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Interval brain imaging for adults with cerebral glioma (Protocol)

Lawrie TA, Kernohan A, Jenkinson MD, Thompson G

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TABLE OF CONTENTS

[Intervention Protocol]

Interval brain imaging for adults with cerebral glioma

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine whether interval brain imaging (performing brain imaging at regular intervals) compared with brain imaging upon clinical indication (performing brain imaging upon the development of new or worsening symptoms) improves outcomes associated with cerebral glioma.

To appraise critically and summarise current evidence on the costs and cost-effectiveness of interval brain imaging compared with symptomatic imaging.

BACKGROUND

Description of the condition

Brain and other central nervous system (CNS) tumours are less common than many other cancers, accounting for around 1.9% of new cancer diagnoses annually; however, they are associated with a higher proportion of cancer deaths, approximately 2.3% or 189,382 deaths worldwide in 2012 (GLOBOCAN 2012). Gliomas are brain tumours that arise from glial cells, usually oligodendrocytes and astrocytes. They occur at an annual incidence of four to 11 people per 100,000 and are more frequent in high-income, industrialised countries (Ohgaki 2009). Gliomas are graded 1 to 4 by the World Health Organization (WHO), according to their potential to turn cancerous. The 2007 WHO classification system (Louis 2007), used in completed clinical studies since 2007, graded gliomas based on histological characteristics only. However, in the 2016 WHO classification system, to be used in future studies, grading depends on both histological and molecular features, for example, isocitrate dehydrogenase (IDH) status, chromosome 1p 19q, and other genetic parameters (Louis 2016). Using the 2007 WHO classification, gliomas graded 1 and 2 have low potential to turn cancerous and are referred to as low-grade gliomas (LGGs); these include pilocytic astrocytomas (grade 1), diffuse astrocytomas, oligodendrogliomas and mixed oligoastrocytomas (grade 2). High-grade gliomas (HGGs) include anaplastic astrocytomas, anaplastic oligodendrogliomas (grade 3) and glioblastomas (grade 4).

Grades correspond to prognosis. Grade 1 has a good prognosis and can often be cured with surgery alone, whereas grade 4 has a poor

prognosis, and can be rapidly fatal (Louis 2007). Thus, tumour grade is a key factor in deciding how to treat gliomas. It also plays a role in determining the timing and frequency of radiographic follow-up.

Description of the intervention

Brain imaging by magnetic resonance imaging (MRI), or computerised tomography (CT), is key to the diagnosis of a glioma. MRI is the preferred technique as it has superior soft tissue resolution and gives a better definition of tumour extent (NCCN 2018; NCI 2017; NICE 2006). However, these imaging techniques are less useful in distinguishing the type of tumour and grade, or differentiating tumours from inflammatory or ischaemic lesions (e.g. following a stroke or radiation). Other imaging techniques, such as magnetic resonance (MR) spectroscopy, MR perfusion imaging, single photon emission computed tomography (SPECT) and positron emission photometry (PET), can be used to provide additional information prior to surgery to improve the accuracy of histopathological examination (NCCN 2018; NICE 2018).

In addition to diagnosis, brain imaging is an integral part of management and follow-up of glioma and informs treatment decisions in the period immediately after diagnosis. After surgery, MRI has been shown to more accurately identify the extent of residual tumour than the neurosurgeon's estimation (Albert 1994). Imaging is also used to assess the tumour's response among people actively receiving treatment and, in clinical studies of glioma treatment, imaging before the start of adjuvant treatment is common practice (e.g. Malmström 2017; Wick 2012). In a study of bevacizumab for glioblastoma, performing a follow-up MRI from as early as four weeks after starting treatment has been reported to be an accurate predictor of both treatment response and survival (Field 2017).

Outside the immediate treatment period, people with glioma might also be offered imaging at regular intervals. 'Interval imaging' is when a clinician submits a request for imaging at a defined time point in the future to monitor the tumour. It is not known at that specific time point in the future whether the person affected will be less symptomatic, the same (i.e. stable), or be more symptomatic at the time of the scan. The imaging is not, therefore, planned based on a deterioration of the person's symptoms. An alternative approach to interval imaging would be to arrange a scan when a person notes deterioration in their symptoms, that is, symptomatic imaging.

There are several scenarios in which interval imaging is used among people with a glioma. Before surgical treatment, among those with a suspected LGG, interval imaging might be performed to ensure that the actual growth of the tumour is not faster than that expected from the anticipated grade. It might also be considered for lesions with radiological features of a very low-grade tumour that do not necessitate immediate treatment, for example, an optic pathway glioma (NICE 2018). After treatment, interval imaging is usually performed for both LGGs and HGGs to check for any new tumour growth and to determine whether treatment has been successful at halting growth. The National Comprehensive Cancer Network (NCCN) recommends MRI follow-up of LGGs every three to six months for five years, then at least annually thereafter (NCCN 2018). For glioblastoma, an MRI two to six weeks after radiotherapy, then every two to four months for three years, then every six months indefinitely, is recommended (NCCN 2018). Possible imaging intervals in National Institute for Health and Clinical Excellence (NICE), guidance are slightly longer (e.g. for glioblastoma the suggested intervals are three to six months up to two years after treatment, then six to 12 months up to three years, then annually indefinitely (Table 1)). In general, though, for both LGGs and HGGs, interval duration increases over time from diagnosis and treatment. SPECT and PET can also be helpful in the post-treatment scenario to distinguish between tumour recurrence and radiation necrosis (NCCN 2018; NCI 2017).

Why it is important to do this review

To our knowledge, there are no existing systematic reviews of this topic. It is not known whether interval brain imaging leads to improved survival among people with glioma compared with symptomatic imaging. In addition, whilst clinical guidelines recommend routine MRI follow-up or active monitoring, the optimal frequency of routine active monitoring has not been established. In existing clinical practice guidelines, it is recommended that the frequency of routine active monitoring decreases with time (NICE 2018; NCCN 2018; SEOM 2017); however, as the risk of LGG recurrence is lower initially and increases with time, frequent imaging early on in the course of the disease, particularly in people with LGG, might be unnecessary. In addition, diagnostic uncertainties raised by brain imaging performed within the first three to six months due to treatment, such as tumour progression versus pseudo-progression, can increase patient and clinician anxiety during this active monitoring period, and negatively affect quality of life. Brain imaging is costly, both for the health system and the individual, and performing it routinely might not always be cost-effective or in an individual's best interest, particularly if the result of imaging is unlikely to change management. The aim of this review, therefore, is to systematically evaluate the evidence on interval imaging versus imaging upon clinical indication, to inform clinical practice guidelines and research agendas.

OBJECTIVES

To determine whether interval brain imaging (performing brain imaging at regular intervals) compared with brain imaging upon clinical indication (performing brain imaging upon the development of new or worsening symptoms) improves outcomes associated with cerebral glioma.

To appraise critically and summarise current evidence on the costs and cost-effectiveness of interval brain imaging compared with symptomatic imaging.

METHODS

Criteria for considering studies for this review

Types of studies

For studies on the effectiveness of brain imaging strategies, we will include randomised controlled trials (RCTs) and non-randomised controlled trials (NRCTs). If we do not find any RCTs or NRCTs, we will include controlled before-after studies (CBAS) with concurrent comparison groups.
Full economic evaluations (cost-effectiveness analyses, cost-utility analyses and cost-benefit analyses), conducted alongside any study design and any model-based economic evaluations.

Types of participants

Adults with a histologically confirmed diagnosis of cerebral glioma.

Types of interventions

Pre- or post-treatment brain imaging, including MRI and other types of imaging, performed at regular intervals (interval imaging) compared with pre- or post-treatment brain imaging performed upon the development of new or worsening symptoms (symptomatic imaging).

Types of outcome measures

Primary outcomes

- Overall survival (time from randomisation to death)

Secondary outcomes

- Progression-free survival (time from randomisation to disease progression)
- Health-related quality of life measured by a standardised instrument, such as the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 or QLQ-BN20 (specific for brain cancer), or the Functional Assessment of Cancer Therapy scale (FACT)-G (general) or FACT-Br (specific for brain cancer)
- Anxiety, measured by a standardised instrument, such as the Hospital Anxiety and Depression Scale (HADS)
- Depression, measured by a standardised instrument, such as HADS and the Beck Depression Inventory (BDI)
- Economic data (cost, cost-effectiveness, cost-utility and cost-benefits)

Search methods for identification of studies

Electronic searches

- For studies on effectiveness we will search the following databases:
    - Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library;
    - MEDLINE Ovid (from 1946 onwards);
    - Embase Ovid (from 1980 onwards);
- For economic evidence we will search:
    - MEDLINE Ovid (from 2015);
    - Embase Ovid (from 2015);
    - NHS Economic evaluation database (EED) to December 2014

The EED database will be searched up to the end of December 2014 (when the last records were added to that database) and MEDLINE and Embase from 1st January 2015, as NHS EED already included comprehensive searches of these databases prior to 2015. We will also consider relevant grey literature, such as health technology assessments, reports and working papers, for inclusion.
Please refer to Appendix 1 for draft MEDLINE search strategies. We will not apply language restrictions to any of the searches.

Searching other resources

We will search the following for ongoing studies:
- ClinicalTrials.gov (clinicaltrials.gov/)
- International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/)

If we identify any ongoing studies that have not been published through these searches, we will approach the principal investigators to ask for an update on the study status and any relevant data if available.
We will use the related articles feature of PubMed and handsearch the reference lists of included studies to identify newly published articles and additional studies of relevance.

Data collection and analysis

Selection of studies

For the results of the search for studies on effectiveness, the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer (CGNOC) Information Specialist will download all titles and abstracts retrieved by electronic searching to Endnote® and remove duplicates. Two review authors (Theresa Lawrie (TL) and one other), will independently screen the remaining records and exclude studies that clearly do not meet the eligibility criteria. For potentially eligible records, we will obtain copies of the full texts and two review authors (TL and Gerard Thompson (GT)), will independently assess them for eligibility. The two review authors concerned will resolve any disagreements by discussion with each other and, if necessary, they will consult at least one other review author. We will use Covidence to facilitate this study selection process and will document reasons for exclusion accordingly.
For the results of searches for economic evidence, two reviewers (Luke Vale (LV) and Ashleigh Kernohan (AK)), will independently screen for, identify and classify eligible studies as above.

Data extraction and management

Data from included intervention studies will be extracted independently by two review authors (TL and GT), to a pre-designed data extraction form to include the following.

- Author contact details
- Country
- Setting
- Dates of participant accrual
- Funding source
- Inclusion and exclusion criteria
- Study design
- Study population and baseline characteristics:
    - number of participants enrolled;
    - number of participants analysed;
    - age of participants;
    - gender of participants;
    - type of glioma (low grade or high grade; tumour size, molecular markers);
    - type of glioma treatment (surgery; radiotherapy; chemotherapy).
- Intervention details:
    - type of intervention (interval imaging), including whether it occurs pre-treatment or post-treatment, the interval period, and the type of scan (e.g. MRI);
    - type of comparator (symptomatic imaging), including indications for imaging, information on the timing of the imaging (e.g. median time to first scan post-treatment), and the type of scan.
- 'Risk of bias' assessment (see below)
- Duration of follow-up
- Primary outcome(s) of the study
- Review outcomes
    - For time-to-event outcomes (overall and progression-free survival), we will extract the hazard ratio (HR) with its 95% confidence interval (CI) for time points as reported by the study authors. We will note the definition of and procedure used to identify progression. Where reported, we will also extract dichotomous data for these outcomes at author-specified time points.
    - For dichotomous outcomes (e.g. anxiety, depression), we will extract the number of participants in each treatment arm that experienced the outcome of interest and the number of participants assessed.
    - For continuous outcomes (e.g. quality-of-life scores, anxiety, depression), we will extract the value and standard deviation of the outcome of interest and the number of participants assessed at the relevant time point in each group. We will also extract change-from-baseline score data where reported and note the type of scale used.
    - We will extract adjusted statistics where reported.
    - Where possible, all data extracted will be those relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned.
    - We will resolve differences between review authors by discussion or by appeal to a third review author when necessary.

We will develop a data extraction form for economic evaluations based on the format and guidelines used to produce structured abstracts of economic evaluations for inclusion in the NHS Economic Evaluation Database (NHS EED), adapted to the specific requirements of this review. In addition to the outcomes described above, economic evaluation studies will also extract the following data.

- Type of evaluations
- Sources of effectiveness data
- Cost data
- Sources of cost data
- Sources of outcome valuations
- Analytical approach

Two review authors, LV and AK, will extract the economic outcomes.

Assessment of risk of bias in included studies

For studies of clinical effects, we will assess the risk of bias using Cochrane's tool and the criteria specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). This includes assessment of:

- random sequence generation;
- allocation concealment;
- blinding of participants and healthcare providers;
- blinding of outcome assessors;
- incomplete outcome data (more than 20% missing data considered high risk);

- selective reporting of outcomes;
- other possible sources of bias, such as lack of a power calculation, baseline differences in group characteristics.

Two review authors (TL and GT) will assess risk of bias independently and will resolve any differences by discussion or by appeal to a third review author. We will summarise judgements in 'Risk of bias' tables along with the characteristics of the included studies. We will interpret the results of the meta-analyses in light of the overall 'Risk of bias' assessment. For more details about the assessment of risk of bias, see Appendix 2.

We will assess economic evaluation studies for bias in two stages. The first stage will involve assessing risk of bias from the sources of the effectiveness data. We will assess economic evaluations carried out alongside clinical studies using the Cochrane 'Risk of bias' tool, as described above. If the economic evaluation is model-based, we will use the ROBIS tool to assess bias in the effectiveness studies (Whiting 2016). The second stage involves assessing the risk of bias of the economic evidence (i.e. assessing the overall methodological quality). We will use the CHEERS and Evers checklists to do this. (hsr.mumc.maastrichtuniversity.nl/consensus-health-economic-criteria-chec-list), (Husereau 2013; Thielen 2016; Van Mastrigt 2016; Wijnen 2016).

Measures of treatment effect

- For time-to-event outcomes (e.g. overall survival) we will extract the hazard ratio (HR) with its 95% CI.
- For continuous outcomes (e.g. quality-of-life scores) we assume that study authors will use different measurement scales, therefore, we plan to estimate the standardised mean difference (SMD) and its 95% CI using the pooled data. However, if the same measurement scale is used, we will estimate the mean difference (MD) and its 95% CI. If studies do not report total values but, instead, report change-from-baseline outcomes, we will combine these change values with total measurement outcomes by using the (unstandardised) mean difference method in Review Manager 5 (RevMan 5), (Review Manager 2014). We will use subgroups to distinguish between MDs of change scores and MDs of final values, and pool the subgroups in an overall analysis (Deeks 2017).
- For dichotomous outcomes, we will calculate the effect size as a risk ratio (RR) with its 95% CI.

Unit of analysis issues

Two review authors (TL and GT) will review unit of analysis issues according to Deeks 2017 and will resolve any differences by discussion. These include reports where:

- groups of individuals are randomised together to the same intervention (i.e. cluster-randomised studies); or
- there are multiple observations for the same outcome (e.g. repeated measurements with different scales or at different time-points, recurring events).

Dealing with missing data

We will not impute missing data. In the event of missing data, we will write to study authors to request the data and describe in the characteristics of studies tables how any missing data were obtained.

Assessment of heterogeneity

We will assess heterogeneity between studies in each meta-analysis by visual inspection of forest plots, by estimation of the percentage heterogeneity between studies that cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2008), and, where possible, by subgroup analyses. If there is evidence of substantial heterogeneity, we will investigate and report the possible reasons for it.

Assessment of reporting biases

If there are 10 or more studies in meta-analyses we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it (Sterne 2017).

Data synthesis

We will conduct meta-analyses if participants, comparisons and outcomes are judged to be sufficiently similar to ensure an answer that is clinically meaningful. We will use the random-effects model with inverse variance weighting for all meta-analyses. If any studies have multiple intervention groups, we will divide the 'shared' comparison group into the number of treatment groups and comparisons between each treatment group, and treat the split comparison group as independent comparisons. We will perform meta-analysis of the results assuming that we find at least two included studies that are sufficiently similar for the findings to be clinically meaningful. When a meta-analysis is not possible due to the availability of single studies only, we will enter the data from single studies into RevMan 5 (Review Manager 2014), without totals, and grade the findings as described below.

We will summarise characteristics and results of included economic evaluations using additional tables, supplemented by a narrative summary that will compare and evaluate methods used and principal results between studies. We will also tabulate unit cost data, when available. We will report the currency and price year applicable to measures of costs in each original study, alongside measures of costs, incremental costs and incremental cost-effectiveness, by study. Where details of currency and price year are

available in original studies, we will convert measures of costs, incremental costs and cost-effectiveness to (latest year) International Dollars value using implicit price deflators for GDP and GDP Purchasing Power Parities (eppi.ioe.ac.uk/costconversion/default.aspx; Shemlit 2011). We will summarise details of the methodological characteristics of individual included health economics studies 'Characteristics of included studies' tables. We will conduct all elements of the economics component of this review according to current guidance on the use of economics methods in the preparation and maintenance of Cochrane Reviews (Shemlit 2011).

GRADE, 'Summary of findings' tables and results reporting

Based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017a), we will prepare a 'Summary of findings' table (see example Table 2) to present the results of the following outcomes, separately for LGGs and HGGs.

- Overall survival
- Progression-free survival
- Quality of life
- Anxiety
- Depression

For each assumed risk cited in the tables, we will provide a rationale, and we will use the GRADE system to rank the quality of the evidence (Schünemann 2017b). Where the evidence is based on single studies, or where there is no evidence on a specific outcome, we will include the outcome in the 'Summary of findings' tables and grade or explain accordingly. Two review authors will grade the evidence together. We will consider downgrading evidence of a clear effect derived from single studies with small sample sizes or few events. We will resolve any differences of opinion by discussion and, if necessary, by involving a third review author. We will report the results of the meta-analyses in the text based on the guidance from Cochrane Effective Practice and Organisation of Care on review results reporting and interpretation (EPOC 2015). For the economic evaluation studies, we will present the following findings in a table.

- Method of economic evaluation
- Costs
- Outcomes
- Incremental cost-effectiveness ratio

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis by the glioma grade (LGG and HGG) and molecular markers, if possible. We will use formal tests for subgroup differences to determine whether the effect of interventions differs according to these subgroups. Depending on these findings, we will consider whether an overall summary is meaningful. We will consider factors such as age, gender, type of treatment, and risk of bias in interpretation of any heterogeneity. If we identify substantial heterogeneity, we will investigate it in sensitivity analyses.

Sensitivity analysis

We will perform sensitivity analysis to investigate substantial heterogeneity identified in meta-analyses of primary outcomes and also to evaluate the effect after excluding studies at high risk of bias, to investigate how study quality affects the certainty of the findings.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. National Institute for Health and Clinical Excellence (NICE) guidance on interval imaging

Tumour grade	Years after end of treatment					
	0 to 1	1 to 2	2 to 3	3 to 4	5 to 10	> 10 (for the rest of life)
Grade 1	Scan at 12 months, then: • consider discharge if no tumour visible on imaging unless completely resected pilocytic astrocytoma • consider ongoing imaging at increasing intervals for 15 years for completely resected pilocytic astrocytoma					

Table 1. National Institute for Health and Clinical Excellence (NICE) guidance on interval imaging (*Continued*)

	• consider if ongoing imaging is needed at a rate of once every 1 to 3 years for the rest of the person's life if the tumour is visible on imaging			
Grade II 1p/19q non-codeleted, IDH mutated	Scan at 3 months, then every 6 months	Annually	Every 1 to 2 years	Consider ongoing imaging every 1 to 2 years
Grade II 1p/19q codeleted				
Grade III 1p/19q codeleted				
Grade II IDH wildtype	Every 3 to 6 months	Every 6 to 12 months	Annually	Consider ongoing imaging every 1 to 2 years
Grade III 1p/19q non-codeleted				
Grade IV (glioblastoma)				

From NICE 2018 (p17) Table 3: Possible regular clinical review schedule for people with glioma depending on grade of tumour

Table 2. Summary of findings

Pre-treatment interval imaging compared with pre-treatment imaging on indication for low-grade glioma						
Patient or population: people with low-grade glioma **Settings:** tertiary care **Intervention:** pre-treatment interval imaging **Comparison:** pre-treatment imaging on indication						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Imaging on indication	**Pre-treatment interval imaging**				

Table 2. Summary of findings (*Continued*)

Overall survival (5 years)	**Low risk population**		**RR (value)** ((value) to (value))	(value) ((value))	(Delete as appropriate) ⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
	[value)per 1000	**(value)per 1000** ((value) to (value))				
	Medium risk population					
	(value)per 1000	**(value)per 1000** ((value) to (value))				
Progression-free survival (5 years)	**Low risk population**		**RR (value)** ((value) to (value))	(value) ((value))	(Delete as appropriate) ⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
	(value)per 1000	**(value)per 1000** ((value) to (value))				
	Medium risk population					
	(value)per 1000	**(value)per 1000** ((value) to (value))				
Post-imaging QoL score*	The mean (outcome) ranged across control groups from (value)(measure)	The mean (outcome) in the intervention groups was **(value)** **(lower/higher)** ((value to value lower/higher))		(value) ((value))	(Delete as appropriate) ⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
Anxiety*	**Low risk population**		**RR (value)** ((value) to (value))	(value) ((value))	(Delete as appropriate) ⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	

Table 2. Summary of findings (*Continued*)

	(value)per 1000	**(value)per 1000** ((value) to (value))				
	Medium risk population					
	(value)per 1000	**(value)per 1000** ((value) to (value))				
	High risk population					
	(value)per 1000	**(value)per 1000** ((value) to (value))				
Depression*	**Low risk population**		**RR (value)** ((value) to (value))	(value) ((value))	(Delete as appropriate) ⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
	(value)per 1000	**(value)per 1000** ((value) to (value))				
	Medium risk population					
	(value)per 1000	**(value)per 1000** ((value) to (value))				
	High risk population					
	(value)per 1000	**(value)per 1000** ((value) to (value))				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **QoL:** quality of life; **RR:** risk ratio; (other abbreviations, e.g. OR, etc)

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

*It is likely that different measurement time points and scales will be used in different studies. Where this is the case, we will attempt to synthesise the evidence narratively.

APPENDICES

Appendix 1. MEDLINE draft search strategy

Draft M*EDLINE* strategy with RCT filter

1. exp Glioma/
2. (glioma* or astrocytoma* or ependymoma* ganglioglioma* or gliosarcoma* or oligodendroglioma* or glioblastoma* or oligoastrocytoma* or GBM*).ti,ab.
3. 1 or 2
4. neuroimaging/
5. exp Magnetic Resonance Imaging/
6. (MRI or MRi or magnetic resonance imag*).ti,ab.
7. (brain* adj5 (imag* or scan*)).ti,ab.
8. Tomography, X-Ray Computed/
9. ((CT or CAT or compute* tomograph*) adj5 (scan* or imag*)).ti,ab.
10. exp Positron-Emission Tomography/
11. (positron-emission tomography* or PET).ti,ab.
12. exp Magnetic Resonance Spectroscopy/
13. (magnetic resonance spectroscop* or MR*).ti,ab.
14. contrast-enhanced computerised tomography or CT.ti,ab.
15. Perfusion Imaging/
16. exp Tomography, Emission-Computed, Single-Photon/
17. SPEC or SPECT.ti,ab.
18. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 3 and 18
20. ((inter* or routin* or regular* or frequen* or sequential or continuous* or serial* or recur*or longitudinal* or repeat*) adj5 (scan* or imag*)).ti,ab.
21. 19 and 20

Key

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
ab=abstract
sh=subject heading
ti=title
pt=publication type

Draft M*EDLINE* strategy with economic filter

1. exp Glioma/
2. (glioma* or astrocytoma* or ependymoma* ganglioglioma* or gliosarcoma* or oligodendroglioma* or glioblastoma* or oligoastrocytoma* or GBM*).ti,ab.
3. 1 or 2

4. neuroimaging/
5. exp Magnetic Resonance Imaging/
6. (MRI or MRi or magnetic resonance imag*).ti,ab.
7. (brain* adj5 (imag* or scan*)).ti,ab.
8. Tomography, X-Ray Computed/
9. ((CT or CAT or compute* tomograph*) adj5 (scan* or imag*)).ti,ab.
10. exp Positron-Emission Tomography/
11. (positron-emission tomography* or PET).ti,ab.
12. exp Magnetic Resonance Spectroscopy/
13. (magnetic resonance spectroscop* or MR*).ti,ab.
14. contrast-enhanced computerised tomography.mp. or CT.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15. Perfusion Imaging/
16. exp Tomography, Emission-Computed, Single-Photon/
17. SPEC.mp. or SPECT.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
18. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 3 and 18
20. ((inter* or routin* or regular* or frequen* or sequential or continuous* or serial* or recur*or longitudinal* or repeat*) adj5 (scan* or imag*)).ti,ab.
21. 19 and 20
22. Economics/
23. exp "costs and cost analysis"/
24. Economics, Dental/
25. exp economics, hospital/
26. Economics, Medical/
27. Economics, Nursing/
28. Economics, Pharmaceutical/
29. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
30. (expenditure$ not energy).ti,ab.
31. value for money.ti,ab.
32. budget$.ti,ab.
33. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. ((energy or oxygen) adj cost).ti,ab.
35. (metabolic adj cost).ti,ab.
36. ((energy or oxygen) adj expenditure).ti,ab.
37. 34 or 35 or 36
38. 33 not 37
39. letter.pt.
40. editorial.pt.
41. historical article.pt.
42. 39 or 40 or 41
43. 38 not 42
44. 21 and 43

Key

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
ab=abstract
sh=subject heading
ti=title
pt=publication type

Appendix 2. Assessment of risk of bias

For randomised controlled trials

We will assess the risk of bias according to the following criteria:

(1) Random sequence generation

- Low risk of bias e.g. participants assigned to treatments on basis of a computer-generated random sequence or a table of random numbers
- High risk of bias e.g. participants assigned to treatments on basis of date of birth, clinic ID-number or surname, or no attempt to randomise participants
- Unclear risk of bias e.g. not reported, information not available

(2) Allocation concealment

- Low risk of bias e.g. where the allocation sequence could not be foretold
- High risk of bias e.g. allocation sequence could be foretold by participants, investigators or treatment providers
- Unclear risk of bias e.g. not reported

(3) Blinding of participants and personnel

- Low risk of bias if participants and personnel were adequately blinded
- High risk of bias if participants and/or personnel were not blinded to the intervention that the participant received
- Unclear risk of bias if this was not reported or unclear

(4) Blinding of outcome assessors

- Low risk of bias if outcome assessors were adequately blinded to the intervention that the participant received
- High risk of bias if outcome assessors were not blinded to the intervention that the participant received
- Unclear risk of bias if this was not reported or unclear

(5) Incomplete outcome data

We will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as:

- low risk of bias, if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
- High risk of bias, if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms
- Unclear risk of bias if loss to follow-up was not reported

(6) Selective reporting of outcomes

- Low risk of bias e.g. review reports all outcomes specified in the protocol
- High risk of bias e.g. It is suspected that outcomes have been selectively reported
- Unclear risk of bias e.g. It is unclear whether outcomes had been selectively reported

(7) Other bias

- Low risk of bias, i.e.no other source of bias suspected and the study appears to be methodologically sound
- High risk of bias: we suspect that the study was prone to an additional bias
- Unclear risk of bias: we are uncertain whether an additional bias may have been present

For non-randomised controlled trials and controlled before-after studies

We will assess the risk of bias in accordance with four criteria concerning sample selection comparability of treatment groups:

(1) Relevant details of criteria for assignment of patients to treatments

- Low risk of bias, e.g. yes, details provided
- High risk of bias, e.g. no details provided
- Unclear risk of bias, e.g. details unclear

(2) Representative group of people who received the experimental intervention

- Low risk of bias, if representative of participants with low and/or high grade gliomas who receive interval brain imaging to assess their condition
- High risk of bias, if groups of participants were selected (non-consecutive)
- Unclear, if selection of the group was not described

(3) Representative group of people who received the comparison intervention

- Low risk of bias, if drawn from the same population as the experimental group
- High risk of bias, if drawn from a different source
- Unclear risk of bias, if selection of group not described

(4) Baseline differences between groups controlled for, in particular with reference to age, gender, grade of glioma and glioma treatment

- Low risk of bias, if at least three of these characteristics were reported
- High risk of bias, if the groups differed in these baseline characteristics and differences were not controlled for
- Unclear risk of bias, if fewer than three of these characteristics were reported even if there were no other differences between the groups, and other characteristics were controlled for

CONTRIBUTIONS OF AUTHORS

Theresa Lawrie wrote the first draft of the protocol. All authors advised on and approved the final version of the protocol.

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Theresa Lawrie: none declared

Ashleigh Kernohan: none declared

Michael Jenkinson: none declared

Gerard Thompson: none declared

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