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Long-term side effects of radiotherapy, with or without chemotherapy, for glioma (Protocol)

Lawrie TA, Evans J, Gillespie D, Erridge S, Vale L, Kernohan A, Grant R

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[Intervention Protocol]

Long-term side effects of radiotherapy, with or without chemotherapy, for glioma

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ABSTRACT

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

To evaluate the long-term neurocognitive and other side effects of radiotherapy (with or without chemotherapy) compared with no radiotherapy, or different types of radiotherapy, among people with glioma (where 'long-term' is defined as at least two years after diagnosis).

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 oligodentrocytes 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 aggressive potential in the near term. The 2007 WHO classification system (Louis 2007), used in completed clinical trials since 2007, graded gliomas based on histological characteristics only. However, in the 2016 WHO classification system, to be used in future trials, grading depends on both histological and molecular features, e.g. 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 aggressive potential in the near term 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 with 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, particularly the need for additional treatment in the form of radiotherapy (RT) or chemotherapy (CT), or both chemo-radiotherapy (chemoRT) after surgery.

Description of the intervention

Most people with glioma first undergo surgery to resect or biopsy the tumour. The latter is usually performed when resection is not possible, either due to the diffuse, infiltrative nature of the tumour, or its location near important structures. Additional RT, targeting the tumour area (focal RT) is usually given immediately after surgery for HGGs, whereas for grade 2 gliomas it can either be given immediately, or postponed until the development of new symptoms or tumour progression (Sarmiento 2015). Fifty per cent of people with grade 2 and grade 3 gliomas survive at least seven years and four and a half years, respectively, after treatment (Buckner 2016; Cairncross 2013). However, for certain grade 2 and 3 gliomas with particular molecular features, median survival can be extended by a further seven years by the addition of CT to RT (Buckner 2016; Cairncross 2013). Approximately 25% of people with grade 4 gliomas that are treated with chemo-radiotherapy are alive two years after diagnosis (Stupp 2005).

Radiation exposure of normal brain tissue adversely affects brain plasticity and repair processes (Dhermain 2016), therefore, the treatment of glioma can be complicated by long-term side effects that present months or years after treatment. These may cause particular problems in people who survive to be followed up in the long term, as the frequency of side effects increases with time. Long-term side effects include neurocognitive, psychosocial and endocrine (hormonal) side effects, which are particularly common among survivors of childhood brain tumours (Grill 1999; Seaver 1994; Spiegler 2004; Williams 2018). Certain parts of the brain, including the hippocampus, fornix and corpus callosum, are more sensitive to irradiation (Connor 2017; Gondi 2012; Peiffer 2013). Therefore, factors that are important to the risk of long-term side effects in glioma treatment are the site of the tumour, the volume of brain tissue irradiated, the RT fraction size and the total RT dose. Using chemotherapy with RT might add to the risk. Among adults treated for LGG, studies suggest that the risk of neurocognitive effects is increased when RT is administered to the whole brain (not done nowadays for gliomas) (Gregor 1996; Surma-aho 2001), but not necessarily when RT is administered to the tumour area only (Brown 2003; Laack 2005; Taphoorn 1994; Vigliani 1996). Endocrine dysfunction affecting adrenal, gonadal and thyroid hormones can also occur due to RT damage to the hypothalamic-pituitary axis (Taphoorn 1995). Whilst historically this was not thought to be a problem in adults (Taphoorn 1995), recent evidence suggests that it may be (Kyriakakis 2016), and in children it frequently leads to hypothyroidism, growth hormone deficiency and precocious puberty (Terashima 2013). Fatigue, disturbed sleep and depression are also commonly reported side effects of cancer therapy among people with primary brain tumours (Armstrong 2017).

Why it is important to do this review

The focus of clinical practice and of clinical trials of glioma treatment is on increasing survival among people with glioma. However, uncertainty about the possible long-term side effects of treatment among people with gliomas that have a good prognosis remains a concern for clinicians, affected individuals, and their families. Furthermore, the impact of treatment on long-term survivors' quality of life remains unclear.

In 2015, this topic was identified among the top 10 priority research questions in neuro-oncology by the James Lind Alliance and the National Cancer Research Institute (NCRI) (JLA 2015). In view of these factors, and in the context of the current trend towards more aggressive early treatments (e.g. chemo-radiotherapy) for LGGs, a Cochrane Review evaluating existing evidence on the long-term effects of RT (with or without chemotherapy) would be helpful to inform individual decisions around glioma treatment options.

OBJECTIVES

To evaluate the long-term neurocognitive and other side effects of radiotherapy (with or without chemotherapy) compared with no radiotherapy, or different types of radiotherapy, among people with glioma (where 'long-term' is defined as at least two years after diagnosis).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and non-randomised trials, and controlled before-and-after studies (CBAS). We will consider non-randomised trials and CBAS for inclusion if the primary outcome data from randomised trials is inadequate. We will exclude cross-over designs, case-control studies, and studies that do not have a control group.

Types of participants

People aged 16 years of age and older with a histopathologically confirmed diagnosis of cerebral glioma who are alive at least two years after diagnosis.

In this review, as we consider late effects to be those that are present at two years or more after diagnosis in people who have a good long-term prognosis, rather than in those that have a short-term prognosis, we will exclude studies only involving people with glioblastoma. In studies with mixed HGG participants (grade 3 and grade 4 gliomas) we will attempt to extract data for the participants with grade 3 glioma only.

Types of interventions

Treatment interventions after surgery (biopsy or resection of the tumour) will include the following.

- Radiotherapy (RT) compared with no RT, which includes the following comparison subgroups.
  - RT versus no adjuvant treatment (NAT).
  - Radiotherapy plus chemotherapy (chemoRT) versus NAT.
  - RT versus chemotherapy (CT).
  - ChemoRT versus CT.
- Low-dose RT compared with high-dose RT.
- ChemoRT versus RT.
- Stereotactic conformal RT (SCRT) compared with conventional RT.

Types of outcome measures

Studies must report the primary outcome in both the intervention and control groups at least two years after receiving the intervention.

Primary outcomes

Cognitive impairment (objective or subjective), as measured by an overall cognitive function score, a change over time score, or as a categorical outcome. We will also evaluate cognitive impairment as individual cognitive function domains, e.g. verbal fluency, processing speed, memory, attention, and executive functioning, using a standardised measurement tool, e.g. Mini Mental State Exam (MMSE), Cognitive Failures Questionnaire (CFQ).

Secondary outcomes

- Functional impairment or disability, as measured by an overall ability score, or as a change of ability over time score, or both, using a standardised measurement tool, e.g. Karnofsky Performance Status Scale, Neurological Functions Score; or as a categorical outcome, as defined by investigators
- Quality of life (QoL), as measured using a standardised questionnaire, e.g. 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))
- Endocrine dysfunction, as determined by use of hormonal treatment, or as defined by study investigators, or both
- Depression, as measured by a standardised scale, e.g. Hospital Anxiety and Depression Scale (HADS)
- Anxiety, as measured by a standardised scale, e.g. HADS
- Fatigue, according to Common Terminology Criteria for Adverse Events (CTCAE), or as defined by investigators
- Sleep disturbances, as defined by investigators
- Imaging evidence of physical deficit, e.g. general brain atrophy, white matter changes, radionecrosis, stroke
- Social outcomes (e.g. carer strain, relationship status, employment status)
- Second cancers
- Cost of care (as a brief economic commentary)

Search methods for identification of studies

Electronic searches

We will search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; latest issue), part of the Cochrane Library.
- MEDLINE (Ovid 1946 to date of search).
- Embase (Ovid 1980 to date of search).

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 trials.

- ClinicalTrials.gov (clinicaltrials.gov).
- International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch).

If we identify through these searches ongoing trials that have not been published, we will approach the principal investigators to ask for an update on the trial status and relevant data. 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. We will search conference abstracts of the following journals.

- *Journal of Clinical Oncology.*
- *International Journal of Radiation Oncology, Biology and Physics.*
- *Neurology.*
- *Neuro-oncology.*

Data collection and analysis

Selection of studies

The Information Specialist at the Gynaecological, Neuro-oncology and Orphan Cancer Group (GNOC) will download all titles and abstracts retrieved by electronic searching to Endnote and remove duplicates and those studies that clearly do not meet the inclusion criteria. Two review authors (TL and another) will independently screen the remaining records and exclude studies that clearly do not meet the inclusion criteria. For potentially eligible references, copies of the full texts will be obtained and independently assessed for eligibility by at least two review authors (TL and at least one other). Disagreements will be resolved by discussion between the two review authors concerned and, if necessary, the other review authors will be consulted. We will use Covidence to facilitate this study selection process (Covidence 2018), and document reasons for exclusion.

Data extraction and management

Two review authors (TL and one other) will independently extract data from included studies to a pre designed data extraction form to include:

- author contact details
- country
- setting
- dates of participant accrual
- trial registration number/identification
- funding source
- participant inclusion and exclusion criteria
- study design and methodology
- study population and baseline characteristics
  - number of participants enrolled/analysed
  - age
  - gender
  - tumour grade/type
  - type of surgery (biopsy or resection)
  - other medication, e.g. anti-epileptics and anti-depressants (selective serotonin reuptake inhibitors (SSRIs))
- intervention details
  - type of intervention
  - type of comparator
- duration of follow-up
- primary outcome/s of the study
- review outcomes
  - for dichotomous outcomes, we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed
  - for continuous outcomes, 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 reviewers by discussion or by appeal to the other review authors when necessary
- risk of study bias (see below).

Assessment of risk of bias in included studies

For randomised trials, 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 2011). 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, e.g. lack of a power calculation, baseline differences in group characteristics.

For non-randomised studies (non-randomised trials and CBASs), we will assess the risk of bias in accordance with four criteria concerning sample selection comparability of treatment groups, namely:

- relevant details of criteria for assignment of people with the condition to treatments;
- representative group of people with the condition who received the experimental intervention;
- representative group of people with the condition who received the comparison intervention;
- baseline differences between groups controlled for, in particular with reference to age, gender, type and grade of glioma and surgical treatment.

Two review authors (TL and at least one other) will assess risk of bias independently and will resolve 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 results of meta-analyses in light of the overall 'Risk of bias' assessment. For more details about the assessment of risk of bias, see Appendix 2.

Measures of treatment effect

- For dichotomous outcomes, we will calculate the effect size as a risk ratio (RR) with its 95% confidence interval (CI).
- For continuous outcomes (e.g. QoL scores) in which different measurement scales have been used, we will estimate the standardised mean difference (SMD) and its 95% CI for 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 attempt to combine these change values with total measurement outcomes by using the (unstandardised) mean difference method in Review Manager (RevMan) (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 (Higgins 2011).

Unit of analysis issues

At least two review authors (TL, RG) will review unit of analysis issues according to Higgins 2011 for each included study; we will resolve differences by group discussion. These include reports where there are multiple observations for the same outcome, e.g. repeated measurements with different scales, or outcomes measured at different time points to those stipulated in the review protocol.

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 included studies' tables how we obtained any missing data. Where missing data are substantial, this will be taken into consideration in our grading of the evidence (see Data synthesis).

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 trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001), and, where possible, by subgroup analyses. If there is evidence of substantial heterogeneity, we will investigate and report the possible reasons for this.

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.

Data synthesis

We will conduct meta-analyses if we judge participants, comparisons and outcomes 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 trials contributing to a meta-analysis 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 a 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, e.g. due to the availability of single studies only, or due to studies reporting findings in different ways, where possible we will enter available data into RevMan without totals (Review Manager 2014), and report the unpooled findings narratively.

'Summary of findings' table and results reporting

Based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we will prepare a 'Summary of findings' table to present the results of the following outcomes (Table 1).

- Cognitive impairment at ≥ 2 years.
- Functional impairment at ≥ 2 years.
- Quality of life (QoL) score at ≥ 2 years.
- Endocrine dysfunction at ≥ 2 years.
- Depression at ≥ 2 years.
- Fatigue at ≥ 2 years.

We will also include evidence for these outcomes measured at later annual time points in the 'Summary of findings' table if available.

We will use the GRADE system to rank the quality of the evidence (Schünemann 2011). Two review authors will independently grade the evidence. Differences will be resolved by discussion and, if necessary, by involving a third review author. 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. We will consider downgrading evidence limited to a single small study, irrespective of the estimate of effect. In addition, we will provide a rationale for each judgement of assumed risk in the table footnotes. We will also grade narrative summaries of outcomes for which meta-analysis is not possible, due to the different ways that investigators have reported or measured outcomes, using a GRADE working group approach (Murad 2017). We will interpret the results of the graded evidence based on Cochrane Effective Practice and Organisation of Care guidance (EPOC 2017).

Brief economic commentary

We will develop a brief economic commentary (BEC) based on current methods guidelines (Shemlit 2011a; Shemlit 2011b), to summarise the availability and principal findings of trial-based and model-based economic evaluations (cost analyses, cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses) that compare the use of different treatments for gliomas. We will identify relevant studies for this BEC during searches conducted for the intervention review and during supplementary searches performed in accordance with search strategies developed by the Economics Methods Group (Shemlit 2017). This commentary will focus on the extent to which principal findings of eligible economic evaluations indicate that an intervention might be judged favourably (or unfavourably) from an economic perspective, when implemented in different settings.

Subgroup analysis and investigation of heterogeneity

For the comparison 'RT versus no RT', we will perform a subgroup analysis according to the type of control group. We will use formal tests for subgroup differences to determine whether the effect of interventions differ 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, treatment regimen, 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 a sensitivity analysis to investigate substantial heterogeneity identified in meta-analyses of the primary outcome, and also to estimate the effect after excluding studies at high risk of bias, to investigate how trial quality affects the certainty of the findings.

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ADDITIONAL TABLES

Table 1. Summary of findings

Radiotherapy compared with no radiotherapy for glioma: long-term side effects

Patient or population: people with glioma surviving at last two years

Settings: tertiary care

Intervention: radiotherapy

Comparison: no radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy				
Cognitive impairment at ≥ 2 years	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**	
QoL score at ≥ 2 years	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**	
Functional impairment at ≥ 2 years	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate**	

Table 1. Summary of findings *(Continued)*

					⊕⊕⊕⊕ **high**
Endocrine dysfunction at ≥ 2 years	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Depression at ≥ 2 years	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Fatigue at ≥ 2 years	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**

*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; **RR:** risk ratio; [other abbreviations, e.g. OR, etc.]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Glioma/
2. (glioma* or astrocytoma* or medulloblastoma* or ependymoma* or craniophyrangioma* or oligodendroglioma* or glioblastoma* or GBM*).ti,ab.
3. 1 or 2
4. exp Radiotherapy/
5. radiotherapy.fs.
6. (radiotherap* or radiat* or irradiat*).ti,ab.
7. exp Antineoplastic Agents/
8. Antineoplastic Combined Chemotherapy Protocols/
9. chemotherap*.mp.
10. exp Chemoradiotherapy/
11. (radiochemo* or chemoradio*).mp.
12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 3 and 12
14. Radiation Effects/
15. exp Radiation Injuries/
16. adverse effects.fs.
17. ((late or adverse* or long term or side or long-term or chronic* or residual* or delay* or undesirable or unexpected) adj5 (effect* or event* or outcome* or reaction* or complication* or harm* or injur* or toxic*)).ti,ab.
18. (adrs or tolerab*).ti,ab.
19. (radiation induced* or radiation-induced).ti,ab.
20. 14 or 15 or 16 or 17 or 18 or 19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized.ab.
24. placebo.ab.
25. clinical trials as topic.sh.
26. randomly.ab.
27. trial.ti.
28. exp Cohort Studies/
29. cohort*.tw.
30. longitudinal*.tw.
31. prospective*.tw.
32. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 13 and 20 and 32
34. exp animals/ not humans.sh.
35. 33 not 34

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

Search with economic filter:

1. exp Glioma/
2. (glioma* or astrocytoma* or medulloblastoma* or ependymoma* or craniophyrangioma* or oligodendroglioma* or glioblastoma* or GBM*).ti,ab.
3. 1 or 2
4. exp Radiotherapy/
5. radiotherapy.fs.
6. (radiotherap* or radiat* or irradiat*).ti,ab.

7. exp Antineoplastic Agents/
8. Antineoplastic Combined Chemotherapy Protocols/
9. chemotherap*.mp.
10. exp Chemoradiotherapy/
11. (radiochemo* or chemoradio*).mp.
12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 3 and 12
14. Radiation Effects/
15. exp Radiation Injuries/
16. adverse effects.fs.
17. ((late or adverse* or long term or side or long-term or chronic* or residual* or delay* or undesirable or unexpected) adj5 (effect* or event* or outcome* or reaction* or complication* or harm* or injur* or toxic*)).ti,ab.
18. (adrs or tolerab*).ti,ab.
19. (radiation induced* or radiation-induced).ti,ab.
20. 14 or 15 or 16 or 17 or 18 or 19
21. 13 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 trials

(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 patients, 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 outcomes 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 follows.

- Low risk of bias, if fewer than 20% of patients 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 patients 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 trial appears to be methodologically sound
- High risk of bias, i.e. we suspect that the trial was prone to an additional bias
- Unclear risk of bias, i.e. we are uncertain whether an additional bias may have been present

For non-randomised trials

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 participants 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 patients with gliomas who receive treatment for their condition
- High risk of bias, if groups of patients 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/type of glioma, type of surgery

- Low risk of bias, if all 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

WHAT'S NEW

Date	Event	Description
11 June 2018	Amended	Address updated.

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

Theresa Lawrie: none known
Jonathan Evans: none known
David Gillespie: none known
Sara Erridge: none known
Luke Vale: Member of NIHR HTA CET Panel until March 2018
Ashleigh Kernohan: none known
Robin Grant: none known

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