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First-line treatments for people with single or multiple brain metastases (Protocol)

Williams M, Chen J, Hart MG, Hunter A, Hawkins N, Si S, Toni F

Williams M, Chen J, Hart MG, Hunter A, Hawkins N, Si S, Toni F.
First-line treatments for people with single or multiple brain metastases.
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[Intervention Protocol]

First-line treatments for people with single or multiple brain metastases

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ABSTRACT

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

To compare the safety and efficacy of surgery, radiotherapy, and chemotherapy as first-line treatment for people with single or multiple brain metastases, either alone or in combination.

BACKGROUND

Description of the condition

Brain metastases refer to a tumour that has spread to the brain after originating elsewhere in the body. Brain metastases are usually multiple, and occur in up to 20% of people with systemic cancer (Nayak 2012; Nussbaum 1996). The most common primary sites are the lung and breast (Posner 1978). Prognostic factors that have been used to stratify participants in clinical trials include: younger age (less than 65 years), control of primary disease, absence of systemic metastases, and good performance status (Gaspar 2000). For many people, treatment of the brain metastasis itself is not performed, because of the extent of the systemic disease (Kaal 2004). In people with a better prognosis, there are a variety of treatments available to improve outcome.

Description of the intervention

Surgical resection usually involves removing a single metastasis, under general anaesthesia. Under some circumstances, such as some cases of cerebellar metastases, or an extensive mass, the decision to operate is solely, and appropriately, guided by a patient's clinical condition.

Whole brain radiation therapy (WBRT) has historically been the accepted palliative treatment of choice. It has the theoretical advantage of treating undiagnosed 'micro' metastases, but it also irradiates the healthy brain, with a possible risk of impairing cognitive function.

Focal radiotherapy techniques, such as stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT), have been developed to focus higher radiation doses on the metastases, with less damage to the surrounding brain than WBRT. The theoretical advantage is less cognitive impairment, but requires more intensive follow-up, and possibly additional treatments, such as repeat SRS, or even surgery.

Chemotherapy has typically been less frequently used as primary therapy, but more recently, it has been given a role, mainly in specific chemo-sensitive tumours (e.g. small cell lung cancer, lymphomas, and breast cancer), or when an effective chemotherapy regime is available. The potential role of immunotherapy remains unclear, but there are early (non-randomised) data that support the combination of SRS and immunotherapy, although randomised data appear to be lacking.

How the intervention might work

Interventions can be broadly classified into focal, whole brain, and systemic therapies. Focal therapies, such as surgery or SRS, directly treat designated brain metastasis, and are specifically designed not to treat the surrounding brain prophylactically from so-called micro-metastases, which are not present on neuro-imaging (e.g. MRI). Whole brain therapies, such as WBRT, provide coverage to the whole brain, and therefore treat the metastasis in question and any other micro-metastases that may be present. Systemic therapies (chemotherapy and immunotherapy) treat the whole body, and therefore, may have an effect on the brain. Focal, whole brain, and systemic therapies are often combined, e.g. surgery and WBRT. In general, there has been a trend to rely on focal therapies (especially SRS), given the sensitivity of modern neuro-imaging to detecting micro-metastases, and the desire to avoid potential long-term neurocognitive adverse events. However, this approach can lead to greater demand for follow-up and salvage therapy on recurrence (e.g. repeat SRS or surgery).

Details of individual interventions and how they may work are covered in a number of single intervention Cochrane Reviews (Fuentes 2016; Hart 2005; Patil 2012; Soon 2014; Tsao 2012).

Why it is important to do this review

Currently, there are a number of Cochrane Reviews that looked at pairwise, independent comparisons for single or multiple brain metastases (Fuentes 2016; Hart 2005; Patil 2012; Soon 2014; Tsao 2012). We will use these as a basis for our review, but we will re-run the literature search and conduct our search and analysis independently. However, using the results of the meta-analyses in practice is difficult, because there is no resource available that synthesises information for all comparisons. Furthermore, many combinations of treatments have not been directly compared with each other. Therefore, a network meta-analysis should allow a better understanding of all available treatment options, and enable clinicians, policy makers and carers to more easily use this evidence.

OBJECTIVES

To compare the safety and efficacy of surgery, radiotherapy, and chemotherapy as first-line treatment for people with single or multiple brain metastases, either alone or in combination.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCT) of participants with newly diagnosed metastases to the brain who were randomised to treatment with any of the interventions of interest.

Types of participants

We will include adult participants (18 years and over) who are receiving an intervention of interest for newly diagnosed metastases to the brain from any primary cancer. We will include participants regardless of primary disease type and number of metastases. Primary disease does not need to be confirmed histologically; brain metastases must be confirmed on neuro-imaging.

We will exclude trials that explored treatment for recurrent disease.

Types of interventions

Interventions of direct interest

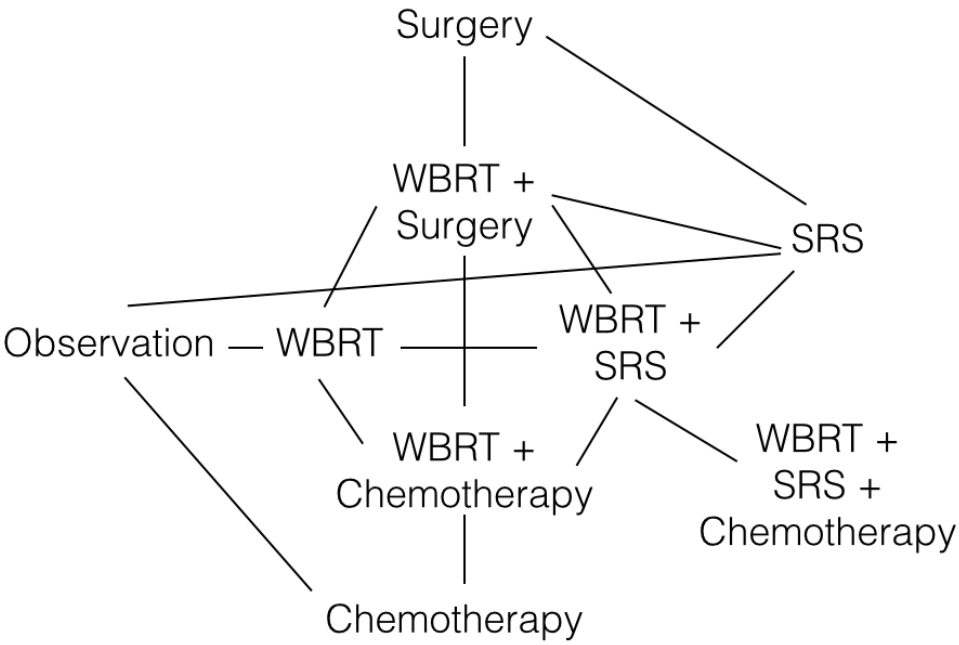
We will include studies that evaluate one or more of the following interventions:

- Surgical resection: all neurosurgical procedures where the preoperative aim was to remove more tissue than was necessary for diagnosis.
- Whole brain radiotherapy (WBRT): any dose, fractionation, or delivery method, providing it was to the whole brain.
- Stereotactic radiosurgery (SRS) or radiotherapy (SRT): a localised high dose of radiation in either single or multiple fractions; defined as 14 Gy or more in a single fraction, or 25 Gy in five fractions, or similar doses or fractionation regimens in between.

- Chemotherapy: any cytotoxic agent delivered either systemically or intrathecally, with the intention of treating the brain metastases.
- Immunotherapy: systemically administered therapy, designed to modulate the immune system, administered to treat the brain metastases.

We will deal with co-interventions (e.g. SRS plus WBRT versus surgery plus WBRT) by considering each treatment pair individually. We will also consider grouping similar treatments, in the same way that we will group primary treatments. Therefore, we will consider interventions individually, but will also consider combined SRS and surgery, and combinations of different chemotherapy. Figure 1 shows the overall network of eligible comparisons in this review. This is based on preliminary results, and there may be additional nodes and links that emerge during the review.

Figure 1. Preliminary network of treatment comparisons



Inclusion of additional interventions to supplement the analysis

If we identify any new interventions, we will consider them eligible, and include them in the network after assessing their comparability with the prespecified set of competing interventions. We will report the findings for these interventions in the results and the conclusions of the review.

Types of outcome measures

We will estimate the relative ranking of the competing interventions according to the following outcomes.

Primary outcomes

- Overall survival (OS): time from treatment to death (or censoring) in months

Secondary outcomes

- Adverse events (AE): we will record both the nature (defined using a standard reference terminology, e.g. MedDRA (Medical Dictionary for Regulatory Authorities) criteria) and timing (MeDRA 2008). We will note any further procedures required for complications. The study report should state both the total number of complications and complications per patient.
- Progression free survival (PFS): time from treatment to confirmed intracranial progression. Progression should be diagnosed using open and thorough criteria according to clinical symptoms, imaging findings, and increased steroid use (Wen 2010).
- Quality of life (QoL): recorded using a reliable and objective grading scale, for example the The European Organization for Research and Treatment of Cancer (EORTC QLQ-C30-BN20) or Functional Assessment of Cancer Therapy-Brain (FACT-Br) (Mauer 2008).

We will present 'Summary of findings' table(s) reporting the following outcomes, listed in order of priority.

- Overall survival at 3, 6, 9, and 12 months, and median value
- Intracranial progression free survival at 3, 6, 9, and 12 months, and median value
- Change in steroid dose at three months
- Change in performance status at three months
- Grade 3 acute toxicity rate
- Grade 3 late toxicity rate
- Radionecrosis rate

Search methods for identification of studies

Trials that compare at least two of the interventions will be eligible. We will search for all possible comparisons formed by the interventions of interest.

Electronic searches

The following databases will be part of our systematic literature search:

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

We have presented the MEDLINE Ovid search strategy in Appendix 1. For databases other than MEDLINE, we will adapt the search strategy accordingly.

Searching other resources

Reference search

We will search the references of included studies to identify additional studies.

Handsearch

We will handsearch the Journal of Neuro-oncology and Neuro-oncology over the past 10 years, including related international conference proceedings of the Society for Neuro-oncology and European Association for Neuro-oncology, the American Society for Clinical Oncology, the American Society for Therapeutic Radiation Oncology, and other relevant conferences that may be found in the Journals.

Personal communication

We will contact authors of included trials and other experts in the field by email to enquire about further potentially relevant RCTs.

Unpublished and grey literature

We will search trial registries, including clinicaltrials.gov and isrctn.com.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to Covidence, a reference management database (Covidence). After de-duplication two review authors (MW and JC) will independently assess the titles and abstracts retrieved. We

will obtain the full-text copies of published reports for all references assessed as meeting the inclusion criteria. We will resolve any disagreement through discussion, or if required, we will consult a third person (MGH). We will identify and exclude duplicate reports and collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review.
Assessment of the full reports will enable the identification of studies for inclusion in the review. Studies that are excluded at this stage will be listed in the 'Characteristics of excluded studies' table and we will state the reasons for exclusion.
Assessors will not be blinded to author, institution, journal of publication or results, as the review authors are familiar with most studies and the typographical layout of journals. However, we do not believe this will add any selection bias, and there is equipoise within the team as to potential benefits and harms of different treatment options.
We will record the selection process in sufficient detail to complete a PRISMA flow diagram.
We will retrieve articles if we feel that an article's reference list should be reviewed for additional relevant studies.

Data extraction and management

Two review authors (JC and MW) will independently extract data using a standard data extraction form. Any disagreements or discrepancies will be resolved by a third assessor (MGH).

Outcome data

From each included study, we will extract the outcome data previously specified:

- Time-to-event data (OS and PFS): we will extract the log hazard ratio (HR) and its standard error (SE)
- Continuous data (QoL): we will extract the final value and standard deviation of the outcome of interest in each treatment arm at the end of follow-up
- Dichotomous data (AE): we will extract the number of participants in each treatment arm who experienced the outcome of interest, in order to estimate a risk ratio (RR).

For continuous and dichotomous data, we will extract the number of participants assessed at endpoint.

Data on potential effect modifiers

From each included study, we will extract data on the following study, intervention, and population characteristics that may act as effect modifiers:

- Industry sponsorship
- Study characteristics: withdrawals, blinding, and randomisation methods; adherence to protocol; duration of follow-up
- Patient characteristics: age, number of metastases, primary site, performance status (Karnofsky 1948; WHO 1982), presence of extracranial disease, control of extracranial disease, recursive partitioning analysis (RPA) or graded prognostic assessment (GPA) or disease-specific GPA (ds-GPA) class, tumour volume or diameter, Mini-mental state exam score
- Intervention details: extent of surgical resection, radiotherapy (SRS, SRT, WBRT) dose and fractionation, chemotherapy and immunotherapy agents and regime. For SRS and SRT - DMax and prescription isodose.

Other data

From each included study, we will extract the following additional information:

- Author, year of publication, and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population
  - Total number enrolled
  - Patient characteristics
  - Age
  - Sex
  - Comorbidities
  - Previous treatment

Assessment of risk of bias in included studies

Two review authors (JC and MW) will apply the 'Risk of bias' tool independently, and resolve differences by discussion or by appeal to a third review author (CH).
We will assess and report on the methodological risk of bias of included studies, in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* for the following items for RCTs (Higgins 2011).

- Selection bias: random sequence generation and allocation concealment
- Performance bias: blinding of participants and personnel (i.e. treatment providers)
- Detection bias: blinding of outcome assessment
- Attrition bias: incomplete outcome data
- Reporting bias: selective reporting of outcomes
- other possible sources of bias (e.g. industry funding)

We will judge each item at high, low, or unclear risk of bias, as set out in the criteria provided by Higgins 2011, and provide a quote from the study report, a statement to justify the judgement, or both, for each item in the 'Risk of bias' table. We will summarise results in both a 'Risk of bias' graph and a 'Risk of bias' summary. When interpreting treatment effects and meta-analyses, we will take the risk of bias for the studies that contribute to that outcome into account. Where information on risk of bias relates

to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. We will assess attrition rates for each outcome (e.g. attrition rates may be different for OS and toxicity). For outcomes with more than 50% attrition, we will conduct a sensitivity analysis to explore the impact of the missing data.

Measures of treatment effect

We will summarise treatment effects for binary outcomes, at fixed time points, as odds ratios (ORs), as they are more convenient for the network meta-analysis. We will summarise treatment effects for time-to-event outcomes as hazard ratios (HR). In addition to summarising the treatment effects for all pairwise comparisons, we will summarise the uncertainty in treatment effect estimates, in term of the probability of each treatment being ranked most-effective, second most effective, etc. We will select appropriate distributions for other endpoints, e.g. continuous endpoints analysed on linear scales. We will pool overall survival and intracranial progression free survival, based on rates at specified time points (3, 6, 9, and 12 months), and provide median values for both outcomes. We will pool quality of life data by normalising each scale and then combining the continuous values.

Unit of analysis issues

If the HR and its variance are not presented, we will attempt to extract the data required to estimate them (Parmar 1998).

Dealing with missing data

In the case of missing data required for the review outcomes, we will contact the study authors. Where possible, we will extract all data for an intention to treat (ITT) analysis. We will not impute any missing data.

Assessment of heterogeneity

We will assess the presence of clinical heterogeneity by comparing the trial and study population characteristics across all eligible trials. We will also assess the extent of heterogeneity with pairwise comparisons, using the I^2 statistic, the Cochrane Q-Test, and by visually inspecting forest plots.

Assessment of transitivity across treatment comparisons

We will evaluate the underlying consistency assumption by comparing direct and indirect estimates of treatment effects where both are available. We will also evaluate overall model fit, using residual deviance.

Assessment of reporting biases

We intend to construct a funnel plot of treatment effect versus precision within pairwise comparisons, in order to investigate the likelihood of publication bias. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, we will consider trim and fill analyses.

Data synthesis

Methods for direct treatment comparisons

We will perform standard pairwise meta-analyses in Review Manager 5 RevMan 2014. Given the likely heterogeneity of the trials, we will use a random-effects model. We will pool outcomes based on overall survival, progression, and toxicities. We will pool overall survival and intracranial progression free survival based on rates at specified time points (3, 6, 9, and 12 months), and provide median values for both outcomes. We will pool quality of life data by normalising each scale and them combining the continuous values.

Methods for indirect and mixed comparisons

We will perform network meta-analysis using Bayesian hierarchical models estimates, using Markov Chain Monte Carlo (MCMC) methods, as implemented in OpenBUGS (OpenBUGS 2009). We will report posterior means, medians, and credible intervals. We will implement the network meta-analysis as a Bayesian hierarchical model as described in Dias 2013a, Dias 2013b, and Hawkins 2015. We will use appropriate likelihood functions for the various data types. We will consider both random-effects and fixed-effect models. We will estimate the model parameters, using MCMC techniques, as implemented in WinBUGS. We will run three chains, starting from different initial values. We will use vague priors for the treatment effects and study level intercepts (e.g. N (0.10^4 for treatment effects on the log hazard or log odds ratio scale). We will use a U (0.5) prior for the standard deviation for the random-effects analysis of binary endpoints on the logit scale. We will run models for sufficient iterations during the burn-in and monitoring periods to provide adequate convergence and precision. We will assess convergence using Brooks Gelman Rubin (BGR) plots and by examining trace plots (Brooks 1998). We will judge the adequacy of Monte-Carlo sampling using the Rhat or similar statistics (Brooks 1998). We will compare model fit using the deviance information criterion (DIC (Spiegelhalter 2002)). We will assess the validity and utility of the network meta-analysis model by examining the consistency between direct and indirect estimates of treatment effects, where both direct and indirect evidence existed for a given treatment comparison (Dias 2013a).

Subgroup analysis and investigation of heterogeneity

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity

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

Investigation of heterogeneity and inconsistency

If sufficient studies are available, we will perform network meta-regression, subgroup analyses, or both, by using the following effect modifiers as possible sources of inconsistency, heterogeneity, or both:

- Primary tumour origin: specifically lymphoma, leukaemia, small or non-small cell lung cancer
- Surgery: complete versus incomplete surgical resection
- WBRT conventional versus altered dose and fractionation schemes
- Primary disease site (as source of metastasis)
- Age profile of participants
- Performance status
- Presence of extracranial disease
- Staging technique used to assess presence or absence of extracranial disease
- Subsequent treatment (salvage, or follow-up treatment)

We recognise that not all studies may provide sufficient information to allow us to include them, and conduct subgroup analyses.

Sensitivity analysis

We plan to undertake a sensitivity analysis using two scores of methodological quality that show the greatest variation. The RCT quality scores that we will derive will be used to identify the strengths or weaknesses of trial designs, and will enable us to assess the effect of study quality on outcomes. As part of this, we will assess whether the results of the network meta-analysis persist when restricted to studies with lower risk of bias.

The study group are also interested in exploring additional novel computational methods to analyse the data. These results will lie outside the review, but will use the same underlying data set. See Williams 2015 as an example.

Summary of findings

We will present the overall certainty of the evidence for each outcome (see Types of outcome measures), according to the GRADE approach, which takes into account issues related to internal validity (risk of bias, inconsistency, imprecision, publication bias), and also to external validity, such as directness of results (Langendam 2013). We will create a 'Summary of findings' table, based on the methods described the *Cochrane Handbook for Systematic Reviews of Interventions* and using GRADEpro GDT (see draft in Appendix 2 (GRADEpro GDT; Higgins 2011)). We will use the GRADE checklist and GRADE Working Group certainty of evidence definitions (Meader 2014). We will downgrade the evidence from high quality by one level for serious (or by two for very serious) concerns for each limitation:

- High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate-certainty: 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-certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low-certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Brain Neoplasms/
2. ((brain or cerebral or intracranial or intra-cranial or intracerebral or intra-cerebral or cerebellum) adj5 (metasta* or cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan* or secondar*)).ti,ab.
3. 1 or 2
4. exp Radiotherapy/
5. radiotherapy.fs.
6. radiotherap*.ti,ab.
7. (radiat* or irradiat*).ti,ab.
8. (radiosurg* or stereota* or linear accelerator* or cyberknife or gamma-knife or gamma knife or linac*).ti,ab.
9. (whole brain radiotherapy or whole-brain radiotherapy or wbrt or WBRT).ti,ab.
10. 4 or 5 or 6 or 7 or 8 or 9
11. exp Antineoplastic Agents/
12. Antineoplastic Combined Chemotherapy Protocols/
13. chemotherap*.ti,ab.
14. drug therapy.fs.
15. exp Combined Modality Therapy/
16. 11 or 12 or 13 or 14 or 15
17. exp Neurosurgical Procedures/
18. surgery.fs.
19. (surg* or neurosurg* or neuro-surg* or neuro surg* or exis* or resect*).ti,ab.
20. 17 or 18 or 19
21. 10 or 16 or 20

22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. clinical trials as topic.sh.
27. randomly.ab.
28. trial.ti.
29. 22 or 23 or 24 or 25 or 26 or 27 or 28
30. (animals not (humans and animals)).sh.
31. 29 not 30
32. 3 and 21 and 31
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
pt = publication type
ab = abstract
sh = subject heading
ti = title

Appendix 2. Draft summary of findings table

Example summary of findings table

Title: Stereotactic radiotherapy versus stereotactic radiotherapy plus whole brain radiotherapy						
Patient or population: Patients with one more newly diagnosed brain metastasis Settings: Hospital Intervention: Stereotactic radiotherapy Comparison: Stereotactic radiotherapy plus whole brain radiotherapy						
Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of participants (studies)	Certainty of evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
1a Overall Survival at 3, 6, 9, and 12 months						
1b Overall Survival (median in months)						
2a. Intracranial progression free survival at 3, 6, 9, and 12 months						

(*Continued*)

2b. Intracranial progression free survival (median in months)						
3 Change in steroid dose at 3 months (proportion of patients with stable or decreased steroid dose)						
4. Change in performance status at 3 months (proportion of patients with improved or stable performance status by ECOG or KPS)						
5. Grade 3 acute toxicity rate (proportion of patients with grade 3 or 4 toxicity)						
6. Grade 3 late toxicity rate						
7. Radionecrosis rate within 12 months of treatment						

*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; HR: hazard ratio; MD: mean difference; RR: risk ratio; OR: odds ratio; ECOG: Eastern Cooperative Oncology Group; KPS: Karnofsky Performace Status

GRADE Working Group grades of evidence
High-certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to

(*Continued*)

change the estimate.
Very low-certainty: We are very uncertain about the estimate

CONTRIBUTIONS OF AUTHORS

MW and JC will conduct the search, review the initial results, and extract the data.

MH will provide a third review author judgement, if MW and JC are unclear about inclusion and exclusion decisions.

SS will provide the statistical analysis, supported by NH.

AH and FT will provide guidance and support for the novel computational methods part of the work.

DECLARATIONS OF INTEREST

This work has received no external funding.

All authors have academic interests that may be supported by this work, and which may lead to the submission and award of further research grants or other work.

MW: I am one of the medical advisors for Matthew's Friends, a charity that supports patients using the ketogenic diet. I receive no income/payment for this.

JC: None known

MGH: None known

AH: None of the declared relationships in the CoI form have any bearing on this review.

NH: None known

SS: None known

FT: None known

MW, JC, and MH have clinical practices that relate to the area being reviewed, and which could potentially benefit from evidence that increases the uptake of some of the treatments included in the review.

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External sources

- No sources of support supplied