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Interventions to reduce the time to diagnosis of brain tumours (Protocol)

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Interventions to reduce the time to diagnosis of brain tumours

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ABSTRACT

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

- To systematically evaluate evidence on the effectiveness of interventions that may influence symptomatic participants to present early (shortening the 'Patient Interval'), thresholds for primary care referral (shortening the 'Primary Care Interval'), and time to imaging diagnosis (shortening the 'Secondary Care Interval' and 'Diagnostic Interval').
- To produce a brief economic commentary summarising the economic evaluations relevant to these interventions.

BACKGROUND

Description of the condition

Primary brain tumours are a heterogeneous group of tumours arising from the brain substance and its surrounding structures and may be high or lower grade. Primary intracranial brain tumours can be divided into *primary intra-cerebral tumours* (e.g. gliomas, pinealomas, medulloblastomas etc) or primary extra-cerebral tumours from structures outside the brain but within the cranium/skull (meningiomas, neuromas, adenomas). Secondary intracranial brain tumours arise from tissues outside the brain and spread to the brain and tissues within the skull (secondary intra-cerebral metastases). All types of intracranial tumours can form mass lesions and can cause similar symptoms e.g. headache, focal neurological symptoms, e.g. neurological weakness or numbness, language problems), epileptic seizures, or cognitive or personality changes, depending on where they are within or pressing on the brain.

Epidemiological studies show about 50% of all intracranial tumours are primary and 50% are secondary with incidences of 10 to 16 per 100,000 per year for each (Barnholtz-Sloan 2004; Counsell 1996; de Robles 2015; Materljan 2004; Nayak 2012; Ohgaki 2009; Walker 1985). Gliomas account for 2% of all cancers and have an incidence of about 6 to 8 cases per 100,000/year (Bell 2019; de Robles 2015; GLOBOCAN 2018; Ohgaki 2009). Incidence varies across regions, with 6 to 7 cases per 100,000 person-years in Europe to around 3 per 100,000 person-years in Africa (de Robles 2015; Bell 2019). Estimated new cases of brain and other nervous system tumours amounted to approximately 24,000 in the USA in 2018 (Siegel 2019).

On average, 10% to 15% of all cancers spread to the brain in developed countries giving an incidence of brain metastases of about 16 cases per 100,000/year in these settings (Nayak 2012). Although most brain metastases occur as a late manifestation of cancer, over 10% of people with lung cancer present with brain metastases as a first symptomatic site (Nieder 2019).

Clinicians often find diagnosis of a brain tumour very difficult, as presenting symptoms, such as headache, cognitive and personality symptoms, may be more commonly attributable to other conditions, such as migraine, anxiety, depression, stress or dementia. Most people with primary brain tumours have seen their general practitioner before diagnosis, often several times (Lyratzopoulos 2013; Swann 2020) and more than 50% subsequently present to, or are diagnosed by, accident and emergency services rather than by their GPs or in clinic settings (Elliss-Brookes 2012). Brain tumours are recognised as one of the most difficult cancers to diagnose in general practice and even expedited pathways to hospital referral or imaging (e.g. maximum of a 'two week wait' for suspected cancer) will be useful in only a small percentage of cases (Hamdan 2013). Although subtle, non-alarming symptoms may predate headaches (Scott 2019, headaches may be the earliest presenting symptom (Grant 2004), and the delay between symptom onset and diagnosis may be greatest in people presenting with headaches or cognitive issues (Ozawa 2018).

The poor detection rate based on referral guidelines and the delays in the pathway to diagnosis may ultimately influence management and prognosis. It is not clear whether Cancer Referral Guidelines, such as the National Institute for Health and Care Excellence (NICE) (Bates 2018; NICE 2006) Scottish Cancer Referral Guidelines (SCRG 2019) or Canadian have been helpful in selecting cases more accurately. It is also uncertain whether any expedited referral pathways in the UK, such as the Suspected Cancer Pathway (NICE 2017) or Direct Access Diagnostic Imaging (NHS 2014), have improved early diagnosis, or whether they are cost-effective (Simpson 2010).

In general, cancer referral guidelines delineate four different presentations of brain tumours that require urgent referral upon suspicion:

- progressive neurological deficit, e.g. progressive weakness or sensory problem down one side of the body, speech or language problem or unsteadiness;
- late onset seizure;
- headache with cognitive or behavioural symptoms; and
- headache with papilloedema (optic nerve head swelling).

According to NICE 2017, an urgent direct access magnetic resonance imaging (MRI)scan of the brain (or computed tomography (CT) scan, if MRI is contraindicated) should be performed within two weeks in adults with progressive neurological deficit. Headache with papilloedema may be a very late presentation, meaning that the tumour has reached a substantial size or is blocking cerebrospinal fluid pathways, and is suggestive of life-threatening disease. Ideally, clinicians will diagnose people based on the history of progressive headache with certain 'red flags' that predict a more serious cause for the headache (such as a headache that is worse in the morning, on stooping and straining, and accompanied by vomiting or drowsiness). In patients with headache and papilloedema, which denotes raised intracranial pressure, clinicians are advised to consider same-day emergency referral or referral within 48 hours (SCRG 2019).

Cancer referral pathway and service re-design have been recommended, including supportive interventions to achieve quality and productivity targets, to facilitate implementation of the NICE Guidelines for Suspected Cancer (Macmillan 2016). Such interventions will require evaluation to see if they speed up diagnosis without adding to increased burden on imaging services (Penfold 2017).

Description of the intervention

Interventions to reduce the time to diagnosis of brain tumours include expedited pathways to diagnose brain tumours based on a person's presenting symptoms and signs. In the UK in the past decade, there have been several local and regional 'service re-design' and 'expedited pathway' initiatives aimed at early identification of people who have symptoms and signs that would suggest brain tumour to be amongst the differential diagnosis. Neurological services have largely been re-designed to expedite pathways associated with focal (stroke-like) neurological presentations, late onset epilepsy ('first fit' clinics) and specialist neurology clinics to manage urgent referrals ('two-week wait' clinics), such as those with 'suspicion of cancer' (NHS 2013). Neuroradiology services have also been re-designed to accept 'direct access' cerebral imaging (MRI or CT) referrals from primary care, whereby a person can be referred for diagnostic imaging without needing specialist referral (NHS 2014). Cases referred for

direct access imaging are more likely to be patients with 'headache suspicious of cancer' and 'recent cognitive problems', rather than those where focal neurological symptoms and signs or seizures that necessitate urgent clinical evaluation and management of the structural cause.

A study of brain tumour cases from a UK national audit of cancer diagnosis in primary care showed that the commonest presentations were progressive focal (stroke-like) neurology (33%), 'fits, faints, or falls' (21%) and headache (21%) (Ozawa 2018). Other studies have used routinely collected English primary care data to estimate the predictive value of common presenting symptoms (Dommett 2013; Hamilton 2007; Kernick 2008). A systematic review of these sorts of studies found that common symptoms, apart from new-onset epilepsy, had low positive predictive values (PPVs) for brain tumours (Schmidt-Hansen 2015). Headache in this review was found to have a PPV of less than one per cent. In a recent large case-control study using five-year data from the UK clinical practice research database, headache as a symptom on its own was also reported to be a weak predictor of adult brain tumours (PPV of 0.1%); however, its predictive value was enhanced when combined with other symptoms (Ozawa 2019). For example, headache combined with cognitive symptoms gave a PPV of 7.2% and combined with weakness gave a PPV of 4.4%. Late onset seizure had the highest PPV of all individual symptoms in this study of 1.6%.

Thus, strategies to reduce the time to diagnosis may include the following:

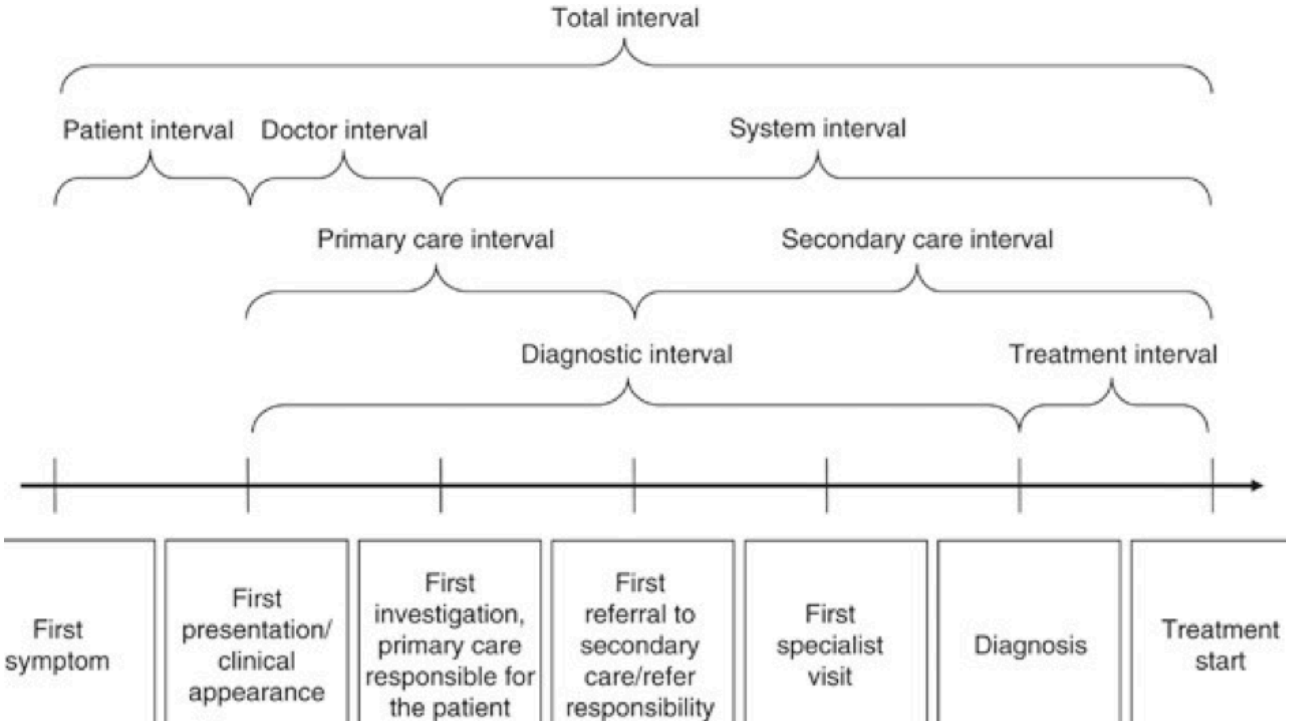
- expedited pathways to diagnose stroke-like presentation;
- expedited pathways to diagnose late onset seizures;
- expedited pathways to diagnose 'suspicion of cancer' within a target referral time;
- expedited imaging pathways to diagnosis 'headache suspicious of cancer';
- expedited imaging pathways to diagnose recent cognitive problems;
- interventions to reduce waiting times for brain imaging pathways (CT or MRI), such as 'direct access' imaging; and
- national awareness and early diagnosis initiatives.

How the intervention might work

These interventions might work to:

- increase population awareness of the presenting features of brain tumours through publicity campaigns, which may lead to people presenting to their GPs earlier (See Figure 1 - *Patient interval*);
- increase awareness of the presenting features of brain tumours (GP education) and of new available pathways to refer patients (e.g. urgent neurology clinics or fast access, direct cerebral imaging) might result a earlier referral for scanning (See Figure 1 - *Doctor Interval)* or hospital opinion (see Figure 1*Primary Care Interval);*
- shorten waiting times for urgent referrals (e.g. electronic system referral for appointments; urgent cerebrovascular clinics; first fit clinics; urgent neurology clinics) to reduce the delays within hospital once the referral has been received (see Figure 1 - *Secondary Care Interval – to diagnosis*);
- reduce time from first clinical appearance to diagnosis (e.g. by increasing number of scanners, increasing hours of scanning within the day, increasing open access imaging for primary care or protocol-based referral for urgent imaging, using private or insurance-based system for direct access imaging) (See Figure 1 - *Diagnostic Interval*).

Figure 1. Diagnostic 'Intervals' established by the Aarhus Statement in line with Olesen's schematic for diagnostic delay



If these interventions reduce time to diagnosis, it might make it less likely that people experience clinical deterioration on waiting lists, necessitating self-referral or primary care referral to accident and emergency units (A&E) for evaluation and imaging. On a national level, changes associated with interventions to reduce time to diagnosis might be evident within the longitudinal, routinely-collected data gathered by national cancer bodies through 'Routes to Diagnosis' (e.g. Elliss-Brookes 2012), National Cancer Waiting Times Monitoring Datasets (NCWTMDS) (e.g. NHS - NCMWMD 2019) and diagnostic test access monitoring (e.g. NCRAS 2012). However, the effectiveness of individual interventions might also be measured through comparative evaluation of local or national waiting times and the proportions of people with brain tumours diagnosed via imaging within target time intervals.

Why it is important to do this review

To our knowledge, no systematic reviews have been conducted to date on this topic. The James Lind Alliance (JLA) brings together participants, carers and clinicians to agree which clinical areas matter most and deserve priority attention (JLA 2015). In 2015, the JLA Neuro-Oncology Priority Setting Partnership identified 10 clinical areas in brain and spinal cord tumours on which the research community should focus. Early diagnosis was one of the top 10 priorities. The specific research question was 'Does earlier diagnosis improve outcomes, compared to standard diagnosis times, in people with a brain or spinal cord tumour?' This is important because brain tumours have a disproportionate mortality and morbidity compared to their incidence. For example, in the USA, central nervous system tumour incidences versus proportion of cancer deaths have been estimated at 1.4% and 2.9%, respectively (Siegel 2019). This effect is greatest in younger people; brain tumours kill more people under the age of 49 in the UK than any other form of cancer (CRUK 2019).

Early diagnosis has also been highlighted by Cancer Research UK as a key target for brain tumour research (CRUK 2016). Interventions that shorten the time to diagnosis of suspected cases may impact on severity of symptoms at diagnosis, allowing different surgical possibilities (e.g. resection of tumour versus biopsy only) and, thereby, influencing the choice of further oncology treatment and facilitating better tolerance and response to radiation therapy and chemotherapy, without the burden of a remaining large intracranial tumour. Earlier diagnosis might, therefore, ultimately improve survival of people with brain tumours. In addition, perceived delays along diagnostic pathways can have a major effect on the psychology of service users, leading to distrust in primary care and disaffection with health systems.

There is also a significant resource implication associated with managing brain tumours. The costs of managing brain tumours in Europe has been estimated to be €PPP 21,590 per person (DiLuca 2014; PPP = purchasing power parity of 2010). It has also been estimated that CNS (central nervous system) cancers resulted in the loss of 721,787 DALYs (Disability Adjusted Life Years – a unit that combines the morbidity and mortality associated with a disease) in Western Europe (GBD 2016 Brain and Other CNS Collaborators 2019). This demonstrates that brain tumours have a significant impact on healthcare resources and population health. Understanding strategies that have the potential to allow early diagnosis and possibly result in better outcomes with less aggressive treatment is crucial when considering future policy.

OBJECTIVES

- To systematically evaluate evidence on the effectiveness of interventions that may influence symptomatic participants to present early (shortening the 'Patient Interval'), thresholds for primary care referral (shortening the 'Primary Care Interval'), and time to imaging diagnosis (shortening the 'Secondary Care Interval' and 'Diagnostic Interval').
- To produce a brief economic commentary summarising the economic evaluations relevant to these interventions.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and non-randomised comparative studies, including controlled before-after studies (CBAs), that control for baseline differences. We will exclude cross-over designs, case-control studies and studies without a comparison group.

Types of participants

People of any age with a presentation that might suggest a primary brain tumour, specifically focal neurological deficit, headache suspicious of cancer; recent cognitive problems, late onset seizures. It is accepted that only a small proportion of people will ultimately have a brain tumour although it would be within the differential diagnosis. We will not exclude participants with past history of systemic cancer but will manage these data as a separate subgroup if found.

Types of interventions

Any active intervention that may influence the diagnostic pathway, e.g. clinical guidelines, direct access imaging, public health campaigns, educational and other interventions that might lead to early identification of primary brain tumours.

Types of outcome measures

Primary and secondary outcome measures are as follows.

Primary outcomes

- Time from first symptom to diagnosis (brain imaging or as defined by study authors)
- Time from first presentation to diagnosis (brain imaging or as defined by study authors)

Secondary outcomes

- Proportion of people identified with brain tumours (any type) out of those people referred with suspicious symptoms
- Performance status at imaging diagnosis (e.g. Karnofsky Performance Status, WHO Performance Status, Barthel Disability Index or Modified Rankin Handicap Scale if available, with thresholds as reported by study investigators)
- Health-related quality of life (QoL) at diagnosis or imaging or other time points up to diagnosis (e.g. the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 or EQ5D-5L
- Proportion of people with possible brain tumour undergoing delayed diagnosis or brain imaging (e.g. more than two weeks after referral)
- Proportion of people with brain tumours diagnosed after emergency presentation (a surrogate for late diagnosis) compared with those diagnosed through primary care referral pathways

We will also present evidence regarding cost of care as a brief economic commentary.

Search methods for identification of studies

Electronic searches

We will search the following databases from 2000 (This is when the UK National Cancer Plan was introduced by the UK's Department of Health with 'Referral guidelines for suspected cancer', which has been updated and replaced by NICE 2017):

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library;
- MEDLINE via Ovid;
- Embase via Ovid.

For economic evidence, the EED database will be searched from 2000 up to the end of December 2014 (when the last records were added to that database) and MEDLINE and Embase from 1st January 2015, as NHS EED already included comprehensive searches of these databases prior to 2015. We will also consider relevant grey literature, such as health technology assessments, reports and working papers, for inclusion.

Please refer to Appendix 1 for CENTRAL, MEDLINE and Embase search strategies.

We will not apply language restrictions to any of the searches.

Searching other resources

We will search the following for ongoing trials:

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

Where we identify ongoing trials that have not been published, we will approach investigators to ask for an update on the trial status and any relevant data. We will use the related articles feature of PubMed, and also handsearch the reference lists of included studies, to identify newly published articles and additional studies of relevance. We will restrict the latter to studies from published from the year 2000.

We also plan to handsearch conference proceedings from 2014 to 2019 (six years) of conferences of the British Neuro-Oncology Society, the Society for Neuro-Oncology, the European Association of Neuro-Oncology and the World Federation of Neuro-Oncology Societies to identify other relevant ongoing or unpublished studies.

Data collection and analysis

We will use Cochrane methodology for data collection and analysis as follows.

Selection of studies

After removing duplicates, 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 Covidence 2018 to facilitate study selection. Two review authors (TL, ET) will independently screen these records and obtain copies of the full texts of potentially eligible references. At least two review authors (TL, ET, DH) will independently assess each full text for eligibility. Disagreements will be resolved by discussion or by consultation with another reviewer (RG) or the wider group of review authors, if necessary. We will document reasons for exclusion in the 'Characteristics of excluded studies' table of the review.

Data extraction and management

Three review authors (TL, ET, DH) will independently extract the following data from included studies to a piloted data extraction form. We will resolve discrepancies through discussion or, if required, we will consult another author (RG).

- Author contact details
- Country
- Setting
- Dates of participant accrual
- Trial registration number/identification
- Funding source
- Declarations of interest
- Participant inclusion and exclusion criteria
- Study design and methodology
- Study population and baseline characteristics
  * Number of participants enrolled/analysed
  * Age
  * Gender
  * Performance status
  * Referral pathway (stroke/epilepsy/brain tumour/self-referral)
  * Presenting symptoms/signs
  * Type of surgery
  * Other treatment
- Intervention details
  * Type of intervention
  * Type of comparator
- Duration of follow-up
- Primary outcome/s of the study
- Review outcomes
  * For dichotomous outcomes, we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed
  * For continuous outcomes, we will extract the value and standard deviation of the outcome of interest and the number of participants assessed at the relevant time point in each group. We will also extract change-from-baseline score data where reported and note the type of scale used
  * We will extract adjusted statistics where reported
  * Where possible, all data we extract 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 the other review authors when necessary
- Risk of study bias (see below)

Assessment of risk of bias in included studies

For randomised trials and non-randomised studies, we will assess the risk of bias using Cochrane's tool and the criteria specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This includes assessment of:

- random sequence generation;
- allocation concealment;
- blinding of participants and healthcare providers;
- blinding of outcome assessors;
- incomplete outcome data (more than 20% missing data considered high risk);
- selective reporting of outcomes;
- other possible sources of bias, e.g. insufficient number of participants, baseline differences in group characteristics.

For non-randomised studies (non-randomised trials and controlled before-after studies), we will use the ROBINS-I tool for assessing risk of bias (Sterne 2016). This includes assessment of the following:

- bias due to confounding (e.g. baseline differences in prognostic factors, or post-baseline prognostic factor differences, or switching interventions);
- bias due to participant selection (both intervention and comparison groups should comprise the same representative group);
- bias in classification of interventions (e.g. differential misclassification of intervention status that is related to the outcome or the risk of the outcome);
- bias due to deviations from intended interventions;
- bias due to missing data (e.g. differential loss to follow-up that is affected by prognostic factors);
- bias due to outcome measures (e.g. outcome assessors are aware of intervention status, different methods are used to assess the outcome, or measurement errors are related to intervention status or effects);
- bias in selection of the reported result.

Two review authors (TL, ET or DH) will assess risk of bias independently and resolve differences by discussion or by appeal to another review author (RG). We will summarise judgements in 'Risk of bias' tables along with the characteristics of the included studies. We will interpret results in light of the 'Risk of bias' assessment. For more details about the assessment of risk of bias, see Appendix 2.

Measures of treatment effect

- For dichotomous outcomes, we will calculate the effect size as a risk ratio (RR) with its 95% confidence interval (CI).

- For continuous outcomes (e.g. QoL scores) in which different measurement scales have been used, we will pool data as a mean difference (MD) with its 95% CI. If studies use different time points and measurement scales we will pool data using the standardised mean difference (SMD) if it is considered clinically meaningful to do so.
- For time to event data, we will calculate the effect size as a hazard ratio (HR) with its 95% CI.

Unit of analysis issues

At least two review authors will review unit-of-analysis issues (TL, ET, RG), as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), for each included study. These include reports where there are multiple observations for the same outcome, e.g. repeated measurements with different scales, or outcomes measured at different time points. When time points differ across studies or there are multiple observations for the same outcome, findings will be synthesised narratively.

We will include cluster-randomised trials in analyses alongside individually-randomised trials and will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population, if the authors have not taken clustering into account. We will report the source of the ICC and conduct sensitivity analyses to investigate the effect of variation in the ICC. We will consider it reasonable to combine the results from both cluster-randomised and individually-randomised study designs if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform subgroup analysis to investigate the effects of the randomisation unit. Differences will be resolved by discussion with a third review author (RG).

Dealing with missing data

For included studies, we will note the levels of attrition but will not impute missing data. In the event of missing data, we will write to study authors to request the data and describe in the 'Characteristics of included studies' table how we obtained any missing data. We will explore the impact of including studies with high level of missing data in the overall assessment of treatment effect by using sensitivity analysis.

Assessment of heterogeneity

We will assess statistical heterogeneity between studies by visual inspection of forest plots (Higgins 2003) and by using a formal statistical test of the significance of the heterogeneity, assessed using the T2, I2 and Chi2 statistics (Deeks 2001). We will regard heterogeneity as substantial if an I^2 is greater than 60% and either T^2 is greater than zero, or there is a low P value (< 0.10) in the Chi^2 test for heterogeneity. Where there is evidence of substantial heterogeneity ($I^2 > 60\%$), we will investigate and report the possible reasons for it, e.g. clinical heterogeneity, high risk of bias studies, etc.

Should a different approach to synthesis be used, which does not support production of a forest plot with effect sizes, it may still be useful to report on heterogeneity in the standardised effect measure used, e.g. effect direction, akin to an informal sensitivity analysis, the results of which are speculative but may be useful for readers.

Assessment of reporting biases

Where there are 10 or more studies in a meta-analysis we will investigate reporting biases, such as publication bias, through visual inspection of funnel plots. If asymmetry is suggested by visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will pool dichotomous data as risk ratios (RRs) and continuous data as mean differences (MDs) (or standardised mean differences (SMDs) if different scales have been used) using the random-effects model with inverse variance weighting in Review Manager 2014 because clinical heterogeneity among included studies is expected. The random-effects summary will be treated as the average range of possible intervention effects and we will discuss the clinical implications of intervention effects differing between trials. If any trials contributing to a meta-analysis have multiple intervention groups, we will divide the 'shared' comparison group into the number of treatment groups and comparisons between each treatment group and treat the split comparison group as independent comparisons.

If different studies report either dichotomous or continuous data for the same outcome, we will attempt to convert continuous data to dichotomous data to facilitate meta-analysis.

We will perform a meta-analysis of the results assuming that we find at least two included studies that are sufficiently similar for the findings to be clinically meaningful. If it is not clinically meaningful to pool data, we will attempt a narrative synthesis of the evidence.

Data from non-randomised studies will be synthesised separately from randomised trials. As different non-randomised studies may report results in different ways, when found we may tabulate this sort of evidence and synthesise it narratively.

In any evidence synthesis (meta-analysis and narrative synthesis), interventions/strategies will be subgrouped according to how they might work (see How the intervention might work). If data are very sparse, we may report raw data from individual studies.

Brief economic commentary

We will develop a brief economic commentary based on current methods guidelines (Shemilt 2019) to summarise the availability and principal findings of trial-based and model-based full economic evaluations (cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses) that evaluate interventions which aim to reduce the time to diagnosis of brain tumours. This commentary will focus on the extent to which principal findings of eligible economic evaluations indicate that an intervention might be judged favourably (or unfavourably) from an economic perspective, when implemented in different settings.

Subgroup analysis and investigation of heterogeneity

If it is meaningful to do so, we will synthesise data from different interventions together in the first instance. If we identify substantial

heterogeneity, we will use subgroup and sensitivity analyses to investigate it. Where there are sufficient data, we anticipate the following subgroup analysis.

- Type of intervention: e.g. clinical guidelines, direct access imaging, public health campaigns, educational and other
- Type of referral: referral for suspected brain tumour or referral for other suspected conditions in which the differential diagnosis includes brain tumour, e.g. epilepsy, stroke, headache
- Age: children less than 16 years old, young adults (16 to 40 years), and adults of more than 40 years
- Setting: high-income country and low-/middle-income country settings

We will use formal tests for subgroup differences.

Sensitivity analysis

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

Summary of findings and assessment of the certainty of the evidence

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

- time from primary care presentation to diagnosis;
- time from first symptom to diagnosis;
- proportion of people identified with brain tumours (any type) out of those referred with suspicious symptoms.

We will use the GRADE system to rank the certainty of the evidence (Schünemann 2011) with two review authors independently grading the evidence and resolving differences by discussion or by involving a third review author. Where the evidence is based on single studies, or where there is no evidence on a specific outcome, we will include the outcome in the 'Summary of findings' table and grade or explain accordingly. A rationale for each judgement will be given in the table footnotes. In the absence of a single estimate of effect (when meta-analysis was not possible), we will rate the certainty of the narrative evidence using the GRADE approach (Murad 2017). We will interpret the results of the graded evidence based on Cochrane Effective Practice and Organisation of Care guidance (EPOC 2017).

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APPENDICES

Appendix 1. Search strategies

MEDLINE search strategy for effectiveness evidence

1. exp Brain Neoplasms/
2. ((brain or intracranial or intra-cranial or cerebr*) adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or metastat* or malignan*)).mp.
3. (glioma* or astrocytoma* or xanthoastrocytoma* or glioblastoma* or gliosarcoma* or oligodendrogli* or oligoastrocyt* or ependym* or subependym* or astroblastoma* or ganglioglioma* or gangliocytoma* or neurocytoma* or liponeurocytoma* or pineocytoma* or pineoblastoma* or medulloblastoma* or neuroblastoma* or ganglioneuroblastoma*or medulloepithelioma*).ti,ab.
4. 1 or 2 or 3
5. exp Clinical practice guideline/
6. exp GUIDELINE/
7. exp Critical Pathways/
8. ((clinical* or treatment* or diagnos* or practice or critical or care or cancer) adj5 (guideline* or guidance* or pathway*)).ti,ab.
9. "Clinical Decision-Making"/
10. (care adj (map* or plan* or interval*)).ti,ab.
11. Health Planning Guidelines/
12. Health Plan Implementation/
13. Public health/
14. professional standard*.tw.
15. Guideline Adherence/
16. exp practice guidelines as topic/
17. Health Promotion/
18. Clinical Protocols/
19. exp Consensus Development Conference/
20. (consensus adj3 (develop* or conference*)).mp.
21. 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
22. exp early diagnosis/
23. "Referral and Consultation"/
24. ((primary or patient or doctor or secondary* or system or total or diagnostic or pre-diagnostic or treatment or time) adj3 interval*).ti,ab.
25. (cancer waiting time* or total pre-therapy interval* or TPTI).mp.
26. ((direct access* or direct-access* or open access* or open-access* or OACT) adj5 (diagnos* or detect* or interven* or investigat* or refer*)).mp.
27. exp "Diagnostic Techniques and Procedures"/
28. diagnos*.ti,ab.
29. 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 4 and 21 and 29

31. (protocol* adj5 (referral* or algorithm* or strateg* or diagnos*)).mp.
32. 29 and 31
33. exp Stroke/
34. (transient ischaemic attack* or TIA* or stroke* or cerebrovascular accident* or CVA*).mp.
35. exp Epilepsy/
36. (seizure* or epilep*).mp.
37. exp Headache/
38. ((seizure* or epilep* or transient ischaemic attack* or TIA* or stroke* or cerebrovascular accident* or CVA* or headache*) adj5 (unexplained or urgent or fast access or rapid or emergenc* or ED or ER or suspicious or suspect* or "two week wait" or wait* time or "time to diagnosis" or neurolog* assessment* or scan* or ?imag* or CT or MRI)).mp.
39. 33 or 34 or 35 or 36 or 37 or 38
40. 32 and 39

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

The Embase strategy is similar to the MEDLINE strategy.

Medline search strategy for economic evidence

Appendix 2. 'Risk of bias' assessment of randomised controlled trials (RCTs)

We will assess the risk of bias of RCTs 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

- Low risk of bias if participants were adequately blinded
- High risk of bias if participants 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

Appendix 3. 'Risk of bias' assessment of non-randomised studies (NRSs) (ROBINS-1)

We will assess the risk of bias of NRSs according to the following criteria. Risk of bias will be assessed as low, moderate, serious or critical depending on the seriousness of the bias. Where there is insufficient information on which to make a judgement, 'no information' will be recorded as the judgement.

1. Possible confounding

Baseline differences, possible post-baseline differences in prognostic factors, or switching interventions will be assessed.

2. Bias from participant selection

Both study groups should comprise same representative group being assessed.

3. Bias from classification of interventions

This relates to differential misclassification of intervention status that is related to the outcome or the risk of the outcome.

4. Bias due to deviation from interventions or protocol

Whether and the extent to which deviations from the protocol or intervention/s allocated occur will be assessed.

5. Bias due to missing data

Differential loss to follow up that may relate to prognostic factors will be assessed.

6. Bias due to outcome measures or outcome assessment

This sort of bias could occur, for example, where outcome assessors are aware of intervention status, different methods are used to assess the outcome, or measurement errors are related to intervention status or effects.

7. Bias due to selection of reported results

How investigators select and report results will be assessed.

CONTRIBUTIONS OF AUTHORS

Robin Grant and Theresa Lawrie wrote the first draft of the protocol and undertook further revisions based on suggestions from the co-authors. All authors approved the final version.

DECLARATIONS OF INTEREST

Robin Grant: none known
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