Quality of Studies

Utilising an appropriate tool for the quality assessment of the retrieved studies is an important aspect of any systematic review. The CHSRI emphasise the importance of the applicability of the findings, the validity of the studies and the design characteristics, as these may impact the interpretation of the results (The Cochrane Collaboration, 2011). CHSRI recommend accounting for four areas of bias: selection, performance, attrition and detection bias (The Cochrane Collaboration, 2011). However, it is important to note that the critical appraisal section of the CHSRI is related to randomised control trials only, since the CHSRI only use randomised control trial studies in their systematic reviews to ensure they are utilising high quality research. Due to the limited quality of
research designs extracted, this thesis will include all research designs, this is supported by Schlosser and Sigafoos (2009), who suggest the construct of evidence-based practice requires that researches seek out the best available evidence. Additionally Pagliaro, Bruzzi, and Bobbio (2010), recognise the quality of Cochrane systematic reviews, but suggest they are not as widely used in clinical decision making because of their emphasis on methodology and rigor rather than on clinical relevance. Thus the present review uses a checklist that assesses potential bias from other research designs. The quality appraisal checklist and further questions in the data extraction form were used to assess each of these aspects; for example, blinding to interventions and outcomes, attrition from the study and reporting of the results. CHSRI suggest using a scale identifying the relationship between a score and the degree to which the study is free from bias (The Cochrane Collaboration, 2011). However, this can pose a challenge as these scales are not supported by empirical evidence and are more suited to the appraisal of an RCT.

The Oxford Centre for Evidence Based Medicine (2011) levels of evidence was also incorporated into the data extraction form. This was used to reflect the quality of the studies assessed in this review, the results of which will be considered in the discussion (Howick et al, 1998) (Appendix III). The levels of evidence table shows five levels of evidence and allows clinicians to appraise studies for prevalence, accuracy of diagnostic tests, prognosis, therapeutic effects, rare harms, common harms and usefulness of (early) screening (Howick et al, 2012).

In addition to the levels of evidence, the Downs and Black (1998) checklist, a quality assessment tool was amalgamated with the data extraction form. In order to identify an appropriate quality assessment tool an Ovid search was conducted in EMBASE, MEDLINE and PsycINFO (9 January 2013), however, the search provided a limited
retrieval, extracting only two papers (Downs & Black, 1998; Slim et al, 2003). Slim et al. (2003) reported a methodological index for non-randomized study instruments. Although the twelve-item scale established good interreviewer agreement, high test-retest and good internal consistency, it could only be used to assess non-randomised studies. The Downs and Black (1998) checklist assessed the quality of both randomised and non-randomised studies.

The Downs and Black (1998) checklist was developed in response to the systematic reviews conducted by organisations such as The Cochrane Collaboration. Generally, reviews conducted within the Cochrane Collaboration have inclined to focus on randomised studies. Non-randomised (or observational) studies are often excluded from reviews of treatment effectiveness because of their potential bias. However, the present review hoped to include both randomised and non-randomised studies. The Downs and Black (1998) checklist is comprised of twenty-seven items, which are distributed between five sub-scales. The five sub-scales include: reporting, external validity, bias, confounding and power. Answers were scored 0 or 1, except for one item in the reporting subscale, which was scored 0 to 2, and a single item on the power sub-scale that was scored 0 to 5. This equates to a total maximum score of thirty-one. The checklist demonstrated high internal consistency for the quality index, as did the subscales apart from external validity. It also demonstrated good test-retest \((r = 0.88)\) and inter-rater reliability \((r = 0.75)\), and had good face and criterion validity (Downs & Black, 1998).

CRD guidelines suggest that papers should be reviewed independently by more than one researcher to increase the reliability of data extraction and decrease bias (Centre for Reviews & Dissemination, 2009). In comparison, CHSRI support the use of a single researcher, as multiple researchers can create the potential for disagreement (The
Cochrane Collaboration, 2011). Thus, it is important to acknowledge that a single researcher undertook the extraction and analysis of the data, the researcher had no conflicting interests and consequently does not need to be blinded to details of authors and journals of the studies.

3.8 Management of References

The references retrieved from the data extraction have been collated in EndNote X5, which facilitated the identification of duplicate studies and also generated a unique identification number for each study. The unique identification number was used as an identifier in the retrieval and extraction process.

3.9 Pilot Study

For the purposes of quality assurance, to establish inter-rater reliability and to ensure the data was coded and synthesised correctly, a pilot study was conducted to highlight any potential problems and challenges. The pilot study included a review of the data extraction form to certify it was concise and could be transposed to the Access database. The individuals involved in the pilot were also asked to give feedback with any comments about particular difficulties in using the form to extract the data.

Two independent coders, both psychologists, undertook the pilot. Six studies were selected from the psychosocial and pharmaceutical intervention searches. This process was supported by the CHSRI who suggest a suitable sample should consist of three to six articles which span a range of low to high risk bias (The Cochrane Collaboration, 2011).
Following the pilot study, appropriate structural changes were made to the data extraction form, to allow space for further comments to be added. Changes were also made to the data screening form, as the pilot study showed that articles were not always explicit about specific aspects of their studies. For example, studies often reported limited information about the specific age range of the participants involved in the study. There was also a general reporting of the results in the abstracts, which often made it difficult to distinguish the results in relation to different populations used in the studies. The data screening form was adapted and the ‘results reported separately for different diagnosis’ category was removed for studies that were ambiguous, in order to prevent appropriate studies from being excluded. An example of this was Butler et al. (2008) multicentre: randomised clinical trials of a cognitive remediation programme for childhood survivors of a paediatric malignancy. It was not clearly reported in the abstract whether the results for leukaemia and brain tumour patients were reported separately in the results section, which made it difficult to understand whether the study met the inclusion criteria of reporting paediatric neurooncology outcomes.

Additional strategies were also identified to ensure the review would be carried out effectively. These included supervisory consultations about studies that required further debate. This was a challenge set by numerous articles that combined the results of a variety of diagnosis. My supervisors and I spent time discussing these articles to ascertain if they could be included in the results section. This was a tedious and long process but guidance from the pilot study was very useful in implementing this strategy and others.

3.10 Data Analysis

The method of data analysis utilised in this review was dependent upon the studies retrieved from the searches. A limited number of studies to be included in this review
were retrieved from the search. The final search retrieved three studies that met the inclusion criteria. The three studies retrieved were all single case studies. The design and limited number of studies included in this review was not considered adequate data for inclusion and analysis via a meta-analysis; therefore, it was not appropriate to integrate the data statistically via a meta-analysis (Garg, Hackam, & Tonelli, 2008). A narrative synthesis of the studies was adopted; this included a descriptive summary of the characteristics and findings of the studies, which are included in the results chapter.

3.11 Ethical Considerations

The methodology for this study involved reviewing previous literature relating to paediatric neurocognitive consequences of paediatric brain tumours and the effectiveness of interventions (pharmaceutical and psychosocial) for cognitive and learning impairment. Thus, no patients were directly involved in the development of this research and consequently ethical approval was not sought.
CHAPTER FOUR: RESULTS

This chapter presents the findings from the search for literature regarding psychosocial and pharmaceutical interventions for paediatric neurooncology populations. The results section contains information from the studies that met the inclusion criteria during the data extraction process.

4.1 Overview of the Search Results

An initial search was conducted on the selected electronic databases (see methodology) on 23rd July 2012. This search was repeated in full in January 2013 to identify any further studies and to check the accuracy of the search procedure. The results of the search process are presented in a PRISMA flow chart (Figure 7) (Liberati et al, 2009). In total, the search retrieved 2,513 studies; after adjusting for duplications and studies that were not written in English, 2,423 studies remained. Of these, 2,084 were discarded after reviewing the abstracts and titles because they did not meet the inclusion criteria (data available in electronic format on request). The full texts of 31 studies were reviewed; 29 of these studies did not meet the inclusion criteria. Two studies were deemed to be appropriate and were included in the review. A further 41 studies were identified via secondary searches; of these studies one paper was identified for inclusion in the review.
Figure 7. PRISMA-: Children AND Brain Tumours AND Treatments AND
Psychosocial Interventions OR Pharmaceutical Interventions

From: (Moher, Liberati, Tetzlaff, & Altman, 2009)
4.1.1 Description of the Included Studies

A total of three studies were included in this thesis.

a) Aims and Outcomes

Table 6 describes the setting and context of the studies extracted. The aim of the studies by Butler (1998) and Kerns and Thomson (1998) are on specific cognitive deficits: attention, non-verbal cognitive processes and memory, whilst the third study focuses on improving academic skills (Penkman & Scott-Lane, 2007). It is important to note that the aim of the third study by Penkman and Scott-Lane (2007) was not to specifically evaluate an intervention, but to determine if an intervention could be conducted while a patient was receiving intensive medical treatment. The study recognises that patients with a diagnosed brain tumour are at risk of cognitive delay, but their focus is not on treating cognitive deficits directly. They hope that the prophylactic academic intervention will enable patients to solidify basic skills before radiotherapy impairs their ability to learn. Thus part of this study also involved determining the effectiveness of one-on-one academic tuition in building skills. For the purposes of this thesis the focus of the data extracted from this study is on the intervention’s (one-on-one academic tuition) ability to improve the patient’s academic skill base. Hence the intervention’s focus is on the patients’ ability to continue leaning new information, an important aspect in cognition and reflected in learning impairment (Dennis et al., 1998).
Table 6. Aims of the Studies Retrieved.

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Main cognitive functions evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Butler, 1998)</td>
<td>The study evaluated an attention process training program with an emphasis on skill-acquisition, massed practice and learning strategies. The intervention was designed to strengthen attentional, perceptual and non-verbal cognitive processes.</td>
<td>Attention, perceptual and non-verbal cognitive processes</td>
</tr>
<tr>
<td>(Kerns &amp; Thomson, 1998)</td>
<td>The study described the development and implementation of a compensatory memory aid.</td>
<td>Memory</td>
</tr>
<tr>
<td>(Penkman &amp; Scott-Lane, 2007)</td>
<td>This study evaluated the feasibility of delivering a prophylactic academic intervention to a child, whilst they are receiving intensive medical treatment. It also determined the effectiveness of one-to-one academic tuition in building skills with a child at risk of cognitive and academic delay.</td>
<td>Academic skills</td>
</tr>
</tbody>
</table>
b) Assessment

The design of the studies retrieved which met the inclusion criteria, were case studies (Table 7). These studies achieve an evidence level of 4 on the Oxford Centre for Evidence Based Medicine (2011). Case studies are often associated with bias related to selection, detection, performance, attrition, reporting and publication (Dalziel et al., 2005). Until like RCTs, which are classified as level 1b, the intervention in case studies does not involve a control group. Thus they are considered one of the weakest study designs to obtain evidence from, with a low position in the hierarchy of research designs.

To consider bias within the studies the sources of funding and other aspects of potential bias were considered (Table 7). However, limited information is given in the studies regarding funding, the location in which the studies were conducted, and the methods of recruitment used. This has further implications for quality of these studies and their results.

Table 7. Settings and Context of the Studies Retrieved.

<table>
<thead>
<tr>
<th>Study</th>
<th>Level of Evidence</th>
<th>Geographical location and study site</th>
<th>Recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Butler, 1998)</td>
<td>4. Case-study</td>
<td>Not identified in the study</td>
<td>Not identified in the study</td>
</tr>
<tr>
<td>(Kerns &amp; Thomson, 1998)</td>
<td>4. Case-study</td>
<td>Location unknown, the study site was the patients’ school</td>
<td>Not identified in the study</td>
</tr>
<tr>
<td>(Penkman &amp; Scott-Lane, 2007)</td>
<td>4. Case-study</td>
<td>Canada, study site unknown</td>
<td>Purposive sample; children treated through the southern Alberta children’s cancer programme</td>
</tr>
</tbody>
</table>

c) Participants

All of the participants in the retrieved studies have been diagnosed with a brain tumour (Table 8). However, the Butler (1998) study does not identify the patient’s tumour type. This may have implications for determining the effectiveness of the intervention, as the degree and type of impairment can be dependent upon the type of tumour (Nejat et al., 2008). Thus the presentation of the patient in Butler’s (1998) study may have minimal impairment compared to patients with other tumour diagnoses.

Two studies used a male patient (Penkman and Scott-Lane, 2007, Butler, 1998). The third study Kerns and Thomson (1998) used a female patient. The mean age for the patients was 10 years (Table 8).

Limited information was given regarding any previous cognitive and learning difficulties prior to the patients’ tumour diagnosis. Only the Kerns and Thomson (1998) study noted that there were no development difficulties prior to the patient’s tumour diagnosis. Furthermore, none of the studies reported information pertaining to the participants’ level/stage of education (Table 8).

All three patients received a course of radiotherapy, with the patient in the Butler (1998) study receiving 2000 cGy and the patient in the Penkman and Scott-Lane (2007) receiving a dose of 5580 cGy in 31 fractions. The dosage for the Kerns and Thomson (1998) study is not reported. Two of the patients underwent a resection of their tumour, with the Kerns and Thomson (1998) patient receiving surgery on two separate occasions due to tumour regrowth (Kerns and Thomson, 1998, Penkman and Scott-Lane, 2007). The patient in Kerns and Thomson (1998) and Penkman and Scott-Lane (2007) studies also received a course of chemotherapy; the chemotherapy (Cisplatin, vincristine,
cyclophosphamide) in the Penkman and Scott-Lane (2007) study was adjuvant to radiotherapy.
Table 8. Patients Recruited in the Included Studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (n), age, gender</th>
<th>Tumour type</th>
<th>Deficits or illness prior to the brain tumour</th>
<th>Primary treatment interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Butler, 1998)</td>
<td>1, 10 years old, male</td>
<td>Not stated in the study</td>
<td>Not stated in the study</td>
<td>Received cranial irradiation (2,000 cGy)</td>
</tr>
<tr>
<td>(Kerns &amp; Thomson, 1998)</td>
<td>1, 13 years old, female</td>
<td>Astrocytoma in the area of the optic chiasm and hypothalamic area, with extension into the third ventricle</td>
<td>No history of developmental difficulties.</td>
<td>Initially underwent craniotomy, with biopsy and debulking of the tumour. At 11-years-old a left and right sided VP shunt was placed and irradiation treatment. Due to continued growth of the tumour, the patient underwent another craniotomy for tumour debulking at 12 years old and a course of chemotherapy.</td>
</tr>
<tr>
<td>(Penkman &amp; Scott-Lane, 2007)</td>
<td>1, 8 years old, male</td>
<td>Medulloblastoma</td>
<td>Not stated in the study</td>
<td>Near gross total resection of the tumour. Additionally cranial irradiation treatment (5580 total cGy in 31 fractions) and adjuvant chemotherapy (cisplatin, vincristine, cyclophosphamide) with four autologous stem cell transplant procedures.</td>
</tr>
</tbody>
</table>
d) Assessment Procedure

All of the patients in the studies were assessed using outcome measures that were directly undertaken with the patient and not with a proxy individual such as a teacher or parent (Table 9). The most commonly used measures were a variation of the Wechsler Intelligence Scale for Children and the WRAML, which were used in all of the studies to assess the cognitive impact of the interventions.

In addition to these measures a variety of other assessments were used to evaluate the impact of the intervention on a patient’s learning outcome. Both the Butler (1998) and Kerns and Thomson (1998) studies used a version of the Wide Range Achievement Test, in comparison to Penkman and Scott-Lane (2007) who used the WIAT-II. Additional measures were used in the Penkman and Scott-Lane (2007) study to further assess the impact of the intervention on the patient’s vocabulary and visual-motor deficits, these included PPVT-III, EOWPVT-R and Beery VMI (Table 9). The CPT was used in the Butler (1998) study to identify potential cognitive deficits. The computer program is commonly used as a screening tool to identify potential attention problems, and as an aid in monitoring treatment effectiveness (Conners & Jett, 1999).

All of the studies utilised pre and post-treatment measures (Table 9). However, the Kerns and Thomson (1998) study compared the pre-treatment results of the WRAT-R, WISC-R and the WRAML to post-treatment scores taken two years post-treatment. The study stated that measures were also taken one year after treatment, but in the interests of brevity and due to little change in the patient’s performance over time they only reported the results two years post-intervention. Penkman and Scott-Lane (2007) also conducted a follow up assessment at eight months post-intervention.
**Table 9.** Outcome Measures used in the Assessment of Patients in Studies Retrieved.

<table>
<thead>
<tr>
<th>Study</th>
<th>Learning outcome</th>
<th>Cognitive outcome</th>
<th>Outcome measures (direct/proxy)</th>
<th>Measurement periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Butler, 1998)</td>
<td>Continuing performance test results, Wide Range Achievement Test 3 (WRAT-3)</td>
<td>Wechsler Intelligence Scale for Children 3rd Edition (WISC-III), the Wide range assessment of memory and learning (WRAML) and Continuing performance test (CPT)</td>
<td>Direct</td>
<td>Pre (three baseline scores were recorded) and post-treatment</td>
</tr>
<tr>
<td>(Kerns &amp; Thomson, 1998)</td>
<td>Wide Range Achievement Test-Revised (WRAT-R)</td>
<td>Wechsler Intelligence Scale for Children – Revised (WISC-R) and WRAML</td>
<td>Direct</td>
<td>Pre and post-treatment (2 years)</td>
</tr>
<tr>
<td>(Penkman &amp; Scott-Lane, 2007)</td>
<td>Wechsler Individual Achievement Test-II (WIAT-II) (word reading, reading comprehension, pseudoword decoding, numerical operations, maths reasoning and spelling subtests)</td>
<td>WISC-III, WRAML, Peabody Picture Vocabulary Test – 3rd Edition (PPVT-III), Expressive One Word Picture Vocabulary Test Revised (EOWPVT-R) and the Beery Test of Visual Motor Integration (VMI)</td>
<td>Direct</td>
<td>Pre (2 months prior to the initiation of the intervention), post-treatment (8 months post-intervention follow up)</td>
</tr>
</tbody>
</table>
e) Intervention

All of the studies assessed different aspects of cognitive functioning and learning outcomes and were given a psychosocial intervention. None of the studies included in this review utilised pharmaceutical interventions. A different intervention was utilised in each study to explore how it might benefit a paediatric neurooncology population. Thus there were limited similarities between the interventions (Table 10). One similarity was the importance of academia in a child’s development, therefore all of the studies worked collaboratively with the patient’s school as part of the intervention. Both the Butler (1998) and Penkman and Scott-Lane (2007) studies utilised a form of hierarchical questions or techniques combined with massed practice (a continuous practice of different cognitive drills), to develop the patient’s skills. However, the Kerns and Thomson (1998) paper use a repetition of learning a strategy and academic information (Table 10).
Table 10. Interventions conducted by the Included Studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Description of the Intervention</th>
<th>Duration of the Intervention</th>
<th>Lead Professional</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Butler, 1998)</td>
<td>Hierarchically graded activities were undertaken to strengthen attentional, perceptual, and non-verbal cognitive processes. An individual therapist identified ineffective strategies and new strategies were taught. The patient received CBT to strengthen their ability to ignore and withstand distraction in addition to a series of activities that promoted arithmetic concept development. To maximise effective encoding, the patient brought their school homework into therapy to monitor and encourage the use of new strategies</td>
<td>Six months, with one per week, over two hours</td>
<td>Not stated</td>
</tr>
<tr>
<td>(Kerns &amp; Thomson, 1998)</td>
<td>The memory notebook was collaboratively developed by the patient, teachers and a school counsellor in accordance with the patient’s needs. The notebook training programme incorporated behavioural techniques, procedural learning, error free learning techniques and effective building strategies. The training programme utilised three stages. The acquisition stage focused on the patient’s understanding of the notebook. During the application stage the patient recorded and referred to the memory system. The final adaption stage was used to modify and adapt the system to the functional needs of the patient and modify any problems. An additional daily checklist was developed for the patient in this study.</td>
<td>The exact time scale is not stated. However, it is estimated ten weeks. Used all day in conjunction with the school timetable.</td>
<td>Teachers and a counsellor</td>
</tr>
<tr>
<td>(Penkman &amp; Scott-Lane, 2007)</td>
<td>An individual programme of the patient’s strengths and weaknesses was developed based upon academic performance and neuropsychological assessment, from which academic objectives were developed. Drills, practice and repetition were used. Lessons were created to build on skills as they had mastered.</td>
<td>Twelve weeks, five days per week, two hours per day</td>
<td>School teacher, Neuropsychologist</td>
</tr>
</tbody>
</table>
Outcomes

i. Cognitive Outcomes

Table 11 demonstrates that the study by Butler (1998) was the only intervention to show improvements in the majority of aspects assessed. Improvements were achieved in areas of arithmetic, sentence memory and on the Continuing Performance Test. Consequently the pre and post scores reflected improvements in the patient’s attention skills. However, the patient’s performance on Digit Span decreased from the first and third baseline scores to the post-treatment scores, but it is interesting to note that there was an increase from the second baseline score.

Cognitive performance was maintained in the Kerns and Thomson (1998) study, with the patient continuing to maintain a high average Full Scale IQ (Table 11). Qualitative feedback from the patient’s teachers indicated the patient had made improvements in everyday activities such as punctuality and remembering to undertake tasks. However, it is important to note that the patients Full Scale IQ dropped by five points, similarly the patient’s verbal IQ (117 to 114) and performance IQ (114 to 111) also reduced, although these were not significant declines. The patient also continued to demonstrate significantly impaired memory and new learning. Furthermore, significant raw and scaled score declines and below average (25th percentile) abilities were observed in information and picture arrangement, indicating the patient was having difficulty acquiring new verbal and social information.

ii. Learning Outcomes

All of the studies demonstrated some improvements in learning outcomes, particularly arithmetic (Butler, 1998; Kerns & Thomson, 1998; Penkman & Scott-Lane, 2007) (Table 11), but these improvements were not maintained long-term in the Penkman and Scott-Lane (2007) study. Furthermore, both Kerns and Thomson (1998) and Penkman and Scott-Lane (2007) highlighted several declines. The Kerns and Thomson (1998) study indicated a slight decline in age-related
percentile ranking. In the Penkman and Scott-Lane (2007) study, despite the maintenance of performance on some subtests, the patient did not achieve his educational objectives in reading and writing. Post-treatment follow up did show an improvement approaching seven standard scores on the reading comprehension subtest though.
Table 11. Outcomes of the Included Studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Learning Outcomes</th>
<th>Cognitive Outcomes</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Butler, 1998)</td>
<td>Improvements noted in arithmetic competence. Improvement in grade levels, after</td>
<td>Pre and post-measures reflect improvements in attentional skills</td>
<td>In addition to the outcome measures, none of the patient’s teachers continued to report any concerns regarding difficulties handing in assignments or getting to class on time.</td>
</tr>
<tr>
<td></td>
<td>the intervention the patient was generally within normal limits (gained 1.5 to 2.0 grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>levels).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Kerns and Thomson, 1998)</td>
<td>There was an increase in scores on the WRAT-R spelling, reading and math subtests.</td>
<td>The patient continued to demonstrate a high average overall intellectual ability. But</td>
<td></td>
</tr>
<tr>
<td></td>
<td>There was a slight decline in age-related percentile ranking.</td>
<td>a decline and below average abilities (25th percentile) in information and picture</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>arrangement. In addition to significantly impaired memory and new learning.</td>
<td></td>
</tr>
<tr>
<td>(Penkman and Scott-Lane,</td>
<td>A Significant improvement on pseudo word decoding and spelling.</td>
<td>Parent satisfaction questionnaires rated the patient’s progress as considerable. The</td>
<td></td>
</tr>
<tr>
<td>2007)</td>
<td>Although performance on the word reading, reading comprehension, numerical</td>
<td>tutor’s perspective suggested that the patient struggled with reading, but had made</td>
<td></td>
</tr>
<tr>
<td></td>
<td>operations and math reasoning showed no significant changes. The patient did not</td>
<td>considerable progress in this domain; progress in mathematics is described as</td>
<td></td>
</tr>
<tr>
<td></td>
<td>achieve his educational objectives, in reading/writing all words up to and</td>
<td>substantial.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>including grade 2 level on the Dolch sight-reading list. Although improvement was</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>demonstrated. Achieved objectives to write and recognise a phonic vocabulary.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>The patient achieved maths objectives set by his tutor.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 12. Overview of the Methodological Criteria Met or Not Met by the Individual Studies. This is Drawn from the Downs and Black (1998) Quality Assessment Tool.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Butler, 1998)</td>
<td>0 0 0 1 0 0 1 0 - 0 0 0 1 0 0 1 0 0 0 1 0 0 0 0 0 0 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>(Kerns &amp; Thomson, 1998)</td>
<td>0 1 1 1 0 1 1 1 - - 0 0 1 0 0 1 0 0 0 1 0 0 0 0 0 0 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>(Penkman &amp; Scott-Lane, 2007)</td>
<td>1 1 1 1 0 1 1 1 - - 1 0 1 0 0 1 0 0 0 1 0 0 0 0 0 0 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
</tbody>
</table>
Due to the limited number of retrievals, no restrictions were made on the methodological quality of the studies included in the results. The methodological quality was measured using the Downs and Black (1998) assessment tool. Table 12 shows the ratings for each of the 5 criteria, if applicable, across all the studies. Each of the criteria is individually numbered and corresponds with the note Downs and Black (1998) assessment tool (Appendix II).

i. Reporting

This section of the tool assesses whether the information provided in the studies is sufficient to allow a reader to make an unbiased assessment of the findings of the study. Butler (1998) does not adequately report the main features, such as the characteristics of the patient (Table 12). Although the hypothesis, main outcomes and interventions are described, further clarification needed to be provided. Additionally, the procedure is described in relation to how the intervention would be administered to a general population, with limited details about how it was administered to the patient described in the study. For example, it does not state which ineffective strategies were identified or what cognitive behavioural interventions were offered to strengthen the patient’s ability to ignore and withstand distraction. Although the study does not provide estimates of random variability in the data for the main outcomes, Downs and Black (1998) suggest that it should be assumed that the estimates used are appropriate.

Alternatively, the Penkman and Scott-Lane (2007) and Kerns and Thomson (1998) studies present a clear hypothesis and adequately describe the interventions utilised in the studies. Similarly, these two studies also provide details of the characteristics of the patients involved in the studies. However the Penkman and Scott-Lane (2007) study does mention the patient’s premorbid presentation (prior cognitive or learning difficulties), which could be an important factor in the results of this study. Furthermore
the Kerns and Thomson (1998) study only comments on the follow up assessment results (two year follow up) due to “interest of brevity and because there was little change” (Kerns and Thomson, 1998, p82). For the purposes of clarity it would have been useful to include all of the results and see what changes the patient made, even if they were small gains or further deficits over the two-year follow up.

ii. External Validity

The Downs and Black (1998) assessment also addressed the extent to which the findings of the studies can be generalised to the population from which the study participants are derived. Only the Penkman and Scott-Lane (2007) study discussed their selection criteria; the sample size of the population from which the patient was drawn was very small, thus only one patient met the inclusion criteria.

All of the studies were undertaken from a case series design; therefore limited generalisations could be made about the results. Although the results do establish mechanisms by which cognitive and learning impairment can be supported.

iii. Internal Validity – Bias

The internal validity is addressed by the measurement of bias in the intervention and the outcome. All of the studies did little to exclude alternative explanations and highlight potential limitations in relationships identified in the studies. There were no attempts to blind the subjects to the interventions they received. There was also no information regarding the blinding of the facilitators measuring the main outcomes. Limited information concerning the patient’s compliance with the interventions was also discussed. However, the facilitators monitored all of the interventions.
Although all of the studies utilised a case series design, none of the measures used the reliable change index to identify significant change (Jacobson & Truax, 1991).

Despite the limitations in the internal validity of the studies, all utilised at least one valid and reliable outcome measure such as the WISC, WRAML, WRAT and WIAT.

iv. Internal validity – Confounding
This section assesses the bias in the selection of participants for the studies. It was difficult to answer the questions in this section, as the participants were all case series designs and limited information was given regarding their recruitment, as previously noted in section ii, external validity. Consequently, randomisation was not used in the selection criteria. Due to limited information in the analysis it is difficult to determine if adequate adjustment was made for confounding aspects.

v. Power
The power section of the assessment tool attempts to assess whether the negative findings from a study could be due to chance. However, as all the studies were case series’, sufficient power to detect a clinically important effect could not be achieved.

vi. Overall Quality
None of the studies achieved the total 31 points from the Downs and Black quality assessment tool. The Penkman and Scott-Lane (2007) study achieved the highest score of 11 points; this is still disappointing though as higher overall scores indicate higher methodological quality.
4.1.2 Excluded Studies

A total of 2,511 studies were extracted from the review for not meeting the inclusion criteria. 1,876 of these studies were not related to paediatric neurooncology. 1,100 involved adults or a combination of paediatric patients and adults. 2,397 of the excluded studies did not focus on an intervention for paediatric neurooncology patients. 24 studies were excluded despite using a paediatric neurooncology population because the results of these studies were combined with paediatric patients with a variety of different non-neurological malignancies.

Of the 41 secondary search results 29 were excluded because they did not focus on an intervention for paediatric neurooncology patients and 8 were excluded because the results were combined with other diagnoses.

4.1.3 Combined Diagnoses.

Despite not meeting the inclusion criteria for this thesis, due to limitations of combined diagnosis, several of the thirty-one papers retrieved may still have been of benefit to paediatric neurooncology rehabilitation literature. Of these studies, nine may have been of importance to the results of this thesis.

The patients utilised in these studies included an amalgamation of acute lymphoblastic leukaemia and brain tumour patients. Although the number of patients from each diagnosis could be identified in the sample, the results for each diagnosis were not reported individually. Therefore the results could not be separated to determine which
results were related to the brain tumour patients and could not be reported in this thesis due to a risk of confounding results.

Despite demonstrating some important results, the excluded studies could not be addressed in this thesis. Yaffe et al., (2012) acknowledged the potential bias from including excluded research in systematic reviews. Hence, the studies identified as being potentially relevant will not be utilised in this thesis. Table 13 and 14 present summaries of the outcomes of the studies that demonstrate potentially important findings for the paediatric neurooncology literature.

The results of Table 13 demonstrate that psychostimulants such as MPH have established improvements in paediatric survivors of brain tumours. Particularly studies by Mulhern and Conklin, who have identified meaningful results such as reductions in attention deficits. These are important findings due to the prevalence of attention problems among the paediatric brain tumour population (Mulhern et al., 2001). It is important to note from table 13 that the Conklin et al., (2007, 2010a & 2010b) papers all used the same data set, but reported on different factors. Consequently these studies all use similar high quality experimental designs, which increase the reliability of their outcomes. This is important as all of the studies demonstrated some form of improvement cognitive deficits, particularly attention.

Table 14 presents studies that may have provided more insight into the use of psychosocial interventions in paediatric patients with cancer of the CNS. The studies demonstrated also positive results with deficits in attention. In comparison to the studies included in the review, these studies utilised higher quality experimental designs, due to
the larger population samples. Thus the outcomes may be a more accurate representation of the paediatric population than the single case study design.

4.1.4 Ongoing Studies

The author knows of no ongoing studies or recently published studies that would be relevant to this review.

4.1.5 Significant Studies Not Retrieved in the Search

A further two studies which may could have been of interest to this thesis were identified after the study had been concluded. These included studies by Callu et al (2008) and Rankin and Hood (2005). Both studies discussed cases which explored the use of cognitive and support strategies to support patients with a diagnosis of medulloblastoma. Despite meeting the inclusion criteria the search did not identify these papers. Although this does not reflect a weakness in the search strategies developed for this thesis, as they were embedded in more general acquired brain injury papers.

4.1.6 Summary and Conclusions

Although all three of the studies have their limitations, particularly the methodological design, they all demonstrate positive advancements in the rehabilitation of cognitive and learning deficits within the paediatric neurooncology population. It is important to acknowledge that all of the interventions retrieved in this thesis are related to psychosocial interventions.
## Table 13. An Overview of the Excluded Studies due to Diagnosis Treated with Pharmaceutical Interventions

<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Design</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netson et al., 2011</td>
<td>Parent and teacher ratings of attention during a year-long methylphenidate trial in children treated for cancer.</td>
<td>A multiphase longitudinal double-blind crossover trial</td>
<td>Dependent upon the trial patients randomly received a variety of doses MPH.</td>
<td>Parents and teachers reported fewer problems in the areas of attention/cognitive problems, hyperactivity and ADHD symptoms one month after receiving MPH.</td>
</tr>
<tr>
<td>Conklin et al., 2010a</td>
<td>Predicting Methylphenidate Response in Long-Term Survivors of Childhood Cancer: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial</td>
<td>A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial</td>
<td>Patients randomly received a single dose of MPH (0.60 mg/kg; maximum dose 20 mg) on day 1 and placebo on day 2, or the reverse, in a double-blind crossover design.</td>
<td>MPH provides improvements for cognitive and behavioural symptoms of inattention in a subset of the population.</td>
</tr>
<tr>
<td>Conklin et al., 2010b</td>
<td>Long-Term Efficacy of Methylphenidate in Enhancing Attention Regulation, Social Skills, and Academic Abilities of Childhood Cancer Survivors</td>
<td>A multiphase, multisite trial Combining numerous randomized, double-blind, placebo-controlled, crossover trials</td>
<td>Dependent upon the trial patients randomly received a variety of doses MPH. The dosage ranged from a low-dose MPH (0.3 mg/kg; maximum dose, 10 mg twice daily to 18 mg daily and was titrated upward to 27 mg/d, and possibly 36 mg/d.</td>
<td>The findings demonstrated the maintenance of attention and behavioural benefits of MPH over a year.</td>
</tr>
<tr>
<td>Conklin et al., 2007</td>
<td>Acute neurocognitive response to methylphenidate among survivors of childhood cancer: a randomized, double-blind, cross-over trial</td>
<td>A randomized, double-blind, cross-over trial</td>
<td>Patients received MPH (0.60 mg/kg of body weight) and placebo that were randomized in administration order across participants.</td>
<td>Performance was evaluated using measures of attention, memory, and academic achievement. MPH has a better response with male patients who were older at the time of...</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Design</td>
<td>Intervention</td>
<td>Outcome</td>
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</tr>
<tr>
<td>Mulhern et al., 2004a</td>
<td>A randomized, double-blind, placebo-controlled trial of methylphenidate for attention problems in survivors of childhood cancer</td>
<td>A randomized, double-blind, placebo-controlled trial of Placebo, low dose MPH (LD; 0.3 mg/kg; maximum dose 10 mg b.i.d.), and moderate dose MPH (MD; 0.6 mg/kg; maximum dose 20 mg b.i.d.).</td>
<td>Short-term treatment with low-dose MPH can reduce attentional problems among survivors of childhood CNS tumours.</td>
<td></td>
</tr>
<tr>
<td>Mulhern et al., 2004b</td>
<td>Short-Term Efficacy of Methylphenidate: A Randomized, Double-Blind, Placebo-Controlled Trial Among Survivors of Childhood Cancer</td>
<td>A randomized, double-blind, placebo-controlled trial of Placebo, low dose MPH (0.3 mg/kg; maximum dose, 10 mg bid), and moderate-dose MPH (0.6 mg/kg; maximum dose, 20 mg bid).</td>
<td>Statistical significance and clinically relevant temporary improvement in attention and cognitive behaviours, with teachers also reporting improvements in academic competence.</td>
<td></td>
</tr>
<tr>
<td>Thompson et al., 2001</td>
<td>Immediate neurocognitive effects of methylphenidate on learning-impaired survivors of childhood cancer</td>
<td>A randomized, double-blinded, placebo-controlled trial of MPH</td>
<td>The results identified a statistically significant improvement on measures of sustained attention and overall index of attention problems. Although verbal memory showed greater improvement than the placebo group this was not significant. Furthermore, the ability to inhibit impulsive responding and reaction times did not improve significantly.</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Title</td>
<td>Design</td>
<td>Interventions</td>
<td>Outcomes</td>
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<tr>
<td>Hardy et al., 2011</td>
<td>Computerized Cognitive Training in Survivors of Childhood Cancer: A Pilot Study</td>
<td>A single-arm design</td>
<td>The Captain’s Log intervention program, consisted of 33 multilevel, entertaining, game-like “brain-training” exercises aimed at improving memory, attention, concentration, listening skills, self-control, patience, and processing speed. The intervention was conducted at least 50 minutes per week for 12 weeks, including the 2 prior cognitive interventions assessed with survivors.</td>
<td>Outcomes demonstrated significant increases in working memory and decreases in parent-rated attention problems.</td>
</tr>
<tr>
<td>Butler et al., 2008</td>
<td>A Multicenter, randomized clinical trial of a cognitive remediation program for childhood survivors of a paediatric malignancy</td>
<td>A multicenter, randomized trial</td>
<td>Participants given the intervention were seen for a total of up to 20 two-hr weekly sessions over 4–5 months. The interventions were programmatic but individualized, with three interdependent components: (a) hierarchically graded massed practice, (b) strategy acquisition, and (c) cognitive–behavioural interventions.</td>
<td>The intervention resulted in reports of improved attention and statistically significant increases in academic achievement.</td>
</tr>
<tr>
<td>Source</td>
<td>Title</td>
<td>Type</td>
<td>Description</td>
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<tr>
<td>Van’t Hooft et al., 2007</td>
<td>Sustained favourable effects of cognitive training in children with acquired brain injuries</td>
<td>A randomized control trial</td>
<td>The Amat-c involves a combination of daily practice and games/exercises in specific attention and memory techniques. It utilises behaviour modification, focused on learning strategies in daily life, and on the accomplishment of school tasks. The exercises are performed for 30 minutes 6 days per week for a period of 17 weeks, and gradually increase in difficulty. The treatment group exhibited significantly more persistent improvements in complex tasks of attention and memory in comparison to the control group. However, there were no differences on simple reaction time tests.</td>
<td></td>
</tr>
<tr>
<td>Butler &amp; Copeland., 2002</td>
<td>Attentional processes and their remediation in children treated for cancer: A literature review and the development of a therapeutic approach</td>
<td>A randomised trial</td>
<td>Twenty-one patients completed a cognitive remediation program. Those in the intervention group demonstrated statistically significant improvement on all attentional measures. In contrast, the comparison group did not manifest any significant changes. Neither group demonstrated statistically significant changes on the arithmetic achievement test.</td>
<td></td>
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</table>
CHAPTER FIVE: DISCUSSION

Recent medical developments have resulted in individuals with paediatric brain tumours living longer, consequently learning and cognitive deficits within this population have become of greater concern to researchers and clinicians. As far as it is known, no systematic reviews of the effectiveness of psychosocial and pharmaceutical interventions have been conducted. To investigate the research that exists for both psychosocial and pharmaceutical interventions, a systematic review was undertaken. The implications of the results for both research and clinical practice are stated.

5.1 The Effectiveness of Interventions for Paediatric Neurooncology Patients

5.1.1 Included Studies

5.1.1.1 Outcomes

A total of three studies were included in this thesis, all of which identify improvements in a patient’s neurocognitive and/or learning abilities as a consequence of specific psychosocial interventions. Despite these promising findings, it has been difficult to evaluate the effectiveness and generalisability of these interventions on the paediatric brain tumour population because each intervention aimed to facilitate the rehabilitation of different deficits such as memory or academic attainments (such as arithmetic) (Kerns & Thomson, 1998; Penkman & Scott-Lane, 2007). The heterogeneity of the patient sample also had consequences for the outcomes of this thesis. With no clear delineation of many important details such as the patient’s tumour type or prior deficits, it has been difficult to make any tangible conclusions. For the purposes of clarity the results will be reviewed in relation to the specific neurocognitive and learning outcomes that were the focus of the intervention.
5.1.1.1 Neurocognitive and Learning Outcomes

The main focuses of the studies were rehabilitation interventions that targeted some of the most prevalent neurocognitive impairments identified in paediatric neurooncology literature. These included attention and memory (Copeland et al, 1999; Mulhern et al, 2001; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008; Mulhern, et al. 2004b). In addition to assessing the outcome of the interventions on neurocognitive deficits, IQ scores and academic attainment were also an important focus. Reddick et al. (2003) proposed a relationship between neurocognitive deficits, academic achievement and declining IQ in his developmental model (Figure 4). This model suggested that declining IQ and diminishing academic achievement scores may be a direct result of attention and memory deficits, which is also linked to a reduction in normal-appearing white matter volume.

a) Attention

Attention can be separated into a variety of different domains/sub-domains, including: focused, sustained, selective, alternating and divided, highlighting the complexities of this aspect of cognition (Mapou & Spector, 1995). With focused attention identified as the main concern for the paediatric neurooncology population (Dennis et al, 1998) Attention has a significant role in information processing, and is thought to be the foundation of most cognitive and neuropsychological functions (Cooley & Morris, 1990; Eysenck & Keane, 2005). Dennis et al. (1998) suggest that attention may be an important factor in the acquisition of new information. The impairment of an individual’s ability to acquire new information could be a significant hindrance to future learning and development, specifically academic achievement. Therefore it is unsurprising that attention is an important aspect of rehabilitation literature and this is addressed by the studies retrieved in this thesis.
An evaluation of an attention process training programme was undertaken by Butler (1998), which aimed to strengthen attention, perceptual and non-verbal cognitive processes. The results of the Butler (1998) study demonstrated an improvement in attention skills and areas of arithmetic competence. The patient’s post-treatment scores increased over time from the second baseline assessment, but it is important to note that the scores never returned to the same level as the initial baseline scores in the WISC-III, which measures intellectual functioning, measuring verbal and performance scales (the verbal scale includes: general knowledge, language, reasoning, and memory skills, while the performance scales measures: spatial, sequencing, and problem-solving skills).

However, improvements in the baseline scores are noted on the WRAML, an assessment which evaluates memory functioning and the WRAT-3, which measures the basic skills of reading, spelling and arithmetic, highlighting potential discrepancy between the WISC-III scores and the scores for the WRAML and the WRAT-3, as these tests utilise similar cognitive functions such as attention and memory.

The discrepancies in the scores may be accounted for by improvements in memory in the WRAML and WRAT-3. Sentence memory in the WRAML evaluates immediate verbal memory and arithmetic skills, which have been linked with visuo-spatial working memory (Ashkenazi, Rosenberg-Lee, Metcalfe, Swigart, & Menon, 2013; Sheslow & Adams, 2009). Whereas digit span and arithmetic both explore freedom from distractibility, which incorporates aspects of attention and working memory (Kaufman, 1994).
i. Limitations of the Butler (1998) study

Although the Butler (1998) study provides some positive results which support the use of an attention process training programme, there are also a number of factors which make it difficult to draw clear conclusions from the findings. Limited information is given about the patients utilised in the study, providing the reader with just the patient’s type of tumour and any previous cognitive or learning difficulties. There is no information regarding the sample from which the patient was drawn or what methods of selection were used. Butler himself recognises that gains made by the patient during the intervention may not have been a direct result of treatment efforts and may instead have been gained via recovery processes and/or typical development. Thus further research considering how different aspects of attention, for example, focused, selective, sustained, alternating and divided, can be incorporated into rehabilitation strategies, needs to be undertaken to support this finding.

Furthermore, the study only presents a brief analysis of the findings. It does not account for the missing results for the post-treatment Verbal IQ score. There is also no explanation for the decrease in functioning between the patient’s baseline and second scores, although it is hypothesised that this may be the consequence of the patient’s radiotherapy treatment. Mulhern et al. (2004a) suggest that a decline in a patient’s IQ may be linked to the loss of cerebral white matter and a failure to develop white matter at an adequate rate in relation to the child’s development. White matter depletion is noted to be associated with radiotherapy and may help to explain the differences between the baseline scores (Moore, 2005).
ii. Recommendations

Attention process training programmes require testing on a larger scale, with more participants. This study was published in 1998 and may have been the initial work for some of Butler’s more recent studies using cognitive behavioural therapy and metacognitive strategies techniques as part of the cognitive remediation intervention (Butler & Copeland, 2002). It is disappointing that Butler’s more recent studies utilised heterogeneous patient populations (brain tumour and leukaemia patients), as they provide support and reinforce the results of this study by demonstrating improved attention and academic achievement via randomised studies.

b) Memory

Memory is a vital storage system, but it also is involved with many other important functions, such as cognitive flexibility and planning ability, as well as the ability to self-monitor, it is also important in higher order thinking, learning, and academic achievement. (Eysenck & Keane, 2005; Just & Carpenter, 1992). Because of these functions memory is an important focus for rehabilitation interventions. The study conducted by Kerns and Thomson (1998) focused on the development and implementation of a compensatory memory aid.

The results of the Kerns and Thomson (1998) study demonstrated that the patient maintained an average overall IQ score on the WISC. Although there was no improvement in the results of the outcome measures, these are positive findings as a compensatory aid should enable the patient to maintain their level of functioning. Previous studies have demonstrated that children who develop a brain tumour and undergo a variety of different primary interventions have an increased risk of cognitive and learning deficits, which are often demonstrated by secondary consequences such as
IQ loss and sub-optimal academic achievement (Butler & Mulhern, 2004). Therefore being able to maintain an overall level of cognitive functioning/academic achievement demonstrates a possible improvement in some areas of cognitive functioning.

Despite these positive findings, it is of concern that the patient demonstrated problems with memory and new learning on the WRAML, and information and picture arrangement on the WISC, which may indicate difficulties in acquiring new verbal and social information. As previously noted Dennis, Hetherington, and Spiegler (1998) suggest cognitive deficits may be related to deficiencies in basic processes by which knowledge is acquired by considering evidence for the negative long-term effects of primary treatments, such as neurosurgery, chemotherapy and radiotherapy, on white matter. Supporting research which links cognitive and academic deficits to a diminished ability to acquire new information, rather than a loss of previously learnt information (Palmer et al., 2001).

Other important findings from the compensatory memory study are related to academic achievement. Although some of the patient's scores increased slightly, the patient demonstrated a slight decline in age-related percentile ranking on the WRAT-R. This may suggest that although the intervention has provided some support for a range of academic challenges, the patient’s level of academic achievement was still below that of the normal population. Improvement was also evident to the patient’s teachers, who reported positive feedback in that they had no concerns about the patient handing in assignments or getting to class on time. However, this functional outcome is susceptible to bias and cannot be appropriately measured.
c) Academic Achievement

The Penkman and Scott-Lane (2007) study focused solely on academic skills. The study’s aim was to primarily evaluate the feasibility of delivering a prophylactic academic intervention to a child, whilst they are receiving an intensive medical treatment. As previously noted, this was not the main focus of this thesis. This thesis was concerned with the outcomes related to the effectiveness of the one-to-one academic tuition, and how it facilitates the development of compensatory skills.

The results suggest that the patient was able to make improvements above the pre-treatment baseline measures in areas of reading, particularly the ability to apply phonetic decoding skills, written language and the ability to spell. Although the results indicate improvements in the areas of word reading, reading comprehension and pseudo word these were not significant improvements. The patient did not improve in the areas of Numerical Operations and Mathematical Reasoning, which are both composite scores on the WIAT-II. As previously described, this may also be related to potential memory deficits (Ashkenazi et al., 2013).

Likewise the patient only met one of his educational objectives, which was to write and recognise a phonic vocabulary of twenty-nine graphemes. The patient was not able to read and spell all words up to and including grade two level on the Dolch sight-reading assessment. It is interesting that the mathematical objectives were not evaluated, particularly when numerical attainment was the only aspect that the patient did not improve upon on the WIAT-II test results. The study stated there were no measures available to systematically evaluate this aspect of academic achievement.
It is evident that there is support for specific educational tutoring programs, which show some efficacy at improving selected academic skills (i.e. mathematics). Although it seems that these programmes do not specifically address the cognitive deficits that underlie survivors’ academic problems.

i. Prophylactic Interventions

This study assessed the feasibility and effectiveness of an individualised prophylactic academic intervention. Although the study is related to a medical treatment, with the aim of improving academic skills in a patient who is at high risk of cognitive delay. It is still important to address the controversy surrounding the ethics of utilising a prophylactic intervention.

Prophylactic interventions are preventative interventions that are used to prevent rather than treat a problem. Hence it is important to determine if the intervention is in the patient’s best interests and if it will be of benefit to the patient. Hodges, Svoboda, and Van Howe (2002) feel that this is of high importance when working with paediatric populations, as children are unlikely to give meaningful informed consent. They believe children should not have to undertake a prophylactic intervention when other more conservative interventions exist. The Penkman and Scott-Lane (2007) do not address the ethics of using a prophylactic intervention, but they note the evidence for cognitive delay and impaired academic achievement in their rational of the study.
5.1.1.2 Impact of Moderating Factors on Interventions

The impact of moderating factors on the results are further aspects which need considering in the context of the results.

a) Age

Research indicates that six years of age is a critical period for determining neuropsychological outcomes during primary treatment, particularly for those under three years of age (George et al., 2003; Palmer et al., 2003; Palmer et al., 2001). It was difficult to determine the impact of age on the results, as the patients’ age ranged between eight and thirteen years of age. This also made it difficult to comment on the impact of the early vulnerability hypothesis, which will be reviewed later in this discussion.

b) Impact of Time since Treatment

Although the interventions utilised in the studies appear to have been of benefit to the patients, there was limited long-term follow-up in many of the studies. Limited long-term follow-up could have potentially negative implications for the effectiveness of the interventions, as previous long-term studies have recognised that cognitive functioning can decline with increasing time since the patient’s primary stage of treatment.

The patient in the Penkman and Scott-Lane (2007) study started the prophylactic academic intervention ten weeks post-radiotherapy and during chemotherapy. In comparison to the other studies, the Penkman and Scott-Lane (2007) intervention was
delivered during a different period of the patient’s treatment pathway. Part of the aims for this study was to identify the effectiveness of a preventative treatment. Therefore the patient did not receive/complete their primary treatment before starting the intervention, which could have implications for the development of neurocognitive impairments and learning outcomes. The outcome measures were recorded eight months post-treatment and demonstrated continued improvement in nearly all areas of academic attainment, but did not achieve all educational objectives.

Similarly the Kerns and Thomson’s (1998) compensatory memory system intervention also used follow-up measures, although these were more longitudinal, two years post-treatment and the results were varied. In comparison, the Butler (1998) study conducted post-treatment assessment immediately after the treatment was completed; demonstrating positive outcomes.

Butler and Mulhern (2005) suggest that the adverse effects of a primary medical intervention have been noted at around one to two years post-therapy. The results of the Kerns and Thomson (1998) were taken at a later stage post intervention in comparison to the Butler (1998) study, thus the Kerns and Thomson (1998) study may reflect a more effective intervention. Although the Butler (1998) study demonstrates more positive results than the other studies, it has limited follow-up results. It is also important to be aware that the study maybe further limited by the variation in the patient’s method and intensity of primary stage of treatments and the time scales at which these were undertaken prior to the assessment of the secondary intervention, as these factors may also have potential negative implications for the effectiveness of the interventions.
5.1.1.3 Comparisons to Normal Development

The studies retrieved demonstrated improvements in learning outcomes, particularly arithmetic (Butler, 1998; Kerns & Thomson, 1998; Penkman & Scott-Lane, 2007). However, the studies fail to account for maturation of the brain and improvement that is expected in normal development as children grow older. Consequently, this makes it difficult to determine whether the improvement made by the patients as a result of the intervention was greater than what is naturally anticipated.

a) Plasticity and the Early Vulnerability Hypothesis

Historically, interventions have focused on compensating for acquired deficits patients incur as a consequence of a brain tumour. Ecological interventions, such as accommodation within the school setting and the use of assistive technology have helped patients to compensate for their deficits (Armstrong & Briery, 2004). Similarly, the Kerns and Thomson (1998) study utilises a compensatory technique, a memory aid, to compensate for the patients’ memory problems. However, the Butler (1998) and Penkman and Scott-Lane (2007) studies were not restricted to compensatory interventions; for example the Penkman and Scott-Lane (2007) gave tutor sessions. Utilising theories of neuroplasticity, research would suggest that younger patients may receive greater benefit from these interventions because the brain can adapt to acquire new skills via these pragmatic approaches (Huttenlocher & Dabholkar, 1997). Thus interventions that enable the brain to develop further methods of functioning as the child develops may be of more benefit to the paediatric neurooncology population.
However, it should be noted that due to the age range of the participants in the studies, the results might be connected to the early vulnerability hypothesis. The patients were aged between eight and thirteen years, therefore, the early vulnerability hypothesis would suggest that the patients had favourable outcomes because they were at later stages of their development and their brain structure may have been further developed. Due to the limited age range and number of patients involved in this review it is difficult to determine the impact of these hypotheses on paediatric neurooncology rehabilitation.

5.2 The Effectiveness of Pharmaceutical Interventions for Paediatric Neurooncology Patients

This thesis aimed to look at the evidence for both psychosocial and pharmaceutical interventions for cognitive and learning impairment for paediatric neurooncology patients. However, none of the papers retrieved in the search met the inclusion criteria for this thesis. Thus no conclusions can be drawn about the effectiveness of this method of intervention for paediatric neurooncology patients.

5.3 Extraction of Additional Studies

The criteria for the search dates utilised in the review of the empirical literature were set in accordance with the first issue of the journals and January 2013 (the final search), which was six months prior to the anticipated completion date of this thesis. From January, the searches were calibrated to receive an automatic alert of all new literature that met the search criteria for the review. Studies that were retrieved by the automatic alert between January 2013 and June 2013 are noted in Appendix IV. None of the studies retrieved from the automatic alerts were of use to this thesis.
The PRISMA statement provides a beneficial tool for the critical appraisal of systematic reviews. Thus the PRISMA statement checklist (2009), reflections of the rigorous methods used in the review and consideration of potential bias on the quality of this thesis has been considered (Moher et al., 2009). The evidence for the PRISMA statement checklist is presented in Appendix V.

It is important to note that as this is a thesis a systematic review registration number was not attained. A protocol was developed to reduce bias and for the assessment report in the transfer viva, however this was not registered. The protocol has been incorporated and acknowledged in chapters two and three of this thesis. In addition to an internal review appraisal the transfer viva was an opportunity to gain an external review appraisal. This helped to reflect and appraise the project and reduce potential bias.

Despite attempts to reduce potential bias, it is challenging to eliminate bias completely, thus steps have been taken to raise awareness and reduce potential bias. A PICO process was used to frame the clinical question, during the development of this review. This ensured the review was useful, creditable and relevant. It may have been useful to develop a systematic descriptive map to help guide the question based on available research and uncover gaps in the research field.

The PICO process also helped to guide the development of the inclusion and exclusion criteria. Although these were devised stringently, it is important to remain mindful of the potential bias this may have introduced.
In an attempt to reduce bias the methodology of this thesis was developed systematically, rigorously and explicitly. The search strategies were developed in collaboration with different members of a multidisciplinary team, thus ensuring an internal review appraisal was utilised. This helped to make certain the search terms were rigorous and inclusive, producing a comprehensive and unbiased attempt to uncover published and unpublished, easily accessible and harder to find studies. Similarly the same extensive procedure was undertaken with the selection of the databases.

Aspects such as the search log included details of both electronic and hand searches which were undertaken to help replicate the study and identify different varieties of literature including studies which may have not been published. Unfortunately due to time constraints it was not possible to contact authors individually to ascertain details that may have aided this thesis. This may have increased the bias of utilising published studies reporting statistically significant results. Utilising reference managing tools such as EndNote was valuable resource to identify duplicates and sort the references.

The data analysis procedure was also at risk of bias. It was challenging to describe the studies during the synthesis, as pooling the details and results into a group of studies could not be achieved. For example assessing the summary of measures section, as the outcomes of primary interest were different between the studies (memory, attention and academic achievement). Thus a common summary measure was not chosen. This had consequences for the planned method of analysis, meta-analysis, which could not be undertaken due to aforementioned differences.
As part of the data analysis a data extraction form was developed. This form also considered the critical appraisal of the extracted research. The aim of the form was to ensure the validity, reliability and potential bias had been acknowledged. The potential weaknesses of the critical appraisal of the data extraction from are discussed further in the limitations of this review.

5.5 Limitations of the review

5.5.1 Number of Included Studies

The aim of systematic reviews are to summarise large quantities of data explicitly and transparently, ensuring the process is accountable, replicable and updateable, thus reducing bias which can occur in other approaches to reviewing research evidence. Only three studies retrieved met the inclusion criteria for this review. Due to the limited number of retrievals it is difficult to present clear findings regarding the effects of psychosocial interventions on paediatric brain tumour populations. Additionally no conclusions could be made regarding the search investigating the effectiveness of pharmaceutical interventions, without the risk of creating potentially biased conclusions; as no studies met the inclusion criteria that utilised pharmaceutical interventions.

A further consequence of the limited retrieval was the method of data analysis that was utilised in this thesis. Only a narrative review of the results could be undertaken, as a meta-analysis required more than three included studies. Although a narrative review has many benefits, such as providing a broad overview of relevant information, it does not allow for the data to be mathematically combined, which may have provided a more precise estimate of the underlying “true effect”.

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5.5.2 **Heterogeneous Patient Samples**

The heterogeneity of the patients recruited in each of the studies was diverse. The variations in the population included their gender, age, tumour type, the primary interventions the patients received, the time span of the patient’s treatment pathway and the cognitive/learning intervention assessed by the study. Literatures suggest that each of these factors can have an impact on the degree and type of impairment, which may also have consequences for the effectiveness of the interventions (Moore, 2005; Nejat et al., 2008; Spiegler et al., 2004).

5.5.3 **Methodological Quality**

A critical appraisal of the studies retrieved in this thesis was undertaken using the Downs and Black quality assessment tool (1998), to ensure a structured, reliable and appropriate appraisal was conducted. The Downs and Black quality assessment tool (1998) was used to identify risk of bias, choice of outcome measure, statistical issues, quality of reporting, quality of the intervention and generalisability. The results of the appraisal identified some important limitations, specifically in the methodological quality of the studies.

The quality of the evidence used in this review is impeded by the methodologies of the studies. Hence Cochrane reviews have a strict inclusion criterion that limits included studies to randomised control studies (RCT) only. Thus, it was important that this thesis was mindful of the quality of the literature in the review as there was an absence of RCTs and other ‘gold standard’ methodological approaches.
The Penkman and Scott-Lane (2007) study achieved the highest score of 11 points out of a total of 31 points on the Downs and Black quality assessment tool. Despite having the highest score of the three studies, it still represents a lower quality study in general research. All three studies had limitations related to insufficient information to allow a reader to make an unbiased assessment of the findings of the study, internal/external validity and power.

On reflection, the Downs and Blacks critical appraisal tool was not the most appropriate method to assess the quality of the studies. The Critical Appraisal Skills Programme has specific critical appraisal checklists, such as the case control study checklist, which would have been more appropriate (Critical Appraisal Skills Programme, 1993). Or the single-case experimental design scale by Tate et al. (2008), a critical appraisal tool which provides a brief and valid evaluation of methodological quality of single-subject designs.

5.5.4 Outcome Measures

The aim of rehabilitation within paediatric neurooncology services is to promote continued learning and help patients maintain an adequate level of cognitive functioning; Limond and Leeke, (2005) equate this to an improvement in daily functioning. Yet in the studies retrieved in this thesis emphasis is generally placed on the results of standardised outcomes, to identify the impact of interventions on general ability. Thus the results of assessments such as the Wechsler Intelligence Scales, Wide Range Achievement Test and the Wechsler Individual Achievement Test-II demonstrated findings that have limited interpretation regarding the adaptive functioning of the patients in the studies. However, it is important to note that the use of such measures does promote replicability, as they are valid and reliable. Despite the validity and
reliability of these measures it is still important to consider interpersonal and contextual factors that may impact upon reliability.

In addition to the above limitations, the Kerns and Thomson, 1998 and the Penkman and Scott-Lane, 2007 studies both comment on the use of non-standardised teacher and parent reports of progress and satisfaction. Although these progress reports do offer some important reflections, Limond and Leeke, (2005) suggest the use of standardised satisfaction measures are “more appropriate” than rehabilitation feedback. This is particularly important as standardised measures can allow clinicians to compare their outcomes with alternative interventions. Such measures also enable the incorporation of the results into a meta-analysis. Furthermore, if the same measures were used across different treatment centres this would allow for further comparative analysis.

5.5.5 Stringent Inclusion Criteria

The stringent restrictions on the diagnosis of the patients used in this thesis were a particular problematic limitation. Many potentially useful studies retrieved in the searches could not be included in the final results. The search demonstrated limitations regarding the integrating of different diagnoses in the results sections of many of the studies retrieved. Thus several of the studies met the inclusion criteria in all aspects but diagnosis (Conklin et al, 2010a; Conklin et al, 2007; Conklin et al, 2010b; Mulhern et al, 2004a; Mulhern et al, 2004b; Netson et al, 2011; Thompson et al, 2001). This was primarily related to pharmaceutical studies, which explored the use of MPH in the rehabilitation of paediatric populations. Similarly a number of psychosocial studies also met the inclusion criteria in all aspects but diagnosis for example Butler et al, 2008, Hardy et al, 2011, Van’t Hooft et al, 2007 and Butler & Copeland, 2002. The majority of
these studies were primarily conducted utilising cognitive remediation. Cognitive remediation provides a systematic approach, utilising different strategies such as: behavioural interventions, cognitive behavioural therapy, instruction in metacognitive strategies, social skills training, traditional brain injury techniques such as massed practice, and supportive and dynamic psychotherapeutic approaches to improve cognitive functioning (Butler & Mulhern, 2005).

These studies amalgamated the results of patients diagnosed with a brain tumour or acute lymphoblastic leukaemia. Consequently, the results could not be separated to identify which results came from which population. As the focus of this thesis was on only paediatric brain tumours, the results of studies which combined patients with a diagnosis of acute lymphoblastic leukaemia and brain tumours would not be utilised in this study as there was a potential risk of confounding results and bias.

5.5.6 Education Literature

Education is an important facet in the continued development of children, particularly those diagnosed with a brain tumour, as it can be used to identify, or facilitate the rehabilitation of, cognitive and learning deficits. Despite the importance of education, the education literature and databases reviewed in this thesis contained nothing of relevance for the rehabilitation of cognitive and learning processes in children diagnosed with a brain tumour. It is astonishing that in their own right education services have not undertaken a key role in rehabilitation in this field, particularly as cognitive and learning deficits are being diagnosed in children from an early age. Subsequently, children with a brain tumour are at a disadvantage. The consequences of this may not often be fully recognised until later life as literature states that cognitive and learning deficits develop with time since treatment, as the child ‘grows into their deficit’ (Mulhern et al, 2004a;
Mulhern et al, 2001; Spiegler et al, 2004). Further research is required utilising educational interventions, as they may have a positive impact on a child’s development and help to reduce or support emerging deficits.

5.6 Recommendations for Further Research and Clinical Practice

With the growing number of survivors of paediatric brain tumours, survival is no longer the only concern to clinicians. Clinicians and researchers also need to address the neurocognitive and academic requirements of this population as they become increasingly recognised by research and literature. Although evidence for the prevalence of neurocognitive deficits and learning impairments exists, the evidence base is limited and no national programme/guidelines have been developed to support the rehabilitation needs or provide educational support for this population (Brown, 2004).

The current volume of literature for paediatric brain tumour is not concordant with the concern that is currently identified for this population. It is hypothesised that this may be a consequence of numerous aspects. Neurooncology is a largely associated with a medical model, with concerns orientated towards survival rather than cognitive and learning deficits. This model has implications for research that is also largely focuses on the survival of this population. Subsequently, from a psychological perspective, this can have an impact on our clinical training and the clinical research we are encouraged to undertake in training.

Therefore it is important to consider the current asymmetry between clinical concern and the research enterprise and what this means for the future involvement of Clinical
Psychology. It is also important not to neglect the important role of the health care and education systems, and to consider what each can bring to rehabilitation services.

5.6.1 Current Clinical Practice

Nationally, paediatric neurooncology rehabilitation services are limited. From a psychological perspective the focus of their work is predominantly on neuropsychological assessment, and rehabilitation services are often restricted to interventions that predominantly focus on helping the patient compensate for their deficits. These include compensatory interventions such as special education support, environmental modification and assistive technology (Brown, 2004). As seen in this thesis, there is limited evidence in favour of these interventions. However, some cognitive function, for example episodic memory cannot be restored. Thus compensatory interventions can be vital to support a patient to achieve an appropriate level of functioning. It is also important to consider the disadvantage of a patient’s geographical location, as different services offer varied levels of support. It seems the NHS has not developed to meet the unique needs and problems of a paediatric neurooncology population and as a consequence these children are at a disadvantage.

Although there is a limited evidence base for neurocognitive and learning interventions in paediatric neurooncology populations a significant evidence base has developed in acquired brain injury and ADHD populations. It would be useful for neurooncology research and clinical practice to take guidance from the MTA trials for the treatment and management of cognitive deficits (MTA Cooperative Group, 1999).
a) Services

In light of the evidence that exists for neurocognitive and learning deficits, uniformed health care services are needed to ensure they are supporting patients and working alongside education systems to provide appropriate interventions in addition to neuropsychological assessment. Value can be added to clinical services by harnessing the skills and expertise of Clinical Psychology and Clinical Neuropsychology to conduct complex neuropsychological assessments and formulation and influence a medical driven model of service. A shared understanding of uniformed outcome measures need to be agreed upon to ensure all deficits and learning problems are being identified and thus supported. A battery of assessments should be developed nationally between services to ensure this collaborative approach. This would also have positive implications for further research.

In addition to health care services, education systems need to be utilised to ensure interventions are being conducted appropriately and children are supported in academia. Links between these services are vital to allow for consistent care, particularly as the child develops. All of the interventions in this thesis placed emphasis on academia; however, as previously noted there are currently limited interventions for children in schools, as there is no evidence base for compensatory interventions. Thus it is important to consider how equipped schools are to work with children with the challenges of cognitive and leaning deficits. The patients and their families are often offered limited support and subsequently schools are lacking in the knowledge and understanding of their educational needs and the ability to provide much needed support to patients and their families. Steps need to be taken to ensure that academic institutions are providing patients with a paediatric brain tumour long-term support within schools.
With an aging population not only do services need to ensure the child is supported as they move through the educational system but that they are also supported as they make the transition into adulthood, careers and adult services. Thus communication between adult and child services is also a key factor.

b) Moderating Factors

A consideration of the moderating factors, which may impact on the effectiveness of interventions, also needs to be addressed in clinical settings and research. This thesis has noted potential implications of the effect of time since treatment. Until further research has been undertaken to determine the impact of this factor, it is important for patients to maintain links with treatment facilities and for teachers to be aware of the phenomenon of ‘growing into a deficit’. Thus it may also be important to consider if rehabilitation strategies should be more appropriate at different developmental stages.

c) Method of Intervention

A vast amount of neurorehabilitation research and literature is limited in that the main focus of the interventions are on the acquisition of strategies designed to improve performance in cognitive and academic outcomes. Likewise this was evident in the studies retrieved in this thesis. These rehabilitation programmes require lots of resources, since one-to-one sessions are often idiosyncratic and are required for a prolonged period of time. Furthermore, the mode of treatment is impractical for larger groups of survivors who live near medical centres that could provide the program. Therefore it is critical that effective home/school-based interventions are developed; interventions that are relevant to a wide-range of potential patients who will not be restricted by time, distance or cost.
5.6.2 Further Research

The findings of this thesis indicate that further evaluations of the effectiveness of different pharmaceutical and psychosocial interventions need to be undertaken to enable the development of evidence-based practice for paediatric neurooncology populations. This thesis has demonstrated limited conclusions, but has highlighted the potential for further research in different aspects of paediatric neurooncology rehabilitation. This also highlights an opportunity for Clinical Psychology to use its skills and research expertise to help develop an evidence base and add further value to clinical practice.

a) Attention

When considering the focus of further research it is important to acknowledge that trying to categorise cognition can be an arbitrary process, as it can be challenging to separate processes and systems in the brain. Pribram (1997) emphasises the importance of the critical relationships among components of cognition and between these components and learning processes. Thus impairments to attention systems and other cognitive processes are of importance to rehabilitation strategies.

Limond and Leeke (2005) suggested that attention rehabilitation strategies fall into four categories which include: attention process training, self-management strategies, environmental modifications and psychosocial support for emotional and social factors; these are often used in combination. Attention process training is identified as being the focus of most intervention research (Limond & Leeke, 2005). This is unsurprising as attention processes have demonstrated to be the foundation of most cognitive and neuropsychological functions (Eysenck & Keane, 2005). However, Ylvisaker and Feeney (1998) identify four more traditional types of approaches, these include: a
processing specific hierarchically organised restorative approach, a task specific skills based approach, a compensatory approach that attempts to improve performance by helping individuals develop strategic procedures and a compensatory approach which modifies an individual’s tasks or environment. All approaches to rehabilitation should be considered and potentially combined to develop an effective and efficient rehabilitation intervention.

Literature indicates that deficits in attention are often the result of damage to the reticular activating system within the brain stem, in addition to bilateral cortical damage (Ylvisaker and Feeney, 1998). Ylvisaker and Feeney (1998) suggest that many patients will experience fatigue, which can negatively impact alertness. Patients will most often experience impairments to prefrontal structures which have consequences for executive or supervisory control attention processes (Shallice, 1988). Executive attention control processes include: sustaining attention, concentrating (directing) attention, sharing (dividing) attention, suppressing attention (filtering), switching (shifting) attention, preparing attention and setting attention (Ylvisaker and Feeney, 1998). These complex systems need to be addressed in rehabilitation interventions.

Dennis, Hetherington, and Spiegler (1998) go on to suggest deficits in areas such as attention may result in difficulties acquiring new information, which can be reflected in a patients IQ and academic achievement. Thus interventions that are aimed at developing attention processes should be promoted within rehabilitation services and be the focus of further research. Literature suggests that cognitive remediation and MPH are two such interventions, which may offer valuable rehabilitation, particularly to those with attention difficulties (Butler & Copeland, 2002; Conklin et al, 2010a)
The MTA studies, which compared four distinct treatment strategies during childhood for patients with a diagnosis of ADHD, are a good example of how combined interventions are demonstrated to be significantly superior to standalone treatments. Thus developing a study that explores the impact of combined psychosocial and pharmaceutical interventions on learning and neurocognitive deficits in a paediatric neurooncology population on a larger scale is required.

In comparison, it is questionable how feasible it would be to commission non-drug related research with a child population; currently less than five percent of all registered studies involve children and a non-drug related intervention (Modi, Clark, Wolfe, Costello, & Budge, 2012). This may explain the limited number of studies retrieved from search one and may also account of the lack of research in educational settings.

A single centre study would not be appropriate; similar to the MPH trails it is recommended that further research should be replicated in numerous centres that may allow for the collection of quality single case studies or higher-level quasi-experimental randomised study designs utilising the same outcome measures.

b) Methodologies

There is a clear need to address the methodological difficulties that are highlighted in this thesis. The methodologies of the studies included in this thesis have limited the generalisability of the findings. Ideally future research should focus on utilising experimental designs, particularly RCTs. The Oxford Centre for evidence-based research identifies that RCTs are level one evidence, which is regarded as the highest level of evidence. However implementing RCTs in this area of research may not be
feasible as paediatric neurooncology populations are small in comparison to other childhood illnesses. As a result compromise about methodological quality and sample size needs to be addressed.

Potential ethical considerations of not giving all patients the best available interventions or at the most appropriate stage during the recovery process would also need to be addressed. RCT’s require control groups thus patients may not receive appropriate treatment at the appropriate stage of treatment. Utilising higher level quasi-experimental randomised study designs that yield more convincing evidence for causal links between interventions and outcomes may help to develop an evidence-base for paediatric neurooncology patients. Alternatively using the RoBIN-T scale for single case design, may help to identify experimental versus non-experimental single-case designs and rate the methodological quality of experimental single-case designs (Tate et al, 2013).

c) Core Outcome Measures and Further Research

Systematic reviews are often limited by the inconsistencies in the outcomes used in clinical trials in specific areas of health care; paediatric neurooncology is no exception. Among the three studies retrieved there were limited consistencies in the outcome measures used. However, without some form of outcome protocol there is no guarantee that similar outcome measures will be used in future research. Williamson, Altman, Blazeby, Clarke, and Gargon (2011) suggest that clinicians/researchers should agree on a set of outcome measures to allow for the development of a further systematic review, which can utilise a meta-analysis to identify appropriate interventions. Agreeing on a set of measures will reduce the risk of measuring inappropriate outcomes, help to simplify the reporting of outcomes, and reduce the reporting of selective reporting of outcomes will be reduced. The Core Outcome Measures in Effectiveness Trails (COMET)
initiative aims to provide guidance for researches to develop consistencies within research and allow for the better reporting of systematic reviews (Williamson et al., 2011). Thus a recommendation for further research would be to utilise the COMET initiative and to agree on a set of outcome measures that would appropriately measure the impact of psychosocial and pharmaceutical cognitive and learning deficits.

d) Update of this Review

It is hoped that the results of this thesis and the recommendations made will be used to continue developing and conducting research in the field of psychosocial and pharmaceutical interventions in paediatric neurooncology. Building upon the results of this thesis, considering its limitations and further research, another systematic review should be undertaken to identify any further developments in this research.

5.7 Summary and Conclusions

Research identifies that tumours of the brain and the CNS account for a quarter of all childhood cancers (Cancer Research UK, 2010). Although brain tumours in the paediatric population are a rare condition, it is the most frequent cause of death from disease in children aged 1-14 years, and accounts for just under a fifth of all bereavements in childhood cancers (Cancer Research UK, 2010). Earlier detection and medical advancements have resulted in increased survival rates and consequently children are living longer with a greater risk of deficits in attention, working memory and processing speed which may lead to the secondary consequences of IQ loss and academic problems (Sands, 2009). Hence the objectives of this thesis were to identify and evaluate the effectiveness of psychosocial and pharmaceutical interventions for cognitive and learning impairment within a paediatric neurooncology population.
The results presented in this thesis demonstrate limited conclusions regarding the effectiveness of psychosocial and pharmaceutical interventions for cognitive and learning deficits. They identify a limited evidence base, which does not contain any RCTs or controlled trials. Additionally, few conclusions, comparisons and generalisations can be made about the results due to the heterogeneity of the patients, treatment variables and outcome measures used in each of the studies. Hence there were difficulties in identifying common aspects among the results and in determining whether the results had been hindered by the methodologies or if the interventions were inefficient. Despite the limitations in the generalisability of the papers reviewed in this thesis, neuropsychology remains an important part of neurorehabilitation, providing information and encouraging the awareness of patients’ cognitive and learning strengths and weakness and utilising their strengths to compensate for their deficits. This thesis highlights that Clinical Psychology, with the support of Neuropsychology needs to be providing and coordinating rehabilitation, in addition to offering neuropsychological assessment and consultation to significant others, teachers and professionals as part of a neuropsychological intervention.

The limited conclusions the studies retrieved in this thesis report some important conclusions that are relevant to paediatric brain tumour populations and may help to guide future clinical interventions and research. Although all of the results come from individual cases, all of the interventions indicate some positive neurocognitive and learning outcomes, specifically in the area of attention (Penkman & Scott-Lane, 2007). It is important to note that this is still a new area of research, as previously discussed, recent medical advancements have reduced rates of morbidity and disability and clinicians and researches are attempting to explore alternative interventions which have
been successful in other population groups, such as MPH and the success it has demonstrated in treating attention deficits in ADHD populations (MTA Cooperative Group, 1999). Developing a national research project on a similar scale to the MTA trials would help to develop a large sample within this small population. If this is to be achieved a national protocol needs to be developed alongside COMET to design a uniformed approach for assessment and intervention. To be of clinical importance, further research needs to consider both psychosocial and pharmaceutical interventions and to develop an appropriate service provision that can address long-term neurorehabilitation and psychological needs. Cognitive remediation and MPH may be potential interventions as they address issues of attention deficits and other cognitive, learning and psychological problems.

These interventions highlight an important research opportunity, the opportunity to determine whether or which stimulants and cognitive interventions should be central to clinical practice in a paediatric brain tumour population by ensuring routine scrutiny of cognition, particularly attention and scholastic outcome. It is important that paediatric rehabilitation services are delivering optimum care as patients may continue to utilise rehabilitation services throughout childhood and as they transition into adulthood and later life.
REFERENCES


**APPENDICES**

Appendix I: Search terms

**Children AND Brain Tumours AND Treatments AND Psychosocial OR Pharmaceutical Interventions**

- **Children**
  Mapping terms: Paediatrics etc (where appropriate)
Search terms: infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR neo-nat* OR perinat* OR postnat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatic* OR paediatric* OR post-nat* OR Preterm* OR Prematur* OR Postmatur* OR Pre-pubescen* OR schools OR school nursery school* OR preschool* OR pre school* OR pre-school* OR Schoolchild* OR secondary school* OR primary school* OR secondary school* OR elementary school* OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools OR nursery OR infant OR newborn


• Brain Tumours

Mapping term: Brain tumours/Brain neoplasms etc

*Search terms:* ("Acquired brain injur*" OR ABI* OR Angiolipoma OR Anaplastic OR "Anaplastic astrocytoma*" OR "Anaplastic ependymoma" OR "Anaplastic ganglioglioma" OR "Anaplastic haemangiendothelioma" OR "Anaplastic haemangioepithelioma" OR "Anaplastic Medulloblastoma" OR "Anaplastic Oligoastrocytoma" OR "Anaplastic Oligodendrogioma" OR "Angiocentric ganglioglioma" OR "Angiocentric glioma" OR Angio* OR Astroblastoma OR Astrocytoma* OR "Astrocytic tumo*r*" OR "Acoustic neuroma*" OR Atypical OR "Atypical choroid plexus papilloma" OR "Atypical teratoid rhabdoid tumo*r*" OR ATRT* OR "Central neurocytoma" OR "Cerebellar liponeurocytoma" OR Chordoma* OR Chondro* OR Choriocarcinoma OR Choroid OR "Choroid glioma of the third ventricle" OR "Choroid plexus papilloma" OR "Choroid plexus carcinoma" OR "Choroid plexus tumo*r*" OR "Clear cell" OR "cerebral lymphoma" OR "cerebral metastases" OR "CNS ganglioneuroblastoma" OR "CNS neuroblastoma" OR CNS AND "primitive neuroectodermal tumo*r*" OR Cranioopharyngioma* OR "Desmoplastic medulloblastoma" OR "nodular medulloblastoma" OR "Diffuse astrocytoma" OR "Diffuse melanocytosis" OR "Dysembryoplastic neuroepithelial tumo*r*" OR DNET OR "Embryoblastoma" OR "Embryonal tumo*r*" OR Ependymoblastoma OR Ependymoma* OR "Ependymal tumo*r*" OR "Epithelioid haemangiendothelioma" OR "Epithelioid MPNST" OR "Ewing sarcoma-PNET" OR "Extraventricular neurocytoma" OR "Fibrillary astrocytoma" OR Fibrosarcoma OR Fibrous OR Fibroblastic OR Ganglio* OR "Gemistocytic astrocytoma" OR "Germ cell tumo*r*" OR Germinoma OR "Giant cell glioblastoma" OR Gliona* OR Gliosarcoma OR "Glioblastoma multiforme" OR Glioblastoma OR "Gliomatosis cerebri" OR "Granular Cell tumo*r*" OR "Granulocytic sarcoma" OR Haemangio* OR "Haematopoietic neoplasms" OR Hemangio* OR
Hemangioblastoma* OR Hibernoma OR "Intracranial solid neoplasm*" OR "Intracranial germ cell tumo?r*" OR "Intracranial germinoma" OR "Kaposi sarcoma" OR "Large cell medulloblastoma*" OR Leiomyo* OR Lipoma OR Lymphoma OR "Lymphomas neoplasms" OR "Lymphoplasmacyte-rich" OR "Malignant fibrous histiocytoma" OR "Malignant lymphomas" OR "Malignant melanoma" OR "Malignant peripheral nerve sheath tumo?r*" OR "Malignant perineurioma" OR "Meningeal melanomatosis" OR Medulloblastoma* OR "Medulloblastoma* with extensive nodularity" OR Medullopithelioma OR "Melanotic MPNST" OR Melanocytoma OR Meningioma* OR Meningothelial OR "Mesenchymal tumo?r*" OR Metaplastic OR "Metastatic neuroblastoma" OR "Metastatic tumo?r*" OR Microcystic OR "Mixed germ cell tumo?r*" OR "MPNST with mesenchymal differentiation" OR "MPNST with glandular differentiation" OR "Myxopapillary ependymoma" OR "Neuroepithelial tumo?r*" OR Neurofibroma* OR Neuro-oncolog* OR neurooncolog* OR Oligodenrogli* OR "Oligoastrocytic tumo?r*" OR Oligoastrocytoma OR "Optic pathway glioma" OR Osteo* OR Papillary OR "Papillary giloneuronal tumo?r*" OR "Papillary tumo?r* of the pineal region" OR Papilloma* OR Paraganglioma OR Perineurioma OR Pilomyxoid OR Pilomyxoid AND astrocytoma* OR Pinealoma OR Pineoblastoma OR Pineocytoma OR "Pineal parenchymal tumo?r* of intermediate differentiation" OR "Pineal region tumo?r*" OR "Pituitary adenoma*" OR "Pituitary tumo?r*" OR "Pilocytic astrocytoma*" OR Pituicytoma OR (Posterior adj2 fossa*) OR Plasmacytoma OR "Pleomorphic xanthoastrocytoma" OR Plexiform OR PNET* OR "Primary melanocytic lesions" OR "Primitive neuro-ectodermal tumo?r*" OR "Primitive neuro-ectodermal tumo?r*" OR "Primitive neuro-ectodermal tumo?r*" OR "Protoplasmic astrocytoma*" OR Psammomatous OR Retinoblastoma* OR Rhabdoid OR Rhabdomyo* OR "Rosette-forming giloneuronal tumo?r* of the fourth ventricle" OR Secretary OR "Solitary fibrous tumo?r*" OR "Spindle cell oncocytopla of the adenohypophysis" OR "Subependymal giant cell astrocytoma*" OR Subependymoma OR BT* OR Teratoma OR "Teratoma with malignant transformation" OR "tumo?r* of the Meninges" OR "Tumo?r* of the sellar region" OR "tumo?r* of meningothelial cells" OR "Tumo?r* of the pineal region" OR Transitional OR "Yolk sac tumo?r*")

- **Treatments**

*Search terms:* ("surgical interven*t*" OR "physical interven*t*" OR (Radiation adj2 therap*) OR radiotherap* OR Irradiat* OR "intracranial biopsy" OR Avastin OR CRT OR "conformal radiotherap*" OR "conformal radio therap*" OR "conformal radiotherap*" OR "conformal radio therap*" OR "craniospinal radiotherapy" OR chemotherap* OR Craniotomy OR cyberknife OR methotrexate OR neurosurg* OR neuro-surg* OR (tumo?r* adj2 resection) OR radiosurg* OR "gamma knife" OR "gliadel wafer" OR (stereotactic adj2 surg*) OR (proton adj2 therap*) OR brachytherap* OR "tumour resection" OR "stereotactic biopsy" OR Interferon OR "intrathecal chemotherapy" OR "Intensity-modulated radiotherapy" OR "Intensity modulated radiotherapy" OR "ventriculo-peritoneal shunt" OR stimulant* OR IMRT OR "intensity modulated radiation therapy" OR methylphenidate OR MPH OR atomoxetine OR dexamphetamine OR modafinil OR concerta OR ritalin OR biphentin OR attenta
OR methylin OR metadata OR equasym OR rubifen OR motiron OR stimdate OR daytrana OR strattera OR "3rd ventricle ostary" OR "Third ventricle ostary" OR temozolomide OR "ventriculoperitoneal shunt" OR "VP shunt" OR dexedrine OR medikinet OR provigil OR amphetamine OR pemoline

- **Psychosocial Interventions**

*Search terms:* (Neuro-psych* adj2 intervent*) OR (Neuro-psych* adj2 rehabilit*) OR remediat* OR intervent* OR assistive technology OR Attention* process train* OR behavio?r* program* OR behavio?r* modification OR behavio?r* OR cognit* OR cognit* aid* OR compensatory strateg* OR (interven* adj2 recommend*) OR (interven* adj2 plan*) OR learn* program* OR ecological adj2 intervent* OR environmen?a* adj2 intervent* OR environmen?a* adj2 modification OR metacognit* strateg* OR metacognit* train* OR (Neuro* adj1 educat*) OR Neuro* behavio?r* OR psycholog* intervent* OR AMAT-C OR Amsterdam memory and attention training for children OR (Cogmed* adj2 train*) OR goal OR management train* OR GMT* OR Assist* technolog* OR adaptive technolog* OR Self-help device* OR assist device* OR multimodal intervent* OR NeuroPage* OR Vicon Revue* OR ViconRevue* OR SenseCam* OR PDA* OR Personal digital assistant OR palmtop computer* OR Psychosocial* intervent* OR Psycho-social* intervent* OR Psycho-educational intervent* OR Psychoeducational intervent* OR Psychotherap* OR pr?ctice drill* OR CBT OR (Cogn* adj2 therap*) OR Cogn* adj2 Remediat* OR educat* support OR Educat* program* OR Famil* function* OR Famil* therap* OR Adjuvant* psych* therap* OR Coping strateg* OR Counsel* OR Group* support* OR Group* meeting* OR (Web-based adj2 intervention) OR Systemic approach* OR School* based intervent* OR Systemic intervention* OR (Internet adj2 intervent*)

- **Pharmaceutical Interventions**

*Mapping term: Psychotropic agent/ Antidepressant/ Anti-psychotic/*

*Search terms:* (cogniti* ad2 enhance*?) OR (memory adj2 enhance*?) OR nootropic* OR stimulant* OR psycho-stimulant* OR neuro-enhance*? OR SMART drug* OR methylphenidate OR Ritalin OR MPH OR Atomoxetine OR Dexamfetamine OR Concerta OR attenta OR Methylin OR metadata OR equasym OR rubifen OR motiron OR stimdate OR daytrana OR strattera OR Dexedrine OR medikinet OR Provigil OR amphetamine OR pemoline OR adderall OR modafinil OR antipsychotic* OR MAOI* OR monoamine oxidase inhibitor* OR isocarboxazid OR pheniprazine OR marplan OR nardil OR SSRI* OR Selective Serotonin Re-uptake Inhibitor* OR fluoxetine OR sertraline OR citalopram OR paroxetine OR dapoxetine OR fluvoxamine OR faverin OR escitalopram OR prozac OR lustral OR cipramil OR seroxat OR cipralex OR serotonin-norepinephrine reuptake inhibitor* OR SNRI* OR venlafaxine OR effexor OR desvenlafaxine OR duloxetine OR tetracyclic antidepressant* OR TeCA* OR mirtazipine OR amoxepine OR loxapine OR maprotiline OR
mianserin OR oxaprotiline OR tricyclic* OR amitriptyline OR triptizol OR imipramine OR trofrani OR cycloserine)

MESH Terms
(child* OR infant* OR pediatric* OR paediatric* OR adolescent*) and (“brain neoplasm*” OR “brain tumor*” OR “brain tumour*”) and (“central nervous system” stimulant*) AND (“psychological intervention*”) OR (“psychotropic drug*” OR “antidepressive agent*” OR “antipsychotic agent*”)

Appendix II: Data screening and extraction form

Date: ..............................................

Record Number: ................................
1. **Study Eligibility** - Based on the title and available abstract

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
<th>MAYBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the study written in English?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were all the participants &lt;19 years?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the tumour investigated neurological?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the study determine the effectiveness of a pharmaceutical or non-pharmaceutical intervention?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the intervention aimed at neurocognitive/learning outcomes?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do not proceed if any of the above answers are ‘No’. If study to be included in ‘Excluded studies’ section of the review, record below the information to be inserted into ‘Table of excluded studies’.

- [ ] Psychosocial intervention
- [ ] Pharmaceutical intervention

Continue review?  
- [ ] Yes
- [ ] No

- [ ] Irrelevant study
- [ ] potentially relevant study

Please give details………………………………………………………………………………………………………………

**Data Extraction From**

1. **Study Characteristics** (Page ........)

Author(s):..........................................................................................................................
Date of article: ........................................

Title: ..................................................................................................................................................

Type of publication (journal name): ...................................................................................................

☐ Full paper ☐ Abstract/ summary only (e.g. unpublished/work in progress)

Rationale (Page .........)

What is the rationale (clear reason and justification for the research): ...........................................................

..............................................................................................................................................................

Is there a clear research question?: ...........................................................................................................

..............................................................................................................................................................

Co-morbidity/other diagnosis examined in the paper: ..................................................................................

..............................................................................................................................................................

Tumour type(s) investigated in the study: .................................................................................................

..............................................................................................................................................................

2. Methodology (Page .........)

Care setting the study was undertaken in: .................................................................................................

Research Design/level & grade of evidence  (Please select from Appendix I): ...........................................

Population from which the sample was drawn: ...........................................................................................

Inclusion criteria: ...........................................................................................................................................

..............................................................................................................................................................

Exclusion criteria: ......................................................................................................................................

..............................................................................................................................................................

Demographics (Page .........)

Patients age (mean/range): .......................................................................................................................  

Gender (please insert the number of each if known):  ☐ Female  ☐ Male
Ethnicity: ............................................................................................................

Socio-economic status: ..........................................................................................

**Sample selection- Appendix III**

<table>
<thead>
<tr>
<th>Multistage</th>
<th>Non probability</th>
<th>Quota</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purposive sample</td>
<td>Opportunistic sample</td>
<td>probability</td>
</tr>
<tr>
<td>Not stated</td>
<td>Stratified random</td>
<td>Prospective</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Method of randomisation: ..............................................................................

Allocation concealment to groups: ......................................................................

**Patients (Page…….)**

<table>
<thead>
<tr>
<th>Number available</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number invited</td>
<td></td>
</tr>
<tr>
<td>Number excluded</td>
<td></td>
</tr>
<tr>
<td>Number participated</td>
<td></td>
</tr>
<tr>
<td>Number completed</td>
<td></td>
</tr>
<tr>
<td>Number in each trial</td>
<td></td>
</tr>
</tbody>
</table>

Is the selection of the participants appropriate to the design?......................

..............................................................................................................................

Methods for handling missing data:.................................................................

Additional Information:.....................................................................................

..............................................................................................................................

**3.Intervention (Page……..)**

Intervention given to the treatment group(s):..................................................

..............................................................................................................................

156
Intervention, if given to the comparison group(s): .................................................................
................................................................................................................................................

**Psychosocial**

Description of the intervention: ..............................................................................................
................................................................................................................................................
Aim of the intervention: ............................................................................................................
................................................................................................................................................

**Pharmaceutical**

Description of the intervention: ..............................................................................................
................................................................................................................................................
Aim of the intervention: ............................................................................................................
................................................................................................................................................

**Duration of intervention:**

Who delivered the intervention: ............................................................................................

Was this person(s) blinded? □ Yes □ No □ Not stated

Was the patient blinded? □ Yes □ No □ Not stated

Blinding: □ Not applicable □

**Outcome Measures (Page: .......)**

□ Psychometrics □ Interviews

When were they measured ........................................................................................................
................................................................................................................................................

**Psychometrics**

□ Direct (with the child) □ Proxy Delete as appropriate - parent, teacher, carer, clinician
Assessments used ..........................................................................................................................

Conducted by..................................................................................................................................

**Interview**

☐ Structured  ☐ Unstructured
☐ Direct (with the child)  ☐ Proxy Delete as appropriate -

parent, teacher, carer, clinician

Conducted by..................................................................................................................................

**Data collection**

Description of data collection:........................................................................................................

Data collected by:............................................................................................................................

Length of follow-up:..................................................................................................................

3. **Analysis** (Page ......)

Description of analysis employed:................................................................................................

Adjustment for confounding:........................................................................................................

4. **Results:**  Outcomes of Interventions (Page .......)

Are the results:  ☐ Psychosocial  ☐ Pharmaceutical
<table>
<thead>
<tr>
<th>Type of outcome</th>
<th>Group</th>
<th>Description of outcome</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro-cognitive</td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ability</td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic Attainment</td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduct</td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affect</td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential side effects</td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional information:........................................................................................................
...........................................................................................................................................
...........................................................................................................................................
...........................................................................................................................................
...........................................................................................................................................

7. Conclusions (Page ........)

Summary of main findings:........................................................................................................
Have they stated clear limitations in the research?

Implications of the literature for clinical and research practice?

Source(s) of funding:
## Quality Appraisals of Studies

<table>
<thead>
<tr>
<th>Questions</th>
<th>Yes</th>
<th>NO</th>
<th>Partially/Unable to determine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Reporting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the hypothesis/aim/objective of the study clearly described?</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Are the main outcomes to be measured clearly described in the Introduction or Methods section?</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>If the main outcomes are first mentioned in the Results section, the question should be answered no.</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Are the characteristics of the patients included in the study clearly described?</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Are the interventions of interest clearly described?</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Treatments and placebo (where relevant) that are to be compared should be clearly described.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are the distributions of principal confounders in each group of subjects to be compared clearly described?</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>A list of principal confounders is provided.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are the main findings of the study clearly described?</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Does the study provide estimates of the random variability in the data for the main outcomes?</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Have all important adverse events that may be a consequence of the intervention been reported?</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>
This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

| Have the characteristics of patients lost to follow-up been described? | 1 | 0 | N/A |
| Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? | 1 | 0 | N/A |

2. **External validity**: All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

| Were those subjects who were prepared to participate representative of the entire population from which they were recruited? | 1 | 0 | 0 |
| Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? | 1 | 0 | 0 |

3. **Internal validity – bias**  

Was an attempt made to blind study subjects to the intervention they have received?

For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

<p>| Was an attempt made to blind those measuring the main outcomes of the intervention? | 1 | 0 | 0 |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>If any of the results of the study were based on “data dredging”, was this made clear?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were the statistical tests used to assess the main outcomes appropriate?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was compliance with the intervention/s reliable?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were the main outcome measures used accurate (valid and reliable)?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Internal validity - confounding (selection bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case control studies where there is no information concerning the source of patients included in the study.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were study subjects randomised to intervention groups?</td>
<td>1 0 0</td>
</tr>
<tr>
<td>Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.</td>
<td></td>
</tr>
<tr>
<td>Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?</td>
<td>1 0 0</td>
</tr>
<tr>
<td>All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.</td>
<td></td>
</tr>
<tr>
<td>Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?</td>
<td>1 0 0</td>
</tr>
<tr>
<td>This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.</td>
<td></td>
</tr>
<tr>
<td>Were losses of patients to follow-up taken into account?</td>
<td>1 0 0</td>
</tr>
<tr>
<td>If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.</td>
<td></td>
</tr>
</tbody>
</table>

5. **Power**

Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

*Sample sizes have been calculated to detect a difference of x% and y%.*

<table>
<thead>
<tr>
<th>Size of smallest intervention group</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A &lt;n1</td>
<td>0</td>
</tr>
<tr>
<td>B n1–n2</td>
<td>1</td>
</tr>
<tr>
<td>C n3–n4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>D</td>
<td>n5–n6</td>
</tr>
<tr>
<td>E</td>
<td>n7–n8</td>
</tr>
<tr>
<td>F</td>
<td>n8+</td>
</tr>
</tbody>
</table>

**Total Quality Score:**

(Downs & Black, 1998)

Analysis.

Confounds.

Interpretation.

Generalisability.

Comments/concerns.
<table>
<thead>
<tr>
<th>Level</th>
<th>Therapy/Prevention, Aetiology/Harm</th>
<th>Prognosis</th>
<th>Diagnosis</th>
<th>Differential diagnosis/symptom prevalence study</th>
<th>Economic and decision analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>SR (with homogeneity*) of RCTs</td>
<td>SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations</td>
<td>SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres</td>
<td>SR (with homogeneity*) of prospective cohort studies</td>
<td>SR (with homogeneity*) of Level 1 economic studies</td>
</tr>
<tr>
<td>1b</td>
<td>Individual RCT (with narrow Confidence Interval‡)</td>
<td>Individual inception cohort study with &gt; 80% follow-up; CDR† validated in a single population</td>
<td>Validating** cohort study with good†† reference standards; or CDR† tested within one clinical centre</td>
<td>Prospective cohort study with good follow-up****</td>
<td>Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>1c</td>
<td>All or none§</td>
<td>All or none case-series</td>
<td>Absolute SpPins and SnNouts††</td>
<td>All or none case-series</td>
<td>Absolute better-value or worse-value analyses ††††</td>
</tr>
<tr>
<td>2a</td>
<td>SR (with homogeneity*) of cohort studies</td>
<td>SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs</td>
<td>SR (with homogeneity*) of Level &gt;2 diagnostic studies</td>
<td>SR (with homogeneity*) of 2b and better studies</td>
<td>SR (with homogeneity*) of Level &gt;2 economic studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study (including low quality RCT; e.g., &lt;80% follow-up)</td>
<td>Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§§ only</td>
<td>Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§§ or databases</td>
<td>Retrospective cohort study, or poor follow-up</td>
<td>Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>2c</td>
<td>&quot;Outcomes&quot; Research; Ecological studies</td>
<td>&quot;Outcomes&quot; Research</td>
<td>Ecological studies</td>
<td>Audit or outcomes research</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>SR (with homogeneity*) of case-control studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
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<td>4</td>
<td>Case-series (and poor quality cohort and case-control studies§§)</td>
<td>Case-series (and poor quality prognostic cohort studies*** )</td>
<td>Case-control study, poor or non-independent reference standard</td>
<td>Case-series or superseded reference standards</td>
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<td>Expert opinion without explicit critical appraisal, or based on economic theory or &quot;first principles&quot;</td>
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</tbody>
</table>
Notes for Oxford Centre for Evidence-based Medicine Levels of Evidence

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because:

EITHER a single result with a wide Confidence Interval
OR a Systematic Review with troublesome heterogeneity.

Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

† Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)

‡ See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.

§ Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

§§ By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.

Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.

Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.

Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.

Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.

By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.

Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 - 5 years chronic)

<table>
<thead>
<tr>
<th>Grades of Recommendation</th>
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<tbody>
<tr>
<td>A</td>
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<td>B</td>
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<tr>
<td>C</td>
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<tr>
<td>D</td>
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</tbody>
</table>
"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation.

(Howick et al., 1998)

Table of Evidence Glossary

**Absolute risk reduction (ARR):** The difference in the event rate between control group (CER) and treated group (EER): \( \text{ARR} = \text{CER} - \text{EER} \).

**Bias:** Any tendency to influence the results of a trial (or their interpretation) other than the experimental intervention.

**Blinding:** A technique used in research to eliminate bias by hiding the intervention from the patient, clinician, and/or other researchers who are interpreting results.

**Case-control study:** The observational epidemiologic study of persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and nondiseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attribute, in each of the groups.

**Case-series:** A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. (NCI Dictionary)

**CER:** Control event rate; see event rate.

**Clinical practice guideline:** A systematically developed statement designed to assist health care professionals and patients make decisions about appropriate health care for specific clinical circumstances.

**Cochrane collaboration:** A worldwide association of groups who create and maintain systematic reviews of the literature for specific topic areas.

**Cohort study:** The analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of cohort study is observation of large numbers over a long period (commonly years) with comparison of incidence rates in groups that differ in exposure levels.

**Confidence interval (CI):** The range around a study's result within which we would expect the true value to lie. CIs account for the sampling error between the study population and the wider population the study is supposed to represent. See p11
Confounding variable: A variable which is not the one you are interested in but which may affect the results of trial.

Critically appraised topic (CAT): A short summary of an article from the literature, created to answer a specific clinical question.

Decision analysis: The application of explicit, quantitative methods to analyse decisions under conditions of uncertainty.

Diagnosis: The process of determining health status and the factors responsible for producing it; may be applied to an individual, family, group or community. The term applied both to the process of determination and to its findings.

Diagnostic Test: Any medical test performed to confirm, or determine the presence of disease in an individual suspected of having the disease, usually following the report of symptoms, or based on the results of other medical tests. Some examples of diagnostic tests include performing a chest x-ray to diagnose pneumonia, and taking skin biopsy to detect cancerous cells. (Harvard Guide to Diagnostic test)

EER: Experimental event rate; see Event rate.

Effectiveness: A measure of the benefit resulting from an intervention for a given health problem under usual conditions of clinical care for a particular group.

Efficacy: A measure of the benefit resulting from an intervention for a given health problem under the ideal conditions of an investigation.

Event rate: The proportion of patients in a group in whom an event is observed.

Forrest plot: A diagrammatic representation of the results of individual trials in a meta-analysis.

Funnel plot: A method of graphing the results of trials in a meta-analysis to show if the results have been affected by publication bias.

Heterogeneity: In systematic reviews, the amount of incompatibility between trials included in the review, whether clinical (i.e. the studies are clinically different) or statistical (i.e. the results are different from one another).

Historically Controlled Study: A control study recruiting control subject(s) for whom data were collected at a time preceding that at which the data are gathered on the group being studied.

Inception cohort study: A group of individuals identified for subsequent study at an early, uniform point in the course of the specified health condition, or before the condition develops.

Incidence: The number of new cases of illness commencing, or of persons falling ill, during a specified time period in a given population.
**Intention-to-treat**: Characteristic of a study where patients are analysed in the groups to which they were originally assigned, even though they may have switched treatment arms during the study for clinical reasons.

**Likelihood ratio**: The likelihood that a given test result would be expected in a patient with the target disorder compared to the likelihood that the same result would be expected in a patient without that disorder.

  - for a positive test result = LR+ = sensitivity/(1 - specificity)
  - for a negative test result = LR- = (1 - sensitivity)/specificity

**Local and current random census**

**Local**: Of or belonging to or characteristic of a particular locality or neighbourhood

**Current**: Occurring in or belonging to the present time

**Random sample**: A sample that is arrived at by selecting sample units such that each possible unit has a fixed and determinate probability of selection.

**Census**: An enumeration of a population, originally intended for purposes of taxation and military service. Census enumeration of a population usually records identities of all persons in every place of residence, with age or birth date, sex, occupation, national origin, language, marital status, income, and relationship to head of household in addition to information on the dwelling place.

**Local and current random sample survey**

**Local**: Of or belonging to or characteristic of a particular locality or neighbourhood

**Current**: Occurring in or belonging to the present time

**Random sample**: A sample that is arrived at by selecting sample units such that each possible unit has a fixed and determinate probability of selection.

**Survey**: An investigation in which information is systematically collected but in which the experimental method is not used.

**Local non-random sample**

**Local**: Of or belonging to or characteristic of a particular locality or neighbourhood

**Non-random sample**: A sample selected by a non-random method, and as a result, some elements of the population have no chance of selection. For example, a scheme whereby units are selected purposively would yield a non-random sample. Again, a sample obtained by taking members at fixed intervals on a list is a non-random sample unless the list was arranged in a random order. (OECD)

**Mechanism-based reasoning**: Involves an inference from mechanisms to claims that an intervention produces a patient-relevant outcome. Such reasoning will involve an inferential chain linking the intervention (such as antiarrrhythmic drugs) with a clinical outcome (such as mortality). (Howick)

**MeSH**: Medical Subject Headings: a thesaurus of medical terms used by many databases and libraries to index and classify medical information.
**Monitoring Test:** Any medical test performed to confirm, or determine the presence of disease in an individual suspected of having the disease, usually following the report of symptoms, or based on the results of other medical tests. Some examples of diagnostic tests include performing a chest x-ray to diagnose pneumonia, and taking skin biopsy to detect cancerous cells. (Harvard Guide to Diagnostic test)

**Nested Case-control study:** A case control study in which cases and controls are drawn from the population in a cohort study. As some data are already available about both cases and controls, the effects of some potential confounding variables are reduced or eliminated. In this type of case control study, a set of controls is selected from subjects, i.e. non-cases, at risk at the time of occurrence of each case that arises in a cohort, thus allowing for the confounding effect of time in the analysis.

**n-of-1 trial:** A variation of a randomized controlled trial in which a sequence of alternative treatment regimens is randomly allocated to a patient. The outcomes of regimens are compared, with the aim of deciding on the optimum regimen for the patient.

**Negative predictive value (-PV):** The proportion of people with a negative test who are free of disease.

**Number needed to treat (NNT):** The number of patients who need to be treated to prevent one bad outcome. It is the inverse of the ARR: \( NNT = \frac{1}{ARR} \). Numbers needed to harm (NNH)-the number of patients who, if they received the experimental treatment, would lead to one additional person being harmed compared with patients who receive the control treatment; calculated as \( \frac{1}{ARI} \).

**Observational study:** A family of studies in which investigators compare people who take an intervention with those who do not. The investigators neither allocate patients to receive the intervention nor administer the intervention. Instead, they compare records of patients who had taken an intervention and been treated in routine practice with similar patients who had not taken the intervention. The most common observational designs are case-studies, case-series, case-control studies, cohort studies, and historically controlled studies. (Howick)

**Odds:** A ratio of events to non-events. If the event rate for a disease is 0.2 (20%), its non-event rate is 0.8 and therefore its odds are 2/8.

**p value:** The probability that a particular result would have happened by chance.

**Positive predictive value (+PV):** The proportion of people with a positive test who have disease.

**Post-test probability:** The probability that a patient has the disorder of interest after the test result is known.

**Pre-test probability:** The probability that a patient has the disorder of interest prior to administering a test.

**Post-marketing surveillance:** A procedure implemented after a drug has been licensed for public use, designed to provide information on the actual use of the drug for a given
indication and on the occurrence of side effects, adverse reactions, etc. A method for epidemiologic study of adverse drug reactions.

**Prevalence:** The baseline risk of a disorder in the population of interest.

**Prevention:** Prevention refers to measures taken by an individual or a society to prevent disease happening or its consequences. In general, prevention includes a wide range of interventions, aimed at reducing risks to health. These are grouped into three categories:

- **Primary prevention:** refers to strategies used to prevent a disease happening in the first place. An example may be salt reduction to prevent an individual becoming hypertensive. Medication can be used in primary prevention such as the use of blood lowering or cholesterol lowering drugs to lower the risk of a stroke or heart attack.
- **Secondary prevention:** refers to strategies used in those with an existing disease which prevent recurrence, or significant morbidity. For example, in someone who has a heart attack cholesterol lowering drugs are used to lower the risk of subsequent heart attack and death.
- **Tertiary prevention:** refers to the prevention of long term chronic disease progression, physical deterioration and attendant suffering. For example, removing allergens which may aggravate asthmatic patients; screening for eye, renal, eye, and foot problems among diabetics to reduce the risks of complications.

**Prognosis:** The prospect of survival and recovery from a disease as anticipated from the usual course of that disease or indicated by special features of the case.

**Prognostic cohort study:**

**Publication bias:** A bias in a systematic review caused by incompleteness of the search, such as omitting non-English language sources, or unpublished trials (inconclusive trials are less likely to be published than conclusive ones, but are not necessarily less valid).

**Quasi-experimental studies**

Participants are allocated to the intervention and the control groups; they do not randomly assign to create the comparison groups.

*Non-randomised controlled studies* – Individuals are allocated to a concurrent comparison group, using methods other than randomisation. *(Increases the risk of bias)*

*Before-and-after study* – Comparison of outcomes in study participants before and after the introduction of an intervention. Comparisons may be in the same sample of participant or in different samples.

*Interrupted time series* - Multiple observations over time that are ‘interrupted’, usually by an intervention or treatment.
**Randomized trial**: An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups.

Randomised cross-over trials – all participants receive all interventions. The sequence of interventions is randomised.

Cluster randomised trials – clusters of people rather than individual are randomised to different interventions

**Relative risk (RR) (or risk ratio)**: The ratio of the risk of an event in the experimental group compared to that of the control group (RR=EER / CER). Not to be confused with relative risk reduction (see below).

**Relative risk reduction (RRR)**: The percentage reduction in events in the treated group event rate (EER) compared to the control group event rate (CER): RRR = (CER-EER) / CER.

**Sensitivity**: The proportion of people with disease who have a positive test.

**Specificity**: The proportion of people free of a disease who have a negative test.

**Systematic review**: The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardized methods for selecting and assessing articles. A systematic review differs from a meta-analysis in not including a quantitative summary of the results.

**Treatment benefits**: Positive patient-relevant outcome associated with an intervention, quantifiable by epidemiological measures such as absolute risk reduction (ARR) and number needed to treat (NNT).

**Validity**: The extent to which a variable or intervention measures what it is supposed to measure or accomplishes what it is supposed to accomplish. The internal validity of a study refers to the integrity of the experimental design. The external validity of a study refers to the appropriateness by which its results can be applied to non-study patients or populations.
## Sampling techniques:

<table>
<thead>
<tr>
<th>Technique</th>
<th>Descriptions</th>
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<tbody>
<tr>
<td>Stratified random</td>
<td>Random sample from identifiable groups (strata), subgroups, etc.</td>
</tr>
<tr>
<td>Multistage</td>
<td>A sample which is selected by stages, the sampling units at each stage being sub-sampled from the (larger) units chosen at the previous stage. The sampling units pertaining to the first stage are called primary or first stage units; and similarly for second stage units, etc.</td>
</tr>
<tr>
<td>Purposive</td>
<td>Hand-pick subjects on the basis of specific characteristics</td>
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<tr>
<td>Quota</td>
<td>Select individuals as they come to fill a quota by characteristics proportional to populations</td>
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<tr>
<td>Opportunistic</td>
<td>Either asking for volunteers, or the consequence of not all those selected finally participating, or a set of subjects who just happen to be available</td>
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<tr>
<td>Non probability</td>
<td>A sample of units where the selected units in the sample have an unknown probability of being selected and where some units of the target population may even have no chance at all of being in the sample. Forms of non-probability sampling are numerous, such as voluntary samples (only responses of volunteers are used), quota samples, expert samples</td>
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<tr>
<td>Probability</td>
<td>Probability samples are selected in such a way as to be representative of the population. They provide the most valid or credible results because they reflect the characteristics of the population from which they are selected (e.g., residents of a particular community, students at an elementary school, etc.). There are two types of probability samples: random and stratified</td>
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<thead>
<tr>
<th>Level</th>
<th>Therapy/Prevention, Aetiology/Harm</th>
<th>Prognosis</th>
<th>Diagnosis</th>
<th>Differential diagnosis/symptom prevalence study</th>
<th>Economic and decision analyses</th>
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</thead>
<tbody>
<tr>
<td>1a</td>
<td>SR (with homogeneity*) of RCTs</td>
<td>SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations</td>
<td>SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres</td>
<td>SR (with homogeneity*) of prospective cohort studies</td>
<td>SR (with homogeneity*) of Level 1 economic studies</td>
</tr>
<tr>
<td>1b</td>
<td>Individual RCT (with narrow Confidence Interval†)</td>
<td>Individual inception cohort study with &gt; 80% follow-up; CDR† validated in a single population</td>
<td>Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre</td>
<td>Prospective cohort study with good follow-up****</td>
<td>Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>1c</td>
<td>All or none§</td>
<td>All or none case-series</td>
<td>Absolute SpPins and SnNouts††</td>
<td>All or none case-series</td>
<td>Absolute better-value or worse-value analyses ††††</td>
</tr>
<tr>
<td>2a</td>
<td>SR (with homogeneity*) of cohort studies</td>
<td>SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs</td>
<td>SR (with homogeneity*) of Level &gt;2 diagnostic studies</td>
<td>SR (with homogeneity*) of 2b and better studies</td>
<td>SR (with homogeneity*) of Level &gt;2 economic studies</td>
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<tr>
<td>2b</td>
<td>Individual cohort study (including low quality RCT; e.g., &lt;80% follow-up)</td>
<td>Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† validated on split-sample§§§ only</td>
<td>Exploratory** cohort study with good††† reference standards; or CDR† after derivation, or validated only on split-sample§§§ or databases</td>
<td>Retrospective cohort study, or poor follow-up</td>
<td>Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>2c</td>
<td>“Outcomes” Research; Ecological studies</td>
<td>“Outcomes” Research</td>
<td>Ecological studies</td>
<td>Audit or outcomes research</td>
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<tr>
<td>3a</td>
<td>SR (with homogeneity*) of case-control studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.</td>
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<td>3b</td>
<td>Individual Case-Control Study</td>
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<td>Case-series (and poor quality prognostic cohort studies**)</td>
<td>Case-control study, poor or non-independent reference standard</td>
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<tr>
<td>Date retrieved from auto retrieval</td>
<td>Study</td>
<td>Reason for exclusion</td>
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<tr>
<td>03/06/13</td>
<td>(Kirshner et al., 2012)</td>
<td>Diagnosis: Pegfilgrastim-induced bone pain</td>
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<td></td>
<td></td>
<td>Intervention: Not an appropriate intervention study. This study conducted an RCT exploring interventions for pegfilgrastim-induced bone pain.</td>
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<tr>
<td>30/05/13</td>
<td>(Gopalakrishnan, Dhakoji, Menon, &amp; Nair, 2012)</td>
<td>Intervention: Not an appropriate intervention study. This study analysed the factors that predispose to persistent hydrocephalus and the need for a postoperative cerebrospinal fluid diversion procedure.</td>
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<tr>
<td>18/05/13</td>
<td>(Easby, Potts, Kirby, &amp; Sartori, 2012)</td>
<td>Intervention: Not an appropriate intervention study. The aim of this study was to adapt the adult ‘distress thermometer’ for a paediatric oncology population</td>
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<tr>
<td>18/05/13</td>
<td>(Hondebrink et al., 2013)</td>
<td>Intervention: Not an appropriate intervention study.</td>
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<tr>
<td>18/05/13</td>
<td>(Vecchio et al., 2013)</td>
<td>Intervention: Not an appropriate intervention study. Abuse of energy drinks among young people.</td>
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<tr>
<td>11/05/13</td>
<td>(Pucci et al., 2012)</td>
<td>Diagnosis: Benign heart tumours</td>
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<td>Intervention: Not an appropriate intervention study. To evaluate the role of histology in diagnosis and management of biologically benign heart tumours causing life-threatening symptoms and even death in children and foetuses.</td>
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<tr>
<td>11/05/13</td>
<td>(Steinhausen &amp; Helenius, 2013)</td>
<td>Diagnosis: ADHD</td>
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<td></td>
<td></td>
<td>Intervention: Not an appropriate intervention study. This study focused on chromosomal abnormalities and suggests concerns that medication with MPH for ADHD might increase the risk of cancer.</td>
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<tr>
<td>09/05/13</td>
<td>(Sung et al., 2013)</td>
<td>Intervention: Not an appropriate intervention study. Children's Oncology Group is conducting randomized controlled trials to determine prophylaxis strategies that will reduce infections in high-risk populations.</td>
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<tr>
<td>11/04/13</td>
<td>(Bilek, 2013)</td>
<td>Intervention: Not an appropriate intervention study. The overall goal of this study was to provide a detailed analysis of the scale and scope of allegations involving illegal marketing and promotion of pharmaceutical products brought by the U.S. government to recover money spent on pharmaceutical products via Medicaid due to alleged activity that violates one or more federal laws related to health care fraud</td>
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<tr>
<td>23/03/13</td>
<td>(Rabah et al., 2013)</td>
<td>Intervention: Not an appropriate intervention study. The study reported a case of chondroblastic osteosarcoma of right humerus presented with right frontal lobe metastasis in a 10-year-old girl with small pulmonary lesions.</td>
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<tr>
<td>Date</td>
<td>(First Author &amp; Co-authors, Year)</td>
<td>Title &amp; Notes</td>
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<tr>
<td>16/02/13</td>
<td>(Bruny &amp; Crombleholme, 2013)</td>
<td>Intervention: Not an appropriate intervention study. The review outlines the</td>
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<td>current approaches to prenatal imaging, differential diagnosis, antenatal</td>
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<td>natural history, and the available treatment options for the most commonly</td>
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<td></td>
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<td>prenatally diagnosed malignant tumours.</td>
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<tr>
<td>14/02/13</td>
<td>(Montano &amp; Young, 2012)</td>
<td>Population: Transitional (paediatrics to adult) Diagnosis: ADHD</td>
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<td></td>
<td></td>
<td>Intervention: Not an appropriate intervention study. The study reviewed, from</td>
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<td></td>
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<td>the adult primary care provider perspective, the barriers to continuity of care</td>
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<td></td>
<td></td>
<td>and their implications for patients with ADHD who transition from paediatric</td>
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<td></td>
<td></td>
<td>to adult health care.</td>
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<tr>
<td>14/02/13</td>
<td>(Nicholls, Hildenbrand, Aggarwal,</td>
<td>Diagnosis: paediatric cancers, traumatic brain injury (TBI), and sickle cell</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>McCarthy, &amp; Daly, 2012)</td>
<td>disease amalgamated in the results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>09/02/13</td>
<td>(Lance, Lanier, Andrew Zabel, &amp;</td>
<td>Diagnosis: Sturge Weber Syndrome</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Comi, 2013)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>09/02/13</td>
<td>(Padovani, André, Constine, &amp;</td>
<td>Intervention: Not an appropriate intervention study. we review the underlying</td>
<td></td>
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<td></td>
<td>Muracciole, 2012)</td>
<td>mechanisms and clinical consequences of CRT-induced neurocognitive damage in</td>
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<tr>
<td></td>
<td></td>
<td>survivors of paediatric brain tumours</td>
<td></td>
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<tr>
<td>09/02/13</td>
<td>(Sharp, Finlay, &amp; Kevitiyagala,</td>
<td>Intervention: Not an appropriate intervention study. The article explored if</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>2013)</td>
<td>methylphenidate was useful in treating fatigue in children with a brain tumour.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

178
<table>
<thead>
<tr>
<th>Date retrieved from auto retrieval</th>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/06/13</td>
<td>(Hales &amp; Wharam, 2012)</td>
<td>Intervention: Not an appropriate intervention study. The paper defines the limitations of using adult high-grade glioma decision making</td>
</tr>
</tbody>
</table>
| 08/06/13 | (Lucena & Moreno-Ortiz, 2013) | Diagnosis: Polycystic ovary  
Population: Adult  
Intervention: Not an appropriate intervention study. This paper present a case of a woman with polycystic ovary who was treated using in vitro maturation techniques |
| 06/6/13 | (Combs et al., 2013) | Intervention: Not an appropriate intervention study. This paper developed a practical prognostic score to predict survival outcome after re-irradiation. |
| 03/6/13 | (Prasad, Mendelow, & Gregson, 2008) | Diagnosis: Hodgkin Lymphoma  
Intervention: Not an appropriate intervention study. This study considers neurocognitive deficits can exist in patients that do not receive traditional cranial nervous system therapy. |
| 03/6/13 | (Wolden et al., 2012) | Diagnosis: Hodgkin's Lymphoma  
Intervention: Not an appropriate intervention study. A randomized comparison study by the children's oncology group of chemotherapy looking at patient with and without radiotherapy with Hodgkin's Lymphoma |
| 03/6/13 | (Ramsey et al., 2013) | Intervention: Not an appropriate intervention study. This study replicated the finding that inherited variations in SLCO1B1 are the most important genetic variations influencing methotrexate clearance. |
| 03/6/13 | (Gordon et al., 2013) | Diagnosis: Advanced Hodgkin lymphoma  
Intervention: Not an appropriate intervention study. The aim of this paper was to determine if failure-free survival was superior in patients treated with the Stanford V regimen compared with doxorubicin, bleomycin, vinblastine, and dacarbazine. |
| 25/05/13 | (Zoicas, Droste, Mayr, Buchfelder, & Schöfl, 2013) | Diagnosis: Obesity  
Population: Adults  
Intervention: Not an appropriate intervention study. The paper tested whether Glucagon-like peptide-1 analogues were also effective in the treatment of obesity and associated metabolic alterations in patients with hypothalamic disease. |
<p>| 18/05/13 | (Brown, Kolade, Staton, &amp; Patel, 2013) | Intervention: Not an appropriate intervention study. The aim of the study was to implementation of a new addiction medicine curriculum at a single internal medicine program provided an opportunity for knowledge assessment in a select population of health professionals. |
| 18/05/13 | (Backberg, Westerbergh, Al-Saffar, Lindeman, &amp; Helander, 2013) | Intervention: Not an appropriate intervention study. The article explores trends in intoxications of novel psychoactive substances. |</p>
<table>
<thead>
<tr>
<th>Date</th>
<th>Reference</th>
<th>Intervention/Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/04/13</td>
<td>Bhalla, 2013</td>
<td>Intervention: Not an appropriate intervention study.</td>
</tr>
<tr>
<td>21/03/13</td>
<td>Yap et al., 2012</td>
<td>Intervention: Not an appropriate intervention study. This paper illustrated the therapeutic benefit of aripiprazole for treatment of mental status changes associated with resection of a posterior fossa tumor.</td>
</tr>
<tr>
<td>16/03/13</td>
<td>Plotkin et al., 2013</td>
<td>Intervention: Not an appropriate intervention study. The authors proposed an updated diagnostic criteria to incorporate new clinical and genetic findings since 2005.</td>
</tr>
<tr>
<td>16/02/13</td>
<td>Chafe, Drodge, Krauze, Dundas, &amp; Wilson, 2011</td>
<td>Intervention: Not an appropriate intervention study.</td>
</tr>
<tr>
<td>16/03/13</td>
<td>Yust &amp; Slattery, 2012</td>
<td>Intervention: Not an appropriate intervention study. The purpose of this article was to review the classes of medications found in over-the-counter, the epidemiology of their use, the pharmacology and clinical toxicity of specific medications, dextromethorphan abuse, and the management of children presenting with overdose or adverse effects.</td>
</tr>
<tr>
<td>02/03/13</td>
<td>Sorrell, Espenschied, Culver, &amp; Weitzel, 2013</td>
<td>Intervention: Not an appropriate intervention study. In this article, they review the clinical relevance of germline mutations in the TP53 tumour suppressor gene to current healthcare practice, including the optimal ways to identify patients with Li-Fraumeni syndrome, to recognize the core cancers associated with Li-Fraumeni syndrome, and to develop strategies for early detection of Li-Fraumeni syndrome-associated tumors.</td>
</tr>
<tr>
<td>09/02/13</td>
<td>Siddique, Sreenivasan, Comi, &amp; Germain-Lee, 2013</td>
<td>Diagnosis: Sturge-Weber syndrome</td>
</tr>
<tr>
<td>09/02/13</td>
<td>Brinkman et al., 2013</td>
<td>Population: Adults Intervention: Not an appropriate intervention study. The study explored the extent to which psychoactive medication treatment is associated with adverse effects on specific neurocognitive processes.</td>
</tr>
<tr>
<td>09/02/13</td>
<td>IŞIK, SILAV, GÜÇLÜER, &amp; Elmaci, 2012</td>
<td>Intervention: Not an appropriate intervention study. The review presents the clinical features, diagnostic methods and management of cranial teratomas based on our experience and the literature.</td>
</tr>
<tr>
<td>09/02/13</td>
<td>Joshi, Singh, &amp; Shellhaas, 2013</td>
<td>Diagnosis: Epilepsy Intervention: Not an appropriate intervention study. The study reviewed a variety of interventions designed to maximize seizure control and thereby optimize their neurodevelopmental outcomes.</td>
</tr>
</tbody>
</table>
Appendix V: PRISMA 2009 Checklist (Moher et al., 2009).

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>#</th>
<th>Checklist Item</th>
<th>Reported on page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td></td>
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</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives;</td>
<td>4-5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>data sources; study eligibility criteria, participants, and interventions;</td>
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<tr>
<td></td>
<td></td>
<td>study appraisal and synthesis methods; results; limitations; conclusions</td>
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<tr>
<td></td>
<td></td>
<td>and implications of key findings; systematic review registration number.</td>
<td></td>
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<tr>
<td>Introduction</td>
<td></td>
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<tr>
<td>Rational</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>13-63</td>
</tr>
<tr>
<td>Objective</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
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<tr>
<td>Methods</td>
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<tr>
<td>Protocols and</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g.,</td>
<td>69-77</td>
</tr>
<tr>
<td>registration</td>
<td></td>
<td>Web address), and, if available, provide registration information including</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>registration number.</td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report</td>
<td>66-67</td>
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<tr>
<td></td>
<td></td>
<td>characteristics (e.g., years considered, language, publication status) used</td>
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<tr>
<td></td>
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<td>as criteria for eligibility, giving rationale.</td>
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<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage,</td>
<td>69-71</td>
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<tr>
<td></td>
<td></td>
<td>contact with study authors to identify additional studies) in the search and</td>
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<td></td>
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<td>date last searched.</td>
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</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including</td>
<td>69-71/150-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>any limits used, such that it could be repeated.</td>
<td></td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
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</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td></td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td></td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td></td>
</tr>
<tr>
<td>Summary of measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td></td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.</td>
<td></td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td></td>
</tr>
<tr>
<td>Additional analysis</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study selection</td>
<td>17</td>
<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
<td></td>
</tr>
<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
<td></td>
</tr>
<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
<td></td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
<td></td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of N/A</td>
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<tr>
<td>Section</td>
<td>Item</td>
<td>Description</td>
<td>Pages</td>
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<td>--------------------------</td>
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<td>-------</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
<td>80-95</td>
</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Discussion</strong></td>
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<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
<td>104-117</td>
</tr>
<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
<td>118-127</td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
<td>123-133</td>
</tr>
<tr>
<td><strong>Funding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
<td>N/A</td>
</tr>
</tbody>
</table>