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Treatment of newly diagnosed glioblastoma in the elderly (Protocol)

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[Intervention Protocol]

Treatment of newly diagnosed glioblastoma in the elderly

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ABSTRACT

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

To determine the most effective and best-tolerated approaches for the treatment of elderly people with newly diagnosed glioblastoma.

To summarise current evidence for the incremental resource use, utilities, costs and cost-effectiveness associated with the different management strategies for newly diagnosed glioblastoma among adults aged over 70 years.

BACKGROUND

Description of the condition

Glioblastoma multiforme is a high grade, aggressive primary tumour of the central nervous system with a poor prognosis. The incidence of glioblastoma is increasing and this rise is most rapid in the elderly (Ferguson 2014). Use of the term the 'elderly' in relation to glioblastoma commonly refers to people over 70 years of age (NCCN 2018). Age is an important consideration in the treatment of glioblastoma as it is a negative prognostic indicator (Lorimer 2017). Median survival drops from 12 to 18 months for younger people with glioblastoma, to three to six months for older age cohorts (Brodbelt 2015). The molecular status of glioblastoma is also an important prognostic factor and several molecular subtypes of glioblastoma have been recognised (Lara-Velazquez 2017). One of the most important molecular signatures is O^6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation, which has been shown to confer predictive and prognostic benefit (Malmstrom 2012; Yin 2014). Treatment for glioblastoma is not curative and the natural history of the disease is that patients will relapse after treatment and it will ultimately be a fatal condition (Louis 2016). Retrospective studies have shown that older people are less likely to get aggressive, multi-modality treatment (Iwamoto 2008; Lorimer 2017; Paszat 2001), but people with glioblastoma across all age groups who do get active treatment live

longer (Brodbelt 2015). Direct healthcare costs for the management of malignant gliomas have been estimated at USD 32,764 per patient (2011 data; Raizer 2015).

Description of the intervention

The 'standard of care' of treatment for patients aged under 70 years of age with glioblastoma consists of surgery, followed by radiotherapy (60 Gy in 30 fractions) and concurrent and adjuvant temozolomide (TMZ) chemotherapy (Stupp 2005; NCCN 2018). This management plan is less often used in the elderly for the following reasons.

- People over 70 years old were not included in the landmark trial (Stupp 2005), and a subsequent communication of the results of an exploratory subgroup analysis revealed that the survival benefit in this trial was not statistically significant for subgroup of people aged 66 to 70 years (Laperriere 2013).
- Shorter radiotherapy courses or chemotherapy alone can lead to better outcomes for the elderly than the standard course of radiotherapy (Malmstrom 2012).
- Treatment toxicity is often greater in the elderly (Lawrence 2011; Sijben 2008).
- The shorter predicted survival time for older people with glioblastoma means that they might spend much of this time recovering from the six-week course of radiotherapy.

Small prospective (Vuorinen 2003), and retrospective studies (Chaichana 2011a; Chaichana 2011b), have shown that, for people aged 65 and over with glioblastoma, maximal debulking (resection) is associated with better survival and a trend to longer time remaining independent versus biopsy alone. Therefore maximal resection, if feasible, is the recommended primary approach to glioblastoma in the elderly (NCCN 2018). Depending on performance status, radiotherapy or chemotherapy, or both, can then be added. As it remains unclear which treatment is best for glioblastoma in the elderly, participation in clinical trials is strongly encouraged (NCCN 2018). There is little evidence to guide treatment of recurrent glioblastoma in the elderly and approaches are based on retrospective studies (Socha 2016).

Treatment with either radiotherapy or chemotherapy

A randomised trial of radiotherapy (50 Gy delivered over a period of 5 to 6 weeks) versus best supportive care showed that radiotherapy conferred a 12-week survival benefit in older people with malignant glioma (malignant glioma encompasses anaplastic glioma, i.e. World Health Organization (WHO) grade 3 and 4) (Keime-Guibert 2007). Another randomised trial found that radiotherapy (60 Gy over a period of 6 to 7 weeks) was as effective as intensive ("dose-dense") adjuvant temozolomide chemotherapy alone (Wick 2012). There is increasing interest in using hypofractionated radiotherapy (radiotherapy delivered over shorter period of time, e.g. 34.0 Gy in 10 fractions over a period of two weeks) for older people with glioblastoma, as it has been found to have similar survival benefits compared to the standard regimen of 60 Gy in 30 fractions over a period of six weeks (Malmstrom 2012; Roa 2004).

Combination treatment

A randomised trial has shown that adding TMZ to hypofractionated radiotherapy for older people with glioblastoma confers a survival advantage compared to hypofractionated radiotherapy alone (Minniti 2012; Perry 2017), but not necessarily for those people with MGMT unmethylated tumours.

How the intervention might work

Surgery is an important step in the treatment of glioblastoma. Also, there is evidence that surgery improves one- and two-year survival rates compared to biopsy alone (Brown 2016). The extent of surgery can be divided into three main categories which have different definitions in the literature: 'maximal' debulking or gross total resection (GTR), subtotal resection (STR), and biopsy. The role of maximal debulking surgery is to minimise the tumour volume that remains to optimise the impact of subsequent treatment modalities, which are likely to be more effective against small volume tumours (Lara-Velazquez 2017).

Radiotherapy is delivered to the primary tumour or the surgical cavity with a margin to account for microscopic spread, patient movement, and set-up error (Niyazi 2016). One of the most important mechanisms of action of radiation therapy is the promotion of double strand breaks in DNA which, if left unrepaired, will result in cell death (Baskar 2014). DNA damage is more likely to occur in rapidly dividing cells, such as glioblastoma tumour cells, rather than normal brain which has a slower rate of cellular turn over. This provides the therapeutic index between the tumour and normal surrounding tissue.

Systemic chemotherapy can enhance the therapeutic effect of radiotherapy but is also an effective treatment on its own. The most widely used chemotherapy agent is TMZ, which acts as a DNA alkylating agent (Zhang 2012). Those tumours with MGMT promoter methylation lack the MGMT enzyme which repairs the cytotoxic damage caused by TMZ, thereby making tumour cells more chemosensitive.

Why it is important to do this review

Is it recognised that treating older people with glioblastoma presents unique challenges and that the standard approach is not always appropriate. There have been several randomised trials in recent years that have tested therapeutic strategies specifically for older people with glioblastoma (e.g. Malmstrom 2012; Perry

2017; Roa 2004; Wick 2012). Other trials including younger people have also performed subgroup analysis to test if therapeutic benefit is maintained in older people. Due to the variation in age thresholds to define the 'elderly', performance status, treatment regimens, and molecular subtypes, it has been difficult to translate these individual studies into clinical practice. This is also because the focus of many intervention trials is on survival, which might not be the most important outcome to elderly people with glioblastoma; rather, the quality of the remainder of their life might be their most important consideration.

Selecting the appropriate management strategy for an elderly patient group is important from a quality of life perspective and also has significant resource implications (Raizer 2015). It has been estimated the average cost for a regimen of temozolomide to treat a person with newly diagnosed glioblastoma is USD 46,693 (USD in 2018 converted from NZD 2005) (Hamilton 2005). It is therefore important to understand the cost and benefits to avoid implementing costly and potentially toxic treatment for little clinical benefit.

Currently there is no clear consensus on how to apply the available evidence to guide treatment of the individual person seen in clinic. A systematic review and network meta-analysis of randomised trials would help to inform the best approach to the treatment of older individuals with newly diagnosed glioblastoma and help to identify research gaps.

OBJECTIVES

To determine the most effective and best-tolerated approaches for the treatment of elderly people with newly diagnosed glioblastoma.

To summarise current evidence for the incremental resource use, utilities, costs and cost-effectiveness associated with the different management strategies for newly diagnosed glioblastoma among adults aged over 70 years.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs) for evidence on effectiveness and safety.
- Full economic evaluations (cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses) conducted alongside any study design and any model-based economic evaluations for economic evidence.

Types of participants

Elderly people undergoing treatment for histologically confirmed newly diagnosed glioblastoma. For the purpose of this Cochrane Review, we define 'elderly' as over the age of 70 years; however, where investigators have defined the 'elderly' as over 65 years of age, we will include these studies. We will include studies of people of all ages that report subgroup findings for elderly people (over 65 or 70 years of age) provided the participants in the subgroup number more than 20. We will consider including the mixed data if it is clear that 80% or more of participants in the study are over the age of 65 years. Similarly, where the study population includes both grade 3 or 4 gliomas (anaplastic astrocytomas or glioblastoma), we will try to obtain separate data for participants with glioblastoma; if this is not possible, we will consider including the study if more than half the study population had glioblastoma.

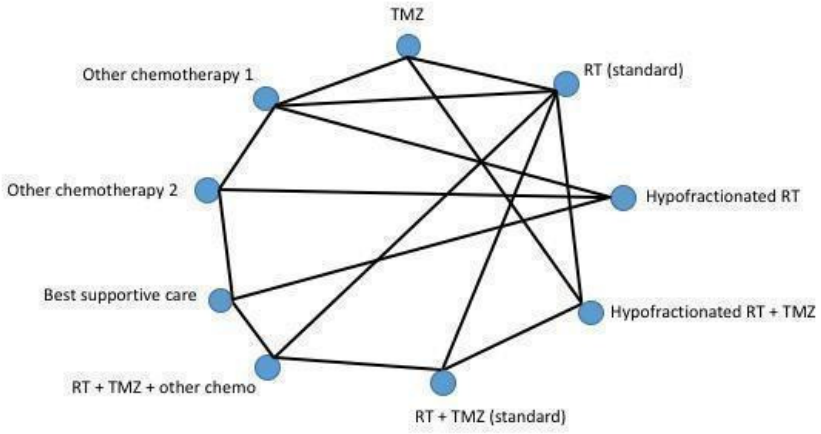
Types of interventions

Interventions to be evaluated alone or in combination with each other versus any of the other interventions include the following.

- Radiotherapy (standard, hypofractionated, and other techniques).
- Chemotherapy (TMZ and other types).

We will include all available regimens of radiotherapy and chemotherapy that have been evaluated in randomised trials. If we identify interventions in the included studies of which we are not aware, we will consider including them after we assess their comparability with those interventions named above. We will exclude phase 1 and 2 studies of novel interventions that have been shown to be detrimental and have not been developed further. The anticipated network graph is in Figure 1.

Figure 1.



RT, radiotherapy; TMZ, temozolomide

Figure 1. Illustrative network example of treatments for glioblastoma in elderly (≥ 65 years of age)

We will create separate networks according to the type of surgical procedure (GTR, STR, and biopsy only). Within each of these networks we will assume that any participants within the network could be randomised to any of the interventions e.g. an elderly person with histologically confirmed glioblastoma could be equally likely to be randomised to standard radiotherapy, chemotherapy, any combination of these or supportive care.

Types of outcome measures

Primary outcomes

- Overall survival (time from randomisation to death from any cause).
- 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]).

Secondary outcomes

- Progression-free survival (time from randomisation to disease progression or death from any cause).
- Severe adverse events, according to standardised scales, e.g. Common Terminology Criteria for Adverse Events (CTCAE).
- Cognitive impairment (objective or subjective), as measured by an overall cognitive function score, as a change-over-time score, or reported 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), EORTC, FACT.
- Functional impairment or disability, as measured by an overall ability score and/or as a change of ability over time score using a standardised measurement tool, e.g., Karnofsky Performance Status Scale, Neurological Functions Score, EORTC, FACT; or as a categorical outcome as defined by investigators.
- Fatigue, according to CTCAE, EORTC, or as defined by investigators.
- Economic outcomes:
  - Resource use for health care.
  - Health state utilities.
  - Costs of health care.
  - Incremental cost-effectiveness.
  - Resource use for health care.
  - Health state utilities.
  - Costs of health care.
  - Incremental cost-effectiveness.

Search methods for identification of studies

Electronic searches

1. For studies on the effects of the interventions, we will search the following databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL; latest issue), in the Cochrane Library.
- MEDLINE via Ovid (from 1946).
- Embase via Ovid (from 1980).

2. For economic evidence we will search the following.

- MEDLINE via Ovid (from 1946).
- Embase via Ovid (from 1980).
- NHS Economic Evaluation Database (EED).

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 1 January 2015, as the 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 the MEDLINE search strategy.
We will not apply language restrictions to any literature searches.

Searching other resources

We will search the following for ongoing trials.

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

If ongoing trials that have not been published are identified through these searches, we will approach the principal investigators to ask for an update on the trial status and any relevant unpublished 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. We do not intend to handsearch journals and conference proceedings as, in our experience, it is resource intensive and yields of additional studies not already identified by electronic searches tend to be very low.

Data collection and analysis

Selection of studies

For the results of search 1 (trials of effectiveness and safety), the Information Specialist at the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group (CGNOC) will download all titles and abstracts retrieved by electronic searching to EndNote X8 and will remove duplicates. Two review authors (TAL, CRH, or ER) will independently screen the remaining records and exclude studies that clearly do not meet the eligibility criteria. For potentially eligible records, copies of the full texts will be obtained and two review authors (TAL and CRH) will independently assess them for eligibility. The two review authors will resolve any disagreements through discussion and, if necessary, will consult at least one other review author. We will use Covidence to facilitate this study selection process and will document the reasons for exclusion of studies accordingly.
To inform the economic outcomes full economic evaluations (cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses), we will consider cost analyses and comparative resource-utilisation studies. Studies carried out alongside relevant RCTs and model-based studies will be considered for inclusion. Two review authors (LV and AK) will independently screen for eligible studies.

Data extraction and management

Two review authors (TAL, CRH, or ER) will independently extract data from included studies using a pre-designed data extraction form (Higgins 2011). We will extract the following data.

- 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.
  - Gender.
- Potential effect modifiers:
  - Molecular type of glioblastoma.
  - Performance status.
- Intervention details:
  - Type of intervention, dose, timing, and other regimen details.
  - Type of comparator.
- 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 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. serious adverse events), 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. QoL scores), 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.

Assessment of risk of bias in included studies

We will assess the risk of bias using Cochrane's 'Risk of bias' 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.

Two review authors (TAL and CRH) will independently assess risk of bias and will resolve any differences in opinion by discussion or by consulting 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 meta-analyses in light of the overall 'Risk of bias' assessment. For more details about the 'Risk of bias' assessment 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. In economic evaluations carried out alongside clinical trials we will assess these 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). This will be done using the CHEERS checklist (Husereau 2013).

Measures of treatment effect

Effectiveness data

- For time-to-event outcomes (e.g. overall survival), we will extract the hazard ratio (HR) with its 95% confidence interval (CI).
- For continuous outcomes (e.g. QoL 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) (RevMan 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).
- For dichotomous outcomes, we will calculate the effect size as a risk ratio (RR) with its 95% CI.

Economic data

Two review authors (AK and LV) will independently extract data from relevant economic studies and summarise this information in tables. We will extract data extracted on the following.

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

Two review authors (AK and LV) will extract data on the economic outcomes.

Unit of analysis issues

Two review authors (TAL and CRH) will assess unit of analysis issues according to Higgins 2011, and will resolve any differences in opinion by discussion. These include reports where there are multiple observations for the same outcome (e.g. repeated measurements with different scales or at different time-points, recurring events). An example of where this might occur is with the outcome 'quality of life'. If meta-analysis is not feasible or meaningful, we will extract data from all scales or time-points, or both; and, where possible, will describe them narratively.

Multi-arm trials

We will include multi-arm trials in this review. We will treat multi-arm studies as multiple independent comparisons in pairwise meta-analyses. However, in the network meta-analysis we will account for the correlation between the effect sizes derived from the same study.

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 on primary outcomes and describe in the 'Characteristics of included studies' tables how any missing data were obtained.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity

We will assess clinical heterogeneity between studies by comparing between the studies characteristics of included participants, and interventions in each meta-analysis of each comparison, 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 consistency across treatment comparisons

We will examine the assumption of consistency by assessing the distribution of potential effect modifiers across the pair-wise comparisons. The assumption will hold if the following is true.

- The common treatment used to compare different interventions indirectly is similar when it appears in different trials.
- All pairwise comparisons do not differ with respect to the distribution of effect modifiers.

Assessment of statistical heterogeneity and inconsistency

Assumptions when estimating the heterogeneity

In standard pairwise meta-analyses we will estimate different heterogeneity variances for each pairwise comparison. In network meta-analysis, we will assume a common estimate for the heterogeneity variance across the different comparisons.

Measures and tests for heterogeneity

We will perform the presence of statistical heterogeneity within the pairwise comparisons using the I^2 statistic, which is the percentage of variability that cannot be attributed to random error.
We will base the assessment of statistical heterogeneity in the network on the magnitude of the heterogeneity variance parameter (τ^2) estimated from the network meta-analysis models.

Assessment of statistical inconsistency

We will evaluate the statistical agreement between the various sources of evidence in a network of interventions (consistency) by global and local approaches to complement the evaluation of consistency.

Assessment of reporting biases

If there are 10 or more studies included 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

Methods for direct treatment comparisons

We will perform standard pair-wise meta-analyses for each comparison using a random-effects model.

Methods for indirect and mixed comparisons

We will conduct network meta-analyses if we consider participants, comparisons, and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful (see illustrative network Figure 1). We plan to use the random-effects model in STATA fitting a multivariate network meta-analysis (White 2015), and other STATA commands for visualising and reporting results in network meta-analysis (Chaimani 2015); alternatively we might use WinBUGS in a Bayesian framework (Lunn 2000).
We will attempt to synthesize narrative summaries of outcomes for which meta-analysis is not possible, due to the different ways that investigators have reported or measured outcomes, and assess these using the GRADE approach (Murad 2017). We will interpret the quality of the evidence based on the Cochrane Effective Practice and Organisation of Care (EPOC) Group's guidance (Cochrane EPOC 2015).
We will summarize 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. Unit cost data will also be tabulated, 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 gross domestic product (GDP) and GDP Purchasing Power Parities (EPPI Centre Cost Converter 2016). Details of the methodological characteristics of

individual included health economics studies will be summarised in 'Characteristics of included studies' tables. All elements of the economics component of this review will be conducted according to current guidance on the use of economics methods in the preparation and maintenance of Cochrane reviews (Higgins 2011; Shemilt 2018; Wijnen 2016).

'Summary of findings' tables and results reporting

Effectiveness summary of findings

- For time-to-event outcomes (e.g. overall survival), we will calculate the observed minus expected events (O minus E) and variance from the reported time-to-event estimates to obtain the log hazard ratio (LnHR) and standard error (SE) of LnHR. We will report the summary estimates as hazard ratios (HR) with its 95% confidence intervals (CI).
- For continuous outcomes (e.g. QoL 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 RevMan 5 (RevMan 2014).
- For dichotomous outcomes, we will summarise data as a risk ratio (RR) with 95% CI.

We will create the 'Summary of findings' tables using GRADEpro Guideline Development Tool (GDT) software (GRADEpro 2015). The summary tables will be designed following the approach suggested by Schunemann 2009 and Puhan 2014. We will provide justification for each assessment about the confidence in the estimates of effect (e.g. reasons for downgrading the quality of the evidence). If meta-analysis is not possible, we will present the results in a narrative 'Summary of findings' table. Two review authors will independently assess the quality of the evidence. We will resolve any differences of opinion by discussion and, if necessary, by consulting a third review author.

Relative treatment ranking

We will compute ranking of probabilities for all included treatments and obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA). For primary outcomes, we will assess the robustness of these findings in sensitivity analysis by considering estimates of mean rank with 95% CIs.

Economic evaluation summary of findings

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

If study investigators use different age thresholds to define the elderly, and if data are sufficient, we will perform subgroup analysis by these thresholds. 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 the baseline characteristics of study participants and risk of bias in the 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 statistical 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 trial quality affects the certainty of the findings. We will also perform a sensitivity analysis by excluding trials that include mixed participant data.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

MEDLINE search strategy for effectiveness evidence

1. Glioblastoma/
2. (glioblastoma* or Glioblastoma* or GB* or astrocyt*).ti,ab.
3. 1 or 2
4. exp Aged/
5. (aged* or old* or ageing* or geriatric*).ti,ab.
6. (elder* or "over 60" or "over 65" or "over 70" or "over 80" or "over 85" or "60 year*" or "65 year*" or "70 year*" or "80 year" or "85 year*").ti,ab.
7. 4 or 5 or 6
8. 3 and 7
9. Neurosurgery/
10. surgery.fs.
11. (surg* or neurosurg* or craniotomy* or resect* or EOR* or intraoperative*).mp.
12. exp Radiotherapy/
13. radiotherapy.fs.
14. (radiotherap* or RT or radiat* or irradiat*).ti,ab.
15. exp Antineoplastic Agents/
16. Antineoplastic Combined Chemotherapy Protocols/
17. (temozolomide or TMZ or Temodal or Temodar or Temodal or Temcad* or chemotherap* or procarbazine or Lomustine or CCNU or vincristine or PCV or cisplatinum or carboplatinum).mp.

18. exp Chemoradiotherapy/
19. (radiochemo* or chemoradio*).mp.
20. exp immunotherapy/
21. immunotherap*.mp.
22. exp steroids/
23. (dexamethasone or prednisolone or methylprednisolone).mp.
24. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 8 and 24
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. randomized.ab.
29. placebo.ab.
30. clinical trials as topic.sh.
31. randomly.ab.
32. trial.ti
33. 26 or 27 or 28 or 29 or 30 or 31 or 32
34. (animals not (humans and animals)).sh.
35. 33 not 34
36. 25 and 35

MEDLINE search strategy for economic evidence

1. Glioblastoma/
2. (glioblastoma* or Glioblastoma* or GB* or astrocyt*).ti,ab.
3. 1 or 2
4. exp Aged/
5. (aged* or old* or ageing* or geriatric*).ti,ab.
6. (elder* or "over 60" or "over 65" or "over 70" or "over 80" or "60 year*" or "65 year*" or "70 year*" or "85 year*").ti,ab.
7. 4 or 5 or 6
8. 3 and 7
9. Neurosurgery/
10. surgery.fs.
11. (surg* or neurosurg* or craniotomy* or resect* or EOR* or intraoperative*).mp.
12. exp Radiotherapy/
13. radiotherapy.fs.
14. (radiotherap* or RT or radiat* or irradiat*).ti,ab
15. exp Antineoplastic Agents/
16. Antineoplastic Combined Chemotherapy Protocols/
17. (temozolomide or TMZ or Temodal or Temodar or Temodal or Temcad* or chemotherap* or procarbazine or Lomustine or CCNU or vincristine or PCV or cisplatinum or carboplatinum).mp.
18. exp Chemoradiotherapy/
19. (radiochemo* or chemoradio*).mp.
20. exp IMMUNOTHERAPY/
21. immunotherap*.mp.
22. exp STEROIDS/
23. (dexamethasone or prednisolone or methylprednisolone).mp.
24. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 8 and 24
26. Economics/
27. exp "costs and cost analysis"/
28. Economics, Dental/
29. exp economics, hospital/
30. Economics, Medical/

31. Economics, Nursing/
32. Economics, Pharmaceutical/
33. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
34. (expenditure$ not energy).ti,ab.
35. value for money.ti,ab.
36. budget$.ti,ab.
37. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. ((energy or oxygen) adj cost).ti,ab.
39. (metabolic adj cost).ti,ab.
40. ((energy or oxygen) adj expenditure).ti,ab.
41. 38 or 39 or 40
42. 37 not 41
43. letter.pt.
44. editorial.pt.
45. historical article.pt.
46. 43 or 44 or 45
47. 42 not 46
48. 25 and 47

key:

mp=title, original title, abstract, name of substance word, subject heading word
pt=publication type
ab=abstract
fs= floating subheading
sh=Medical Subject Heading
Similar strategies were devised for Embase.

Appendix 2. 'Risk of bias' assessment

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 identification-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 or personnel, or both, 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, if we suspect that the trial was prone to an additional bias
- Unclear risk of bias, if we are uncertain whether an additional bias may have been present

CONTRIBUTIONS OF AUTHORS

Theresa A Lawrie and Catherine R Hanna wrote the first draft of this protocol and revised the first draft according to comments from the other authors and peer reviewers. All protocol authors approved the final version.

DECLARATIONS OF INTEREST

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