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Early palliative interventions for improving outcomes in people with a primary malignant brain tumour and their carers (Protocol)

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[Intervention Protocol]

Early palliative interventions for improving outcomes in people with a primary malignant brain tumour and their carers

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A B S T R A C T

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

To assess the evidence base for early palliative care interventions, including referral to specialist palliative care services for improving outcomes in people diagnosed with a primary brain tumour and their carers.

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BACKGROUND

Description of the condition

Primary brain tumours account for an estimated 2% of malignancies worldwide (Ferlay 2015). Approximately 5000 people are diagnosed with a primary malignant brain tumour each year in the UK (Cancer Research UK 2015). Gliomas are the most common type of primary brain tumour, accounting for up to 80% of malignant brain tumours overall (Goodenberger 2012). Gliomas are graded from 1 to 4 according to the World Health Organization (WHO) classification (Louis 2016). Grades 1 and 2 are low-grade slow-growing tumours. Grades 3 and 4 are high-grade fast-growing tumours. High-grade primary malignant glioma occurs most commonly between the fifth and seventh decades (Stupp 2010). It is a particularly aggressive disease, with a median survival time of 12 to 15 months (Stupp 2009). The five-year survival rate is 10% (Tran 2010).

The symptom burden for people diagnosed with a high-grade glioma is substantial. There can be profound effects on physical, neurocognitive, and social functioning from an early stage in the illness (Faithfull 2005; Long 2016; Moore 2013). Neurological deficits can include motor weakness, epilepsy, and dysphasia. This population of patients also frequently experience personality changes, a decrease in mental capacity, and mood disturbance. These effects can be exacerbated by aggressive treatment regimens (Aziz 2003; Long 2016).

The disease trajectory is unpredictable. It is often characterised by periods of sudden acute deterioration followed by a period where the clinical condition appears to plateau (Philip 2015). This makes prognostication difficult. Patients become increasingly dependent and isolated, which combined with the symptom burden can result in a reduction in perceived quality of life.

Informal care providers of patients with high-grade glioma are reported to experience significant burden and distress (Jacobs 2014; Wasner 2013). Collins 2014 reported significant needs in relation to the challenge of caring, the lack of support available to carers, and the suffering of caregivers (Collins 2014). The neurocognitive effects of the disease coupled with the increased dependency and social isolation can result in changes to relationships with family members/care providers, which are not so commonly observed in the context of other malignancies (Ford 2012; Lipsman 2007).

Palliative care seeks to improve the quality of life of patients and families facing a life-limiting illness through the identification, assessment, and treatment of physical, psychosocial, and spiritual needs (NCHSPCS 2002). In addition, it provides assistance with decision making and supports caregiver burden and well-being. Specialist palliative care has specific areas of expertise that can address complex symptoms, psychosocial, end-of-life, and bereavement issues for patients with a life-limiting illness (NCHSPCS 2002). Specialist palliative care teams are multi-disciplinary in nature and specifically trained to deal with multidimensional problems, such as those encountered in high-grade glioma.

Demonstrating the benefit of specialist palliative care in improving patient and carer-reported outcomes is an ongoing focus of research. A systematic review by Higginson 2010 concluded that home, hospital, and inpatient specialist palliative care teams significantly improved patient outcomes in the domains of pain and symptom control, anxiety, and reduced hospital admissions for cancer patients. There is a need to better understand the effects of different models of palliative care. Initiatives, such as the European-funded collaborative PRISMA, have focused on establishing standardised outcome measures for palliative care to improve the quality of research in this field (Harding 2010).

Previous studies have highlighted the lack of existing evidence surrounding the services needed to support this patient cohort and their care providers (Ford 2012; Moore 2013). The timing of such interventions has also not been well-defined. The National Institute for Health and Clinical Excellence (NICE) recommends that patients with a primary brain tumour could benefit from specialist palliative and supportive care early in the process, at diagnosis if possible, with continued integration of services throughout the course of the patient's illness (NICE 2018). However, the provision of palliative and supportive care for this patient population has historically been ill-defined and ad hoc (Faithfull 2005; Moore 2013), and the nature of the interventions that are most beneficial has not been confirmed.

Description of the intervention

The emphasis of palliative care is on dealing with the whole person: identifying and managing physical, psychological, and spiritual symptoms that profoundly affect quality of life. It also focuses on assistance with decision making, including advance care planning and addressing issues of relevance to significant others in terms of caregiver burden and well-being (Radbruch 2009; Rietjens 2017; WHO 2018).

Palliative care interventions may be initiated individually by the oncologist, neurosurgeon, or primary care team; by members of the wider supportive care team in a coordinated care approach; or be provided by specialist palliative care teams as part of an integrated model. A specialist palliative care service is defined as one delivered by a multi-professional team, usually comprising of doctors, nurses, and psychosocial workers with higher training in palliative care provision, possibly commissioned to provide palliative care at a specialist level.

The concept of 'early' palliative care has been introduced more recently to differentiate palliative interventions delivered earlier in the disease trajectory from those in the terminal phase or last days of life. There is, however, no universally accepted definition, with significant heterogeneity in description of what constitutes 'early' in reported studies in cancer and in other serious illnesses. This has ranged from definitions based on time since diagnosis or recurrence (Bakitas 2015), likely prognosis (Zimmermann 2014), in tandem with oncological review (Temel 2010), or based on symptom burden (Groenvold 2017). The American Society of Clinical Oncology practice guidelines suggest a definition of as early as "within 8 weeks of diagnosis" (Ferrell 2016).

This Cochrane Review will focus on palliative care interventions either in the form of a specialist palliative care service or interventions undertaken by other healthcare professionals with the specific intent of palliation. The review will include interventions delivered to both the person with the brain tumour and the carer or either alone. It will include interventions delivered in both community and secondary care settings. The timing, nature, and duration of the intervention must be clearly stipulated. Studies included in this review will include an explicit intent to provide 'early palliative care' or provide a clear study definition of 'early' in relation to time

since diagnosis or provision during ongoing active anticancer intervention.

How the intervention might work

People diagnosed with a primary brain tumour often experience significant disability early on in their illness. A wide range of physical symptoms have been reported in existing literature including fatigue, pain, seizures, and cognitive impairment (Armstrong 2016; Faithfull 2005; Ford 2012). Depression and anxiety are also common. A longitudinal study of 600 patients by Batchelor 2006 identified that 15% of people with a malignant glioma had depression in the early postoperative period and a further 93% described depressive symptoms. A systematic review by Ford 2012 reported prevalence rates of depression and anxiety in up to 48% of people diagnosed with a primary malignant brain tumour.

A recent systematic review by Moore 2013 reviewed qualitative literature looking at the palliative and supportive care needs of people with high-grade glioma and their care providers. Key themes identified included: the need for consistent, well-delivered information around disease sequelae, treatment, and resources available; health service needs including key professionals to coordinate care; the need for psychological and social support and clear avenues of communication with treating professionals. Vierhout 2017 conducted a qualitative study that explored the views of people diagnosed with a brain tumour on palliative care. A key theme identified was that people were keen to be aware of palliative care options early in their illness.

In the wider literature there is increasing evidence that palliative care interventions are associated with improved patient outcomes in both malignant and non-malignant life-limiting conditions (Bakitas 2015; Harding 2010; Higginson 2010; Kristjanson 2006; Temel 2010; Temel 2017; Zimmermann 2014), although not all studies demonstrate benefit (Davis 2015; Groenvold 2017). The systematic review by Davis 2015 highlighted significant heterogeneity in patient populations, intervention types, settings, and outcome measurements making comparisons difficult. Nonetheless, a recent random-effects meta-analysis of palliative care interventions on patient and carer outcomes by Kavalieratos 2016 included 43 studies across a range of conditions and demonstrated improvements in patient quality of life and symptom burden. A more recent Cochrane Review compared early palliative care interventions with more standard treatment care in advanced cancer (but not specifically brain cancer) and again observed a significant improvement in quality of life and symptom burden in patients receiving care shortly after diagnosis compared to closer to end of life (Haun 2017). An unexpected finding in some studies has been the presence of a survival advantage in those receiving early palliative care intervention (Bakitas 2015; Temel 2010). Although this has not been replicated in the Kavalieratos 2016 or Haun 2017 reviews, the importance of assessing for survival, and exploration of potential underlying reasons, has been highlighted.

Why it is important to do this review

People diagnosed with a primary brain tumour experience a high symptom burden, uncertain prognosis, and unpredictable disease trajectory. This is often characterised by rapid physical and neurocognitive decline that can place significant burden on care providers. Specialist palliative care services are well-placed to be able to support the complex needs of this patient population. However there are currently no systematic reviews that have looked specifically at the evidence base for early referral to specialist palliative care services or other designated early palliative care interventions for improving quality of life, carer outcome, and overall survival in patients diagnosed with a primary brain tumour.

Previous studies that have looked at the supportive and palliative care needs of patients diagnosed with a high-grade glioma have consistently concluded that the quality of evidence remains limited (Catt 2008; Collins 2014; Lin 2012; Moore 2013). In particular, there has been a lack of studies conducted in a palliative care setting. There is low-quality evidence to support multidisciplinary rehabilitation in reducing short- and long-term disability in patients with brain tumours compared to best supportive care (Khan 2015). Collins 2014 concluded that carers of patients with primary malignant glioma have distinct supportive and palliative care needs which differ from those of other cancer trajectories, although the existing literature has yet to define how these needs might be best addressed, by whom and at what point in a patient's care (McConigley 2012). Defining the nature of effective interventions in this context will help develop a more collaborative, needs-based model of care.

The importance of this topic is recognised at a national level. The National Institute for Health and Clinical Excellence (NICE) recommends that people with brain tumours could benefit from specialist palliative and supportive care early in the process, at diagnosis if possible with continued integration throughout the course of the person's illness (NICE 2006). NICE also recommend the co-operation of neuro-oncology and specialist palliative care to "ensure an appropriate balance between treatment and palliative care" (NICE 2006 p.121). Through doing so, NICE anticipates that not only will communication be improved, but service provision will be more responsive to patients' needs with more timely transfer of patients from services and treatments, patients, and their families/caregivers will be more satisfied and patients may be able to stay in their preferred place of care through improved continuity of care. The recent James Lind Alliance Neuro-Oncology Priority Setting Partnership Report gives context to the priority of research in this area (MacDonald 2015).

Ultimately, understanding the role early referral to specialist palliative care services or effectiveness, or both of other palliative care interventions has on the parameters outlined would help guide improvement to service provision and the development of an evidence-based model of supportive and palliative care for this patient population.

OBJECTIVES

To assess the evidence base for early palliative care interventions, including referral to specialist palliative care services for improving outcomes in people diagnosed with a primary brain tumour and their carers.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials and non-randomised intervention studies. We will also include qualitative studies and mixed-methods studies where both qualitative and quantitative

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data is included. Non-randomised trials are susceptible to greater risk of bias so to ensure an acceptable quality of included non-randomised studies, we will scrutinise risk of bias using the ROBINS-I tool (Sterne 2016), specifically designed for this purpose.

Types of participants

Inclusion criteria

- Adults (aged 18 years and older) who have a confirmed radiological or histological diagnosis, or both, of a primary malignant brain tumour.
- Informal adult carers of people with a confirmed diagnosis of a primary malignant brain tumour. This will usually be at an individual level but we will also include family level.

Exclusion criteria

- Participants who have a diagnosis of a benign brain tumour.
- Participants who have metastatic disease from an extra cranial primary.

Types of interventions

We will include studies where there is explicit intent to provide 'early palliative care' or where there is a clear study definition of 'early' in relation to time since diagnosis or ongoing active anticancer intervention. We will include studies reporting specialist and non-specialist palliative care intervention defined as any intervention by a healthcare professional that addresses palliation in any or all of the following areas:

- Symptom control.
- Physical function.
- Cognitive function.
- Psychological support.
- Information giving.
- Advance or future care planning.

A specialist palliative care service is defined as one delivered by member(s) of a multi-professional team with higher training in palliative care provision, or commissioned to provide palliative care at a specialist level, or both.

We will include interventions delivered in community and secondary care settings, and interventions delivered to both participant and carer or either alone. We will only include interventions where the specific components of an intervention are described and the timing (commencement) and duration of the intervention are clearly stipulated.

The comparators of interest will be usual care, including as part of a waiting list control. Usual care is defined as that normally provided by the neuro-oncology team. It might include provision of generalist or specialist palliative care support but not intentionally activated for all people at the time of diagnosis or initiation of anticancer treatment.

Types of outcome measures

We will include trials looking at early referral to specialist palliative care services, or early targeted palliative interventions by other healthcare professionals for improving quality of life, symptom control, carer outcomes, or overall disease survival as a primary or secondary outcome measure.

Primary outcomes

The primary outcomes will be quality of life, symptom control, psychological outcomes, and overall survival. We will report outcomes separately for participants and, where appropriate, carers in 'Summary of findings' tables using GRADEpro software (GRADEpro GDT 2014). Further details on the outcome measures that we will accept, where reported by included studies, are shown below.

Participants

- Survival from time of enrolment, to include one year and overall survival.
- Quality of life using validated Quality of Life tools e.g. FACT-G (Cella 1993) and FACT- Br (Weitzner 1995), EORTC QLQ C30 and BCM 20 (Osoba 1996), McGill Quality of Life Questionnaire (Cohen 1995), 36-Item Short Form Health Survey (SF-36) (Ware 1992), 46-item Functional Assessment of Chronic Illness Therapy– Palliative Care (FACIT-Pal) (Lyons 2009); qualitative analysis of participant experience using validated and clearly described methodologies.
- Symptom control using validated symptom assessment tools e.g. Edmonton Symptom Assessment Scale (ESAS) (Bruera 1991); Palliative Outcomes Scale (POS) (Hearn 1999); Quality of Life at the End of Life (QUAL-E) (Steinhauser 2004); Symptom Experience Scale (SES) (Samarel 1996); physical and cognitive function using validated assessment tools.
- Psychological outcomes including anxiety and depression using validated assessment tools e.g. Beck Depression Inventory (BDI) (Beck 1961), Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960), Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983).

Informal carer(s)

- Psychological outcomes including anxiety and depression using validated assessment tools (as mentioned above; carer burden using validated assessment tools e.g. Caregiver Strain Index (CSI) (Robinson 1983), Supportive Care Needs Survey for Partners & Caregivers (SCNS-P&C) (Girgis 2011), the Carer Experience scale (CES) (Al-Janabi 2008), Quality of Life During Serious Illness-Family Carers (QOLLTI-F) (Cohen 2006), Zarit Burden Inventory (Seng 2010), and FAMCARE (Kristjanson 1993)).

Secondary outcomes

The secondary outcomes will be: care coordination and information giving by participants and carers, receipt of planned anticancer treatment for participants, bereavement outcomes for informal carers, carer experience, and resource use and costs. Further details on the outcome measures that we will accept, where reported by included studies, are shown below.

Participants

- Care coordination and information giving based on qualitative assessment of participant feedback, or objective measures of satisfaction, or both.
- Receipt of planned anticancer treatment: completion of initial neuro-oncology multidisciplinary team (MDT) treatment.

- Resource use to include hospital and hospice utilisation measured in length of inpatient stay in days, number of outpatient appointments.

Informal carer(s)

- Care coordination and information giving based on qualitative assessment or carer feedback or objective measures of satisfaction, or both.
- Qualitative analysis of carer experience using clearly described and validated methodologies.
- Bereavement outcomes using validated measures.
- Resource use and costs. To include opportune costs of loss of income.

Important information on participants and carer experience of interventions may be published as part of a controlled trial or separately.

We will report outcomes separately for participants and carers in 'Summary of findings' tables (Appendix 1; Appendix 2).

Search methods for identification of studies

Electronic searches

We will identify relevant studies by conducting searches of electronic databases, and will include the Cochrane Central Register of Controlled Trials (CENTRAL: latest issue), MEDLINE via Ovid (1946 to present), Embase via Ovid (1980 to present), Cumulative Index to Nursing and Allied Health Literature (CINAHL from 1982 to present), Web of Science, and PsychInfo. We will conduct searches to incorporate both qualitative and quantitative search terms.

We will search for any currently recruiting trials in ClinicalTrials.gov (http://clinicaltrials.gov/) and in the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/).

The detailed search strategy for Ovid MEDLINE is shown in Appendix 3. For databases other than MEDLINE we will adapt the search strategy accordingly.

Searching other resources

We will handsearch the reference lists of any included articles to identify any other relevant studies. Experts in the field will be contacted to suggest relevant unidentified studies (published or unpublished). In addition we will find all included articles using citation tracking via Scopus.

We will handsearch the most relevant journals. In addition, we will source Dissertations and Theses, searching key authors via Web of Science and search SIGLE – System for information on grey literature in Europe.

Data collection and analysis

Selection of studies

Two review authors (ATB, AB) will independently screen and shortlist all abstracts and study titles identified by the search strategy to assess eligibility against the inclusion criteria. We will obtain full-text copies of all papers considered to be potentially eligible for further assessment to determine if the study met the inclusion/exclusion criteria. A second review author will then check identified pa-

pers (divided between AB, MB, FM, HB, AN, or SS). We will resolve any disagreement by discussion with a third review author if necessary (from AB, MB, FM, HB, AN, or SS) to reach a consensus. If necessary, we will contact the authors of primary papers for clarification. The review authors will not be masked to the name(s) of the author(s), institution(s), or publication source at any level of the review. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

Two review authors (from ATB, AB, MB, FM, HB, AN, or SS) will independently complete the data extraction using a standardised data collection form and a third review author (from ATB, AB, MB, FM, HB, AN, or SS) will independently check the data to minimise errors and reduce potential bias. We will initially complete data extraction forms electronically for ease of distribution between review authors. In cases where we use a paper copy, one review author (ATB) will type up the extracted data verbatim. We will pilot the data collection forms against the checklist provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and all review authors will agree the included items. Extracted data will include but not be limited to participants (including sample size), study design, setting, intervention details, outcomes, results, and information to facilitate the assessment of the risk of bias (i.e. sequence generation, allocation sequence concealment, blinding). For multiple reports of the same study, we will collate data into a single collection form. For any data that is missing and cannot be included in the form, we will attempt to obtain by contacting the primary authors.

For all studies that meet the inclusion criteria, we will summarise in the 'Characteristics of included studies' table provided in Review Manager 5 software (Review Manager 2014) . This will include details on design, participants, interventions, and outcomes. For non-randomised studies, we will provide appropriate additional study features in line with the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2011), such as any comparisons included, how groups were created, and which aspects of the study were prospective.

Assessment of risk of bias in included studies

Two review authors (from ATB, AB, MB, FM, HB, AN, or SS) will independently assess the risk of bias using the criteria and guidelines from the 'Risk of bias' tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Shuster 2011), which a third review author (ATB, AB, MB, FM, HB, AN, or SS) will independently check. We will report the following seven domains: allocation concealment (checking if allocation methods could be foreseen); sequence generation (checking method of generating allocation sequence); blinding (participants and personnel i.e. methods to blind participants' knowledge of which intervention given); blinding (outcome assessment i.e. blinding assessors from which intervention given to the participant); incomplete outcome data (checking differences between intervention and control groups); selective outcome reporting (checking how outcomes are reported); and 'other bias' (including recruitment bias, stopping early for benefit, carry-over effects in cross-over studies, and non-validated outcome measures).

We will give each domain a judgement of risk of 'low risk', 'high risk', or 'unclear risk' if insufficient details are provided in the study. This will be accompanied with a 'Support for judgement' statement

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summarising how we made risk judgements to ensure transparency of the decisions made. We will consider studies to be of high methodological quality if the risk of bias for all domains is low. We will deem these 'high-quality' studies. We will consider studies to be of low methodological quality if the risk of bias is high or 'unclear' one or more domains. We will deem these 'low-quality' studies. We will resolve any disagreement on the judgement of bias by discussions between the review authors.

For non-randomised studies, we will use the *Cochrane Handbook for Systematic Reviews of Interventions* for guidance for the types of biases these types of studies are susceptible to which are similar to randomised trials i.e. blinding (outcomes) and for biases that cannot be compared with those randomised studies i.e. allocation methods. We will assess risk of bias using the ROBINS-l tool (Sterne 2016), designed specifically for a non-randomised design.

Measures of treatment effect

We will enter and analyse all of the quantitative data in Review Manager 5 (Review Manager 2014). Where possible we will calculate risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous data, and mean differences or standardised mean differences with 95% CIs for continuous data where different scales are used across trials. For time-to-event data for survival, we will analyse as death hazard ratios under the assumption that the hazard ratio is consistent across the follow-up period. Where data aggregation is not possible, we will present the results of individual studies in table format and describe the primary findings narratively.

Unit of analysis issues

We anticipate that the appropriate unit of analysis will be by type, timing, and duration of specialist palliative intervention for improving quality of life, carer outcomes, and survival in people diagnosed with a primary brain tumour. We anticipate a limited number of randomised controlled trials and non-randomised intervention studies.

Dealing with missing data

Where data is missing, we will contact the primary study authors in an attempt to obtain this data. Where data is missing and cannot be derived by contacting the primary authors, we will undertake a complete case analysis. If the data remains missing, we will report the study but not include it in the final analysis.

Assessment of heterogeneity

We will follow the statistical analysis method as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Shuster 2011). We expect heterogeneity due to differences in participant populations, types and timing of interventions, and differences in outcome scales used. We will assess for the presence of variation in effects observed across studies using a Chi^2 test. To quantify the degree of heterogeneity we will employ the I^2 statistic, which reflects the percentage of variability in effect estimates that is due to heterogeneity rather than to chance (Deeks 2011). We will consider a 0% to 40% threshold to be a low level of heterogeneity, 30% to 60% to be a moderate level of heterogeneity, and 50% to 90% to be a substantial level of heterogeneity as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We will also describe, where possible, the potential sources of heterogeneity rather than simply quantify its existence. Non-randomised studies would be expected to be more heterogeneous compared to randomised trials and the most effective method of observing variation is through the visual inspection of the forest plots.

Assessment of reporting biases

We will aim to minimise publication bias by sourcing unpublished data where possible. If we identify an individual meta-analysis containing at least 10 studies, we will assess publication bias using funnel plots and by Egger's test (Egger 1998).

Data synthesis

We will conduct preliminary synthesis by entering all data into Review Manager 5 (Review Manager 2014). The included studies will be summarised using the 'Characteristics of included studies' table provided by the Review Manager 5 software. Where there is substantial and unexplained heterogeneity (P < 0.10), we will consider pooling data using the random-effects model.

Where studies compare more than one intervention or a combination of interventions, we will analyse each comparison separately. If possible we will calculate a weighted treatment effect using Review Manager 5 software. We will express the results as risk ratios with 95% CIs for dichotomous outcomes and mean differences and 95% CIs for continuous outcomes.

We will describe the qualitative data alongside the quantitative data and where appropriate correlate findings for example in terms of possible domains of impact, and explorations of heterogeneity.

Summary of findings for assessing the certainty of the evidence

We will present the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results (Langendam 2013; Schünemann 2011). We will use the GRADE approach to assess the certainty of the evidence related to each of the key outcome measures listed in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Shuster 2011). We will create 'Summary of findings' tables using GRADEpro GDT software (GRADEpro GDT 2014; see Appendix 1 and Appendix 2). We will use the GRADE checklist and GRADE Working Group certainty of evidence definitions (Meader 2014). We will downgrade the evidence from 'high' certainty 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

Subgroup analysis and investigation of heterogeneity

Where sufficient studies and data exist, we will undertake the following subgroup analyses.

- Tumour type.
- Age group (18 to 70 years and over 70 years).
- Type of intervention (individual vs group), frequency of intervention (less than once a week, once a week, 2 to 3 times a week), and duration of specialist palliative care intervention.
- Time from definitive treatment (surgery, radiotherapy, or chemotherapy) to specialist palliative care intervention.
- Type of treatment received; surgery and adjuvant chemotherapy or radiotherapy, or both; surgery alone; chemotherapy alone; radiotherapy alone; combined chemotherapy and radiotherapy with no surgery.

We will investigate whether the results of subgroups are significantly different by performing the test for subgroup differences available in Review Manager 5 (Review Manager 2014).

Sensitivity analysis

If we identify heterogeneity across the included studies, we will undertake sensitivity analyses to determine the effect of excluding studies at high risk of bias. In addition we will use sensitivity analyses to explore the effect of the primary aims of the study (early referral to specialist palliative care to improve quality of life, carer outcomes, and overall survival for people diagnosed with a primary brain tumour).

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A P P E N D I C E S

Appendix 1. Draft 'Summary of findings' table for participants

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Title: Early palliative interventions for improving outcomes in people with a primary malignant brain tumour and their carers

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Participant or population: adults (18 years and older) with confirmed or historical diagnosis of a primary brain tumour, or both

Settings: community and secondary care settings

Intervention: early specialist or general palliative care

Comparison: usual care and waiting list control

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(Continued)

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comment
	Assumed risk	**Corresponding risk**				
1. Survival from time of enrolment, to include one year and overall survival.						
2. Quality of Life using validated Quality of Life tools;qualitative analysis of participant experience using validated and clearly described methodologies.						
3. Symptom burden using validated symptom assessment tools;physical and cognitive function using validated assessment tools.						
4. Psychological outcomes including anxiety and depression using validated assessment tools.						
5. Care coordination and information giving based on qualitative assessment of participant feedback and/or objective measures of satisfaction.						
6. Receipt of planned anticancer treatment: completion of initial neuro-oncology MDT treatment plan.						
7. Resource use to include hospital and hospice utilisation measured in length of inpatient stay in days, number of outpatient appointments.						

*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% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; HR: hazard ratio; MD: mean difference; RR: risk ratio; OR: odds ratio

GRADE Working Group grades of evidence

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

Appendix 2. Draft 'Summary of findings' table for carers

Title: **Early palliative interventions for improving outcomes in people with a primary malignant brain tumour and their carers**

(Continued)

Participant or population: informal adult carers of people with a confirmed diagnosis of a primary brain tumour: individual and family level

Settings: community and secondary care settings

Intervention: early specialist or general palliative care

Comparison: usual care and waiting list control

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comment
	Assumed risk	**Corresponding risk**				
1. Psychological outcomes including anxiety and depression using validated assessment tools						
2. Care coordination and information giving based on qualitative assessment of carer feedback or objective measures of satisfaction, or both						
3. Qualitative analysis of carer experience using clearly described and validated methodologies						
4. Bereavement outcomes using validated measures						
5. Resource use and costs including opportune costs of loss of income						

*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% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; HR: hazard ratio; MD: mean difference; RR: risk ratio; OR: odds ratio.

GRADE Working Group grades of evidence

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.

Appendix 3. MEDLINE search strategy

Ovid MEDLINE

1. exp Palliative Care/
2. exp Terminal Care/
3. exp Terminally Ill/

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4. exp Hospices/
5. exp Hospice Care/
6. exp "Hospice and Palliative Care Nursing"/
7. ("last year of life" or LYOL or "life's end").ti,ab.
8. ((macmillan or marie curie or district) adj nurs*).mp.
9. (hospice* or (nursing adj3 home*)).mp.
10. exp Palliative Medicine/
11. exp Advance Care Planning/
12. (advance* adj5 care plan*).ti,ab.
13. (future adj5 care plan*).ti,ab.
14. exp Caregivers/
15. ((early or specialist or general or primary) adj5 palliat*).ti,ab.
16. (support* adj3 care).ti,ab.
17. palliat*.tw.
18. "advanced disease*".tw.
19. ("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage").tw.
20. (end adj6 life).tw.
21. (terminal* adj6 (disease* or ill* or care*)).ti,ab.
22. ("terminal-stage*" or dying).ti,ab.
23. (close adj6 death).tw.
24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. ((home* or in-home* or domicile or outreach or residential or housing or posthospital or post-hospital or communit* or moblie or ambulatory or door to door) adj2 (team* or centre* or center* or treat* or care or interven* or therap* or manag* or model* or program* or service* or nurs* or support or plan or assist*)).ti,ab.
26. (self adj3 (help* or care)).ti,ab.
27. ((psycholog* or pharmacolog* or psychiat* or social* or emotion* or spiritual* or relig* or faith or bereavement or grief or complement* or alternative) adj3 (car* or service* or plan* or interven* or support* or assist* or prog*)).ti,ab.
28. (symptom* adj3 (care or manag* or support* or modif* or control* or assess*)).ti,ab.
29. 25 or 26 or 27 or 28
30. exp Brain Neoplasms/
31. exp Glioma/
32. (brain adj3 (tumor* or tumour* or neoplas* or malignan* or cancer* or carcinoma*)).ti,ab.
33. (glioma* or astrocytoma* or meningioma* or oligodendroglioma* or oligoastrocytoma* or glioblastoma* or GBM* or Glioblastoma multiforme or "Primary brain tumo?r*").ti,ab.
34. 30 or 31 or 32 or 33
35. (early or advance* or forward or simultaneous).ti,ab.
36. 24 or 29
37. 35 and 36
38. 34 and 37

CONTRIBUTIONS OF AUTHORS

AB drafted the protocol.
SS drafted the protocol.
HF completed protocol updates and modifications.
ATB completed protocol updates and modifications.
FM contributed to drafting the protocol.
AN contributed to drafting the protocol.
MB contributed to drafting the protocol.
HB contributed to drafting the protocol.
All authors agreed on the final version of the protocol for publication.

DECLARATIONS OF INTEREST

Anthony Byrne has no known conflicts of interest.
Stephanie Sivell has no known conflicts of interest.
Fabio Ynoe Moraes has no known conflicts of interest.
Helen Bulbeck has no known conflicts of interest.
Anna Torrens-Burton has no known conflicts of interest.
Mark Bernstein has no known conflicts of interest.
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SOURCES OF SUPPORT