Interventions to reduce the time to diagnosis of brain tumours

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Abstract

Background

Brain tumours are recognised as one of the most difficult cancers to diagnose because presenting symptoms, such as headache, cognitive symptoms, and seizures, may be more commonly attributable to other, more benign conditions. Interventions to reduce the time to diagnosis of brain tumours include national awareness initiatives, expedited pathways, and protocols to diagnose brain tumours, based on a person's presenting symptoms and signs; and interventions to reduce waiting times for brain imaging pathways. If such interventions reduce the time to diagnosis, it may make it less likely that people experience clinical deterioration, and different treatment options may be available.

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.

Search methods

For evidence on effectiveness, we searched CENTRAL, MEDLINE, and Embase from January 2000 to January 2020; Clinicaltrials.gov to May 2020, and conference proceedings from 2014 to 2018. For economic evidence, we searched the UK National Health Services Economic Evaluation Database from 2000 to December 2014.

Selection criteria

We planned to include studies evaluating any active intervention that may influence the diagnostic pathway, e.g. clinical guidelines, direct access imaging, public health campaigns, educational initiatives, and other interventions that might lead to early identification of primary brain tumours. We planned to include randomised and non-randomised comparative studies. Included studies would include people of any age, with a presentation that might suggest a brain tumour.

Data collection and analysis

Two review authors independently assessed titles identified by the search strategy, and the full texts of potentially eligible studies. We resolved discrepancies through discussion or, if required, by consulting another review author.

Main results

We did not identify any studies for inclusion in this review. We excluded 115 studies. The main reason for exclusion of potentially eligible intervention studies was their study design, due to a lack of control groups. We found no economic evidence to inform a brief economic commentary on this topic.

Authors' conclusions

In this version of the review, we did not identify any studies that met the review inclusion criteria for either effectiveness or cost-effectiveness. Therefore, there is no evidence from good quality studies on the best strategies to reduce the time to diagnosis of brain tumours, despite the prioritisation of research on early diagnosis by the James Lind Alliance in 2015.

This review highlights the need for research in this area.

Plain language summary

How effective are initiatives that aim to speed up the diagnosis of brain tumours?

Why this question is important

A brain tumour is a group of cells in the brain that develop in an abnormal and uncontrollable way. There are two main types of brain tumour:

- Non-cancerous (benign) brain tumours: these grow slowly and do not spread throughout the body.
- Cancerous (malignant) brain tumours: these grow faster and can spread to other parts of the body.

Brain tumours that start in the brain are known as primary tumours. If they have spread to the brain from elsewhere, they are called secondary tumours.

All types of brain tumour are a serious health threat, since the brain controls all the functions of the body. Both benign and cancerous brain tumours can be fatal. Even when they are not, they can be very disabling. Symptoms can include:

- Headaches
- Epileptic seizures (fits)
- Persistent nausea (feeling sick), vomiting, and drowsiness
- Changes in behaviour or personality, trouble thinking, memory problems
- Weakness, or paralysis that develops on one side of the body
- Problems with speech or vision

It is difficult to diagnose brain tumours, because symptoms can all be mistaken for those of less serious conditions. It may take some time before their true cause – a brain tumour – is identified. Yet diagnosing a brain tumour as early as possible is important, because the bigger a tumour grows, the more difficult it is to treat, and the greater the potential for the treatment to cause collateral damage.

A range of initiatives has been designed to speed up the diagnosis of brain tumours. This includes campaigns to increase doctors' and the public's awareness of the symptoms they cause, and professional guidelines to speed up referral for diagnostic scans or specialist assessment. To find out how effective these initiatives are, we set out to review the research evidence. We also wanted to investigate the cost of initiatives.

How we searched for evidence

Our team of researchers searched the medical literature for studies that compared the effectiveness of an initiative designed to speed up the diagnosis of brain tumours against normal practice or another initiative, and included people of all ages with signs or symptoms that might suggest a brain tumour.

What we found

We found 115 studies that investigated the diagnosis of brain tumours, but none of them met all of our inclusion criteria, and we excluded them. We found no studies with information about the cost of initiatives.

What this means

Currently, there is no evidence from good quality studies to inform patients, health professionals, or service planners about how to reduce the time to diagnosis of brain tumours. Nor is there any information on the cost of these initiatives. This review highlights the need for research in this area.

How up-to-date is this review?

We last searched for evidence in January 2020. This review covered research that was available up to that date, but did not consider any evidence that may have been produced since then.

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 intracerebral tumours (e.g. gliomas, pinealomas, medulloblastomas, etc), or primary extracerebral tumours, arising from structures outside the brain but within the cranium or skull (i.e. meningiomas, neuromas, adenomas). Secondary intracranial brain tumours arise from tissues outside the brain, and spread to the brain and tissues within the skull (secondary intracerebral metastases). All types of intracranial tumours can form mass lesions and can cause similar symptoms, e.g. headache, or 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 per 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 (Bell 2019; de Robles 2015). Estimated new cases of brain and other nervous system tumours amounted to approximately 24,000 in the USA in 2018 (Siegel 2019).

In high-income countries, on average, 10% to 15% of all cancers spread to the brain, giving an incidence of brain metastases of about 16 cases per 100,000 per 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 it very difficult to make a diagnosis of a brain tumour, as presenting symptoms, such as headaches, or 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 (GP) before diagnosis, often several times (Lyratzopoulos 2013; Swann 2020; Walter 2019), but more than 50% subsequently present to, or are diagnosed by emergency services rather than by their GP, or in a clinic setting (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). Subtle, non-alarming symptoms and signs may predate headaches (Scott 2019); these, such as personality changes, are often first noticed by a spouse (Salander 1999). 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. There is a lack of data on whether cancer referral guidelines, such as the National Institute for Health and Care Excellence (NICE; Bates 2018; NICE 2006), the Scottish Cancer Referral Guidelines (SCRG 2019), or the Canadian guidelines have been helpful in selecting cases more accurately. A 2019 study demonstrated that the positive predictive value of the NICE symptom-based referral guidelines was very low, at only 2.9% (Zienius 2019).

In addition, 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 problems, or unsteadiness;
- late onset seizure;
- headache with cognitive or behavioural symptoms; and
- headache with papilloedema (swelling of the optic disc).

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 people 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).

A 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 an 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 suggest brain tumour should be one of the differential diagnoses. 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), for 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 a specialist's referral (NHS 2014). Cases referred for direct access imaging are more likely to be people who present with headache, suspicious of cancer and recent cognitive problems, rather than those who present with 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 most common 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); in this review, headache was found to have a PPV of less than 1%. 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 = 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 those with stroke-like presentation;
- expedited pathways to diagnose those with late-onset seizures;
- expedited pathways to diagnose those with suspicion of cancer within a target referral time;
- expedited imaging pathways to diagnosis those with headache, suspicious of cancer;
- expedited imaging pathways to diagnose those with 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 people (e.g. urgent neurology clinics or fast access, direct cerebral imaging) might result in an 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 in 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).

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 emergency units 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, for example, Routes to Diagnosis (Elliss-Brookes 2012), National Cancer Waiting Times Monitoring Datasets NHS 2019), and diagnostic test access monitoring (NCRAS 2012). However, the effectiveness of individual interventions might also be measured through comparative evaluation of local or national waiting times, and the proportion 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 on this topic to date. 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, it has been estimated that central nervous system tumours (1.4% of all cancers) causes 2.9% of cancer deaths (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 the severity of symptoms at diagnosis, allowing different surgical possibilities (e.g. resection of tumour versus biopsy only), and influencing the choice of further oncology treatment. This may result in better tolerance and response to radiation therapy and chemotherapy, and reduce the burden of a remaining large intracranial tumour. Therefore, earlier diagnosis might ultimately improve the survival of people with brain tumours. Reducing delays along the diagnostic pathway can also reduce service users' distrust in primary care and dissatisfaction with the healthcare system.

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 (PPP = purchasing power parity of 2010; DiLuca 2014). It has also been estimated that 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 2019). This illustrates 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 cluster-RCTs and controlled before-after studies (CBAs) that control for baseline differences. We excluded 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, and late onset seizures. It is accepted that only a small proportion of people would ultimately have a brain tumour, although it would be within the differential diagnosis. We did not plan to exclude participants with a past history of systemic cancer, but had planned to manage these data as a separate subgroup if we found any.

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) of those 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 experiencing 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 also planned to present any evidence regarding cost of care, as a brief economic commentary.

Search methods for identification of studies

Electronic searches

We searched 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) to 13 January 2020:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 1), in the Cochrane Library;
- MEDLINE via Ovid (2000 to December week 4 2019);
- Embase via Ovid (2000 to 2020 week 1).

For economic evidence, we searched the EED database from the end of December 2014 (when the last records were added to that database) to January 2000, and MEDLINE and Embase from 1 January 2015 to January 2020, as NHS EED already included comprehensive searches of these databases prior to 2015. We also considered 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 did not apply language restrictions to any of the searches.

Searching other resources

We searched Clinicaltrials.gov on 1 May 2020. We also handsearched conference proceedings from 2014 to 2018 (five 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 used 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 (GNOC) downloaded all titles and abstracts retrieved by electronic searching to Covidence to facilitate study selection. Two review authors (TL, ET) independently screened these records and obtained copies of the full texts of potentially eligible references. At least two review authors (TL, ET, DH, TD) independently assessed each full text for eligibility. Disagreements were resolved by discussion, or by consultation with another reviewer (RG), or the wider group of review authors, if necessary. We have documented reasons for exclusion in the Characteristics of excluded studies tables of the review.

In this version of the review, we did not identify any studies eligible for inclusion. In future versions, if any studies meet the inclusion criteria, we will use the following methods:

Data extraction and management

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

- Author contact details
- Country
- Setting
- Dates of participant accrual
- Trial registration number or 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 extracted will be those relevant to an intention-to-treat analysis, in which participants are 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, 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:

- 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 TD) will independently assess risk of bias, 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 any 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 the same measurement scales were used, we will pool data as a mean difference (MD) with its 95% CI. If studies used different time points and measurement scales, and we consider it

clinically meaningful to do so, we will pool data using the standardised mean difference (SMD).

- 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 independently review unit-of-analysis issues (TL, TD), 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, we will synthesise the findings narratively.

We will analyse cluster-randomised trials 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 had 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 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 we consider the interaction between the effect of intervention and the choice of randomisation unit to be unlikely. We will acknowledge heterogeneity in the randomisation unit, and perform subgroup analysis to investigate the effects of the randomisation unit. We will resolve differences 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 T^2, I^2, and Chi^2 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 we use a different approach to synthesis, 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, which is 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. We will use the random-effects model with inverse variance weighting in Review Manager 2014, because we expect clinical heterogeneity among included studies. We will treat the random-effects summary 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.

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

We will synthesise data from non-randomised studies 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), we will subgroup interventions and strategies 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, 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 that aim to reduce the time to diagnosis of brain tumours (Shemilt 2019). 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 younger than 16 years old, young adults (16 to 40 years old), and adults older than 40 years
- Setting: high-income country and low- or middle-income country settings

We will use formal tests for subgroup differences.

Sensitivity analysis

We plan to perform sensitivity analyses (i) to investigate instances of substantial heterogeneity identified in meta-analyses of the primary outcomes, and (ii) to investigate how study quality affects the estimate of effect 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:

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

We will use the GRADE system to rank the certainty of the evidence, with two review authors independently grading the evidence, and resolving differences by discussion, or by involving a third review author (Schünemann 2011). 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. We will provide a rationale for each judgement 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).

Results

Description of studies

We did not identify any studies for inclusion in this review.

Results of the search

Intervention study searches

Electronic searches conducted from January 2000 to 8 August 2019 and 9 January 2020, identified a total of 3032 records after de-duplication. We identified nine additional records by searching conference proceedings, and three through study reference lists and related articles searches. Out of the total of 3041 records, we retrieved the full text of 115. We excluded all potentially eligible studies (see Figure 2).

Economic studies searches

We conducted searches for economic studies on the same dates as above. The August 2019 search identified 114 records, and the January 2020 search identified 12 records; we excluded all of them at the screening stage.

Included studies

Not applicable.

Excluded studies

We excluded 115 studies or reports mainly for study design reasons, although most studies had more than one reason for exclusion, e.g. they may also have assessed an ineligible intervention or ineligible outcomes. Ineligible study designs included:

- studies without an intervention and/or control group, e.g. audits (Abernethy 2008; Ahmad 2009; Baughan 2011; Bergqvist 2017; Braun 2006; Chiesa 2019; Chrastina 2011; Daverio 2016; Davis 2008; Dommett 2019; Gocan 2016; Grant 2017; Griffiths 2005; Gray 2018; Grooss 2016; Handschu 2015; Harris 2000; Hatzitolios 2008; Knox 2012; Lange 2011; Lee 2018; Mohammad 2016; Munoz-Ceron 2019; Pengiran 2003; Simpson 2010; Tatencloux 2017; Umotong 2017; Webb 2015; Weddell 2017; Williams 2007; Zienius 2019)
- reviews (Abend 2010; Aghi 2015; Albert 2016; Al-Okaili 2006; Altindag 2017; Bartleson 2006; Brat 2008; Brouwers 2009; Cahill 2015; Carter 2007; Faehndrich 2011; Ferro 2017; Fouke 2015; Fowler 2004; Friedman 2011; Furtwangler 2014; Gaillard 2011; Giguere 2012; Kahn 2014; Langen 2008; Langen 2011; Langen 2017; Langen 2018; Long 2017; Wilne 2007)
- uncontrolled before-after studies (Dutto 2009; Guilfoyle 2011; Haneef 2010; Laursen 2012; Laursen 2012a; Nahab 2012; Rittman 2012; Shack 2016; Shanmugavadivel 2016; Shanmugavadivel 2020; Walker 2015; Walker 2016)
- retrospective case-control studies (Ahrensberg 2016; Kernick 2009)
- diagnostic test accuracy studies (Asimos 2014; Titlic 2008)
- clinical practice guidelines, recommendations, or consensus reports (Barisic 2012; Bhat 2011; ESMO 2007; Frappaz 2003; Gago-Veiga 2017; Haswali 2015; Jiang 2016; Larner 2006; Mirsky 2017; Richards 2009; Stupp 2009; Weller 2014; Weller 2017; Wilne 2010)Bhat 2011
- qualitative studies (Llewellyn 2018; Molassiotis 2010; Vedelo 2018)
- discussion papers (Chenevert 2006; Cianfoni 2007; Cote 2017; Cross 2006; Gaini 2004a; Galiano Fragua 2011; Harada 2007; Kabbouche 2010; Langdon 2017; Leal 2019; Le Bas 2005; McCrea 2013; Medina 2002; Penfold 2017; Pitfield 2012; Scharl 2017)
- other types of papers (Bachli 2018; Cowan 1999; Davies 1997; Halperin 1996; Moller-Hartmann 2002; Thust 2018)

See Characteristics of excluded studies. Five of these studies evaluated potentially relevant interventions (Dutto 2009; Laursen 2012; Pengiran 2003; Walker 2016; Webb 2015). Although we excluded these studies on methodological grounds because they lacked control groups, for completeness, and to provide pointers for future research, we describe their findings below.

The HeadSmart study evaluated a UK-wide public and professional awareness campaign to raise awareness of brain tumour symptoms, and to promote appropriate assessment, and timely referral and diagnosis of children and adolescents with relevant

symptoms (Walker 2016). Different symptom checklists were prepared depending on the child's age at symptom onset (under 5 years, 5 to 11 years, 12 to 18 years). Checklists and campaign materials were designed for easy implementation (one symptom for medical assessment, and two or more for urgent referral to a specialist centre for further investigations). Campaign materials were made available to health professionals (general practitioners (GPs), paediatricians, and professional trainers) and to the public, through mass and social media campaigns, and via cancer charities. Outcomes included time from symptom onset to first presentation (patient interval); time from presentation to diagnosis (diagnostic interval); and time to treatment. Public and professional awareness were also monitored.

Using records of children referred to 18 participating centres, a series of observations were carried out in the six months before and two years after the launch of the intervention (monthly observations were recorded during the pre-launch period (January to June 2011), and in the months following implementation of the campaign (July 2011 to May 2013). Results were presented for 710 children and adolescents with pre-launch (January to May 2011) observations for 165, and post-launch (June 2011 to May 2013) observations for 545 participants. The median time from symptom onset to diagnoses was reported to have been reduced from 9.1 weeks in the pre-launch period (January to June 2011) to 6.7 weeks in the second year of the campaign (P = 0.197). Although the distribution was skewed, the mean time to diagnosis over the same two periods, reduced from 25.2 weeks to 21.3 weeks. The interval between the first professional contact to central nervous system imaging was reported to be reduced from a median of 3.3 weeks to a median of 1.4 weeks during the second year of the campaign (P = 0.009).

Overall, it is not easy to interpret the data from this study. The results described in the text were very limited, while the graphs displaying monthly observations suggested considerable month by month variation in outcomes. There were no clear comparisons in the text between the before and after periods for most outcomes; rather, authors reported medians from the pre-launch period and the second year post-launch. There was also a lack of information on participant characteristics before and after the launch of the campaign, so it was not clear if there were differences between these groups. The discussion in the evaluation report points out that the net effect of the campaign was difficult to separate from the effects of the introduction of a clinical guideline, other changes in health services, and MRI availability over the study period. In a related abstract, the study authors stated that between 2006 and 2011 (pre-HeadSmart), median time to diagnosis had already fallen from a median of 13.4 to 6.3 weeks (Walker 2015). So the added effect of HeadSmart was not easy to disentangle. We also found it difficult to interpret the effects of the campaign in different settings. In the discussion section of the HeadSmart evaluation report, they stated that children attending the emergency department had the most rapid referral for diagnostic imaging; it was not clear whether GPs (who were a major focus of campaign materials) referred children any more rapidly before or after the campaign.

In another before-after study conducted in Italy, Dutto 2009 examined the implementation of a headache diagnosis protocol (a series of decision charts) in an urban hospital emergency department. Participants were adults presenting with non-traumatic, non-fever headaches over the six-month study period from April 2006 to September 2006. These participants were compared with retrospective controls (using case notes for people attending between April 2005 and September 2005). The aim of the intervention was to improve the diagnosis of headaches associated with serious conditions (e.g. stroke or neoplasms). Outcomes included resource use (CT scans, neurological consultations, and hospital admission), early diagnosis, and death. Two independent observers examined the case records of people who met the eligibility criteria in the six months before (N = 312) and after (N = 374) the introduction of the

intervention. Altogether, they identified a total of 30 serious, secondary headaches. The trial authors reported that during the 'after' period, during which the protocol had been 'strictly applied (66%), there was an 11.3% reduction in neurological consultations. However overall, there was little difference in outcomes before and after the diagnosis protocol was introduced, with only a small number of neoplasms identified during both periods (two before and five after the intervention). The lack of a control group and the low number of neoplasms identified in this before-after study meant that results were difficult to interpret.

Laursen 2012 examined the implementation of the Danish Integrated Cancer Pathway, which aimed to improve diagnosis and clinical management for 34 types of cancer. The brain tumour pathway set out clear criteria for the referral of people suspected of having brain malignancies. Evaluation was carried out over two years (with data for eight three-month periods) after the introduction of the pathway. We excluded the study as it had no control group or data prior to the intervention. Outcomes included the number of appropriate referrals, and time from hospital admission to diagnostic tests and final diagnosis. The study authors reported that the clear criteria for referral resulted in a reduction of approximately 25% in participants enrolled in the brain tumour pathway over the study period. Data for 241 participants showed that the mean time from hospital admission to final diagnoses was reduced from approximately three days during the first quarter following the introduction of the pathway, to approximately two days by the end of the two-year study period.

We excluded two other UK studies because they lacked control groups. Pengiran 2003 evaluated the impact of an urgent (two-week) referral guideline for suspected brain tumours using retrospective audit, without a control group. The guideline set out specific criteria for GPs to use to refer for specialist care. The aim was to reduce inappropriate referral and reduce delay for those with symptoms of serious neurological conditions. Prior to the implementation of the guideline, there was no fixed system to refer people with cancer, although people deemed to be urgent in the GP referrals, were seen within one week. In the three months before the introduction of the guideline, neurological clinic records indicated that of 12 people urgently referred, none had cancer. The subsequent case audit over a nine-month period, from July 2000 to April 2001 (after guideline implementation) included 43 people. Four people included in the audit had malignancies; two primary brain tumours and two brain metastases, and all four had met the referral criteria. However, 30% of urgent referrals did not adhere to guidelines. The authors concluded that specific criteria for referral may reduce inappropriate resource use, and thereby, improve timely access for with serious disease.

Webb 2015 evaluated the same urgent referral pathway as Pengiran 2003, using a retrospective case review of referrals between January 2009 and September 2013. The study sought to determine the number of people who were appropriately referred, and the effectiveness of the pathway on the numbers of people offered specialist appointments within 14 days, and on the time to scan report. All 105 people referred received an offer of a specialist appointment within 14 days; the median time to scan report after referral was 18 days (interquartile range (IQR) 9 to 23 days). Ten brain tumours were identified from the 105 people referred. The trial authors concluded that there were frequent, inappropriate, low-risk referrals. Although the study suggested that people on the urgent referral pathway were generally seen within the two-week target period, it was not clear how this may have differed from previous care, as no data on the period before the introduction of the pathway were presented.

Risk of bias in included studies

Not applicable.

Effects of interventions

Not applicable.

Discussion

Summary of main results

In this version of the review, we did not identify any studies evaluating intervention effectiveness that met the review inclusion criteria.

Brief Economic Commentary

We did not identify any economic studies that analysed the use of any strategies to reduce time-to-diagnosis for brain tumours. The apparent shortage of relevant economic evaluations indicates that there is a paucity of economic evidence on the efficiency of potential strategies that aim to reduce the interval for diagnosis of brain tumours.

Overall completeness and applicability of evidence

This review, for which no studies met the inclusion criteria, highlights that evidence on how to reduce the time to diagnosis of brain tumours is an important knowledge gap.

Quality of the evidence

In this version of the review, we were unable to include any of the studies identified by our search strategy. The main reason for exclusion of potentially eligible studies was study design. We did not identify any randomised controlled trials or controlled before-after studies examining relevant interventions. As we describe above, we did identify a small number of studies focusing on eligible participants and interventions, but these studies were all at high risk of bias as they did not include control groups. Under these circumstances, we were not able to ascertain whether outcomes were due to interventions or were influenced by other possible confounding factors. For example, in the Headsmart study, we were unable to conclude, with any confidence, whether the positive effects identified were attributable, even in part, to the effects of the awareness campaign, or were related to other background factors, such as changes in health policy, or diagnostic technologies, or both, over the study period (Walker 2016). At the same time, such studies do offer useful information on potentially promising interventions, and clarification of the participant subgroups most likely to benefit from more timely diagnosis; this may help to target interventions and inform the design of future evaluations.

Potential biases in the review process

We are mindful that the review process itself may introduce bias. We took steps to minimise the potential for such bias by ensuring that at least two members of the review team, working independently, screened titles identified by the search strategy. A minimum of two reviewers independently assessed the full text of reports for potentially eligible studies. Where we had any doubt, or where there was discrepancy between review authors on whether or not a study should be included, we consulted the wider review team. In future versions of the review, if we identify any studies for inclusion, we will apply the strategies set out in the methods section, in a bid to reduce bias.

Agreements and disagreements with other studies or reviews

We excluded a number of studies evaluating potentially relevant interventions on methodological grounds. These included before-after studies and retrospective studies without control groups. Although we were unable to include these studies in our results, they may offer some useful insights into possible settings, participant groups, and interventions for assessment in future controlled trials.

Authors' conclusions

Implications for practice

There is no evidence from good quality studies to inform service users, health professionals, or service planners on to how to reduce the time to diagnosis of brain tumours, despite the prioritisation of research on early diagnosis by the James Lind Alliance in 2015.

Implications for research

This review highlights the urgent need for research in this area. Research studies should include concurrent control groups, so that effects of the interventions can be clearly ascertained when compared with no or other interventions. Due to the relatively low incidence of brain tumours, investigators should consider multi-centre collaboration to ensure that studies are adequately powered to detect a difference. The following types of studies should be considered:

- To reduce the patient interval: studies comparing the effects of a regional campaign in one area with another area that is not exposed to the intervention;
- To reduce the doctor or primary care interval: studies comparing new pathways (e.g. fast access clinic) to refer people in one region with another region without the intervention (control); or 'point of care' randomisation to a given pathway, such as (a) open access MRI, or (b) neurology referral, with the end point of time to scanning diagnosis;
- To reduce the secondary care interval: randomisation of referral centres to a new protocol-based referral for expedited imaging versus the usual pathway; or randomisation to central imaging centres compared with a standard pathway;
- To reduce the diagnostic interval: studies comparing the impact of new service developments (e.g. new scanners, more scanner time, direct access imaging) in regions with regions with no change in services.

The role of a serum-based blood test as a triage tool is currently undergoing evaluation in a clinical trial (Gray 2018). This intervention is aimed at reducing the primary care interval by identifying those people with suspicious symptoms most at risk of a brain tumour and prioritising them for further investigation.

Studies that determine whether early diagnosis impacts survival would be of interest.

What's new

Date	Event	Description
4 September 2020	Amended	Author order amended.

History

Protocol first published: Issue 3, 2020
Review first published: Issue 9, 2020

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. Theresa Lawrie and Therese Dowswell wrote the first draft of the review with input from other authors. Eve Tomlinson assisted with study selection. All authors approved the final version.

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Robin Grant: none known
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Internal sources

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External sources

- NIHR 16/144 Cochrane Programme Grant Scheme, UK

Differences between protocol and review

None.

Characteristics of studies

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abend 2010	This is a review looking at the assessment and management of secondary headaches in children and adolescents. There was no intervention, and the study was excluded as it did not meet study design criteria.
Abernethy 2008	This letter describes two post-intervention audits following the introduction of a 2-week referral guideline for people suspected of having cancer, and referred to an outpatient neurology clinic. There was no control group, and the study is not eligible for inclusion in the review as it did not meet study design criteria.
Aghi 2015	This is a review looking at patients with newly diagnosed, WHO grade 2 oligodendroglioma, astrocytoma, or oligo-astrocytoma, or imaging suggestive of these. The study focused on the accuracy of diagnosis; there was no intervention. The study is not eligible for inclusion in the review as it did not meet study design criteria.
Ahmad 2009	This is a retrospective study examining the introduction of a rapid access neurovascular clinic (TIA). There was no control group, and the study is not eligible for inclusion in the review as it did not meet study design criteria.
Ahrensberg 2016	This is a retrospective case control study exploring the use of primary care pre-cancer diagnosis services in adolescents and young adults. There was no intervention or control group, and the study is not eligible for inclusion in the review as it did not meet study design criteria.
Al-Okaili 2006	This is a descriptive review of imaging techniques for brain tumours in adults. It is not eligible for inclusion in the review as it did not meet study design criteria.
Albert 2016	This is a review of imaging techniques, providing recommendations for PET imaging in gliomas. The focus was on tumour differentiation. It is not eligible for inclusion in the review as it did not meet study design criteria.
Altindag 2017	This is a review of management and treatment of epilepsy in children. There was no intervention. There was no control group, and it is not eligible for inclusion in the review as it did not meet study design criteria.
Asimos 2014	This is a retrospective study evaluating the sensitivity and specificity of two out-of-hospital stroke diagnosis screening tools. It is not eligible for inclusion in the review as it did not meet study design criteria.
Bachli 2018	This is a laboratory study analysing 13 paediatric CNS tumour samples. It is not eligible for inclusion in the review as it did not meet study design criteria.
Barisic 2012	This is a description of a Croatian guideline outlining the diagnosis and treatment of headaches in children. There was no intervention or control group, and it is not eligible for inclusion in the review as it did not meet study design criteria. The original paper was in Croatian, and we made the assessment of eligibility based on an abstract in English.
Bartleson 2006	This is a review discussing the management of people with headache. There was no intervention. The study had no control group, and it is not eligible for inclusion in the review as it did not meet study design criteria.

Study	Reason for exclusion
Baughan 2011	This is a retrospective case review of urgent, suspected cancer referrals over a 6-month period. There was no control group, and it is not eligible for inclusion in the review as it did not meet study design criteria.
Bergqvist 2017	This is a retrospective register-based study looking at the most common intracranial tumour types. There was no intervention, and the study had no control group. It is not eligible for inclusion in the review as it did not meet study design criteria.
Bhat 2011	This is a consensus report prepared after a national consultation on paediatric brain tumours in India in 2008. It was not eligible for inclusion in the review as it did not meet study design criteria.
Brat 2008	This is a review assessing the role of neuropathology in the diagnosis of malignant glioma. It is not eligible for inclusion in the review as it did not meet study design criteria.
Braun 2006	This is a retrospective study looking at the process of diagnosis in children with stroke. There was no intervention and the study had no control group. It is not eligible for inclusion in the review as it did not meet study design criteria.
Brouwers 2009	This is a systematic review exploring the optimal organisation for the delivery of diagnostic cancer services. It is not eligible for inclusion in the review as it did not meet study design criteria.
Cahill 2015	This is a systematic review and guideline looking at the role of neuropathology in the management of people with diffuse low grade glioma. It is not eligible for inclusion in the review as it did not meet study design criteria.
Carter 2007	This is a review exploring the use of CT and MRI imaging in the characterisation of intracranial mass lesions. It is not eligible for inclusion in the review as it did not meet study design criteria.
Chenevert 2006	This is a descriptive article discussing diffusion imaging. It is not eligible for inclusion in the review as it did not meet study design criteria.
Chiesa 2019	This is a conference abstract discussing the OMNYBuS project, which aimed to investigate the impact of multidisciplinary meetings in brain tumour management. There was no control group, and it is not eligible for inclusion in the review as it did not meet study design criteria.
Chrastina 2011	This is a descriptive study of the use of a biopsy technique to assist diagnosis of brain tumours. The study had no control group and it is not eligible for inclusion in the review as it did not meet study design criteria.
Cianfoni 2007	This is a descriptive article discussing the principles, technique and applications of brain perfusion CT imaging. It is not eligible for inclusion in the review as it did not meet study design criteria.
Cote 2017	This is an article discussing the use of MRI for uncomplicated headache. It is not eligible for inclusion in the review as it did not meet study design criteria.
Cowan 1999	This study was of an ineligible intervention (CT scan with and without contrast) and was also excluded as it was pre-2000, and the review search strategy stated that only studies published after 2000 would be considered.
Cross 2006	This is a descriptive expert commentary on the referral, diagnosis, and management of children with epilepsy for surgery. It is not eligible for inclusion in the review as it did not meet study design criteria.
Daverio 2016	This is a retrospective study exploring process and participant factors associated with the type of, and timing to neuroimaging in childhood arterial ischaemic stroke in the emergency department. There was no intervention and the study had no control group. It is not eligible for inclusion in the review as it did not meet study design criteria.
Davies 1997	This clinical practice guideline was excluded on study design and also because it was pre-2000, and the review search strategy stated that only studies published after 2000 would be considered.
Davies 2002	This is a prospective case review looking at infants under one year of age, presenting to an emergency department after life-threatening events. There was no intervention or control group. It is not eligible for inclusion in the review as it did not meet study design criteria.
Davis 2008	This is a review discussing issues around diagnosis in brain tumour studies. It it is not eligible for inclusion in the review as it did not meet study design criteria.

Study	Reason for exclusion
Dommett 2019	This is a retrospective study assessing clinical pathways for teenagers and young adults in a regional cancer service. There was no intervention or control group and it is not eligible for inclusion in the review as it did not meet study design criteria.
Duranovic 2008	This is an article discussing diagnostic procedures in paediatric migraines. There was no intervention or control group, and it is not eligible for inclusion in the review as it did not meet study design criteria.
Dutto 2009	This is a before-after study exploring the impact of a clinical pathway, implemented in 2006, on adults presenting to the emergency department with atraumatic headache. The study compared a time period before the clinical pathway was implemented with a time period after implementation. It is not a controlled study, and the focus is not on brain tumours. It is not eligible for inclusion in the review as it did not meet study design criteria.
ESMO 2007	This is an article outlining clinical recommendations from a guidelines group for people with malignant glioma. It is not eligible for inclusion in the review as it did not meet study design criteria.
Faehndrich 2011	This is a review about the use of MRI in space-occupying brain lesions. It is not eligible for inclusion in the review as it did not meet study design criteria.
Ferro 2017	This is a review exploring the diagnosis of epilepsy, treatment of epilepsy, and rare causes of stroke. There was no intervention or control group, and it is not eligible for inclusion in the review as it did not meet study design criteria.
Fouke 2015	This is a review and clinical guideline for the role of imaging in the management of adults with diffuse low-grade glioma. It is not eligible for inclusion in the review as it did not meet study design criteria.
Fowler 2004	This is a review and clinical guideline for headache in older adults. It is not eligible for inclusion in the review as it did not meet study design criteria.
Frappaz 2003	This is an article outlining recommendations for management of intracranial glioma. It is not eligible for inclusion in the review as it did not meet study design criteria.
Friedman 2011	This is a review and commentary about the management of people with headache in the acute care setting. It is not eligible for inclusion in the review as it did not meet study design criteria.
Furtwangler 2014	This is an article giving an overview of diagnosis and treatment of paediatric intracranial tumours. It is not eligible for inclusion in the review as it did not meet study design criteria.
Gago-Veiga 2017	This is an article discussing recommendations of the Spanish Society of Neurology's Headache Study Group, specifically focusing on the management of people with secondary headache, and other craniofacial pain, in the emergency department and primary care. It is not eligible for inclusion in the review as it did not meet study design criteria.
Gaillard 2011	This is a review and commentary of guidelines for imaging in people with epilepsy. It is not eligible for inclusion in the review as it did not meet study design criteria.
Gaini 2004a	This is an article discussing the categorisation and diagnostic options for people presenting with headaches in the emergency department. It is not eligible for inclusion in the review as it did not meet study design criteria.
Galiano Fragua 2011	This is a discussion paper, in Spanish, on a protocol for diagnosis and management of status epilepticus that does not meet the review inclusion criteria.
Giguere 2012	This is a Cochrane Review looking broadly at the effect of printed educational materials on professional practice and healthcare outcomes. It is not eligible for inclusion in the review as it did not meet study design criteria.
Gocan 2016	This is a retrospective data analysis of differences in practice and referral type across five stroke prevention clinics. It is not a controlled before-after study. It is not eligible for inclusion in the review as it did not meet study design criteria.
Grant 2017	This conference abstract describes the development of a rapid, GP referral system for people presenting with headache. The system enables GPs to directly refer people for diagnostic testing (optometry and CNS imaging). Evaluation of the referral system was not reported. The report did not meet study inclusion criteria.
Gray 2018	This is a model-based health pre-trial economic assessment of the role of spectroscopic technology in the diagnosis of brain tumours, explored in primary and secondary care neuroimaging in the UK and USA. The authors used proof-of-concept studies and modelling. It is not related to an intervention study. It is not eligible for inclusion in the review as it did not meet study design criteria.

Study	Reason for exclusion
Griffiths 2005	This is a case series of adults with localisation-related epilepsy in the UK undergoing MRI, using the same imaging tool: MR imaging at 3.0 T. There is no control group. It is not eligible for inclusion in the review as it did not meet study design criteria.
Grooss 2016	This is a population-based cohort study using prospectively collected data from Danish nationwide registers, to explore the rate of change of general practitioner in people with and without cancer. It is not eligible for inclusion in the review as it did not meet study design criteria.
Guilfoyle 2011	This is a retrospective before-after study looking at the management of glioma before and after the introduction of Improving Outcomes Guidance from NICE UK, in the Anglian Cancer Network. It was not a controlled study, and it is not eligible for inclusion in the review as it did not meet study design criteria.
Halperin 1996	This study was excluded as it was pre-2000 and the review search strategy stated that only studies published after 2000 would be considered.
Handschu 2015	This study used a retrospective survey of 1500 tele-consultations between October 2008 and September 2009, from a large, tele-stroke network in Germany, for people with and without stroke. It is not eligible for inclusion in the review as it did not meet study design criteria.
Haneef 2010	This is a before-after study study using referral data from people with temporal lobe epilepsy, to see if the introduction of a guideline led to change in referral patterns to a surgical epilepsy centre. It is not eligible for inclusion in the review as there was no control group and it did not meet study design or participant criteria.
Harada 2007	This is an article discussing the diagnosis of brain lesions and imaging techniques. It is not eligible for inclusion in the review as it did not meet study design criteria.
Harris 2000	This is a case series looking at whether simple clinical criteria can be usefully applied to people in the emergency department, to target those most likely to require an urgent cranial CT scan. It is not eligible for inclusion in the review as it did not meet study design criteria.
Haswali 2015	This is a discussion paper about American guidelines for neuroimaging of people with headaches. It is not an intervention study, and it is not eligible for inclusion in the review as it did not meet study design criteria.
Hatzitolios 2008	This is a retrospective study, using information from 362 elderly people hospitalised at a stroke centre between 2005 and 2007, to see if their final diagnosis agreed with initial diagnosis of stroke, on admission. It is not eligible for inclusion in the review as it did not meet study design or participant criteria.
Jiang 2016	This is a description of a Chinese clinical guideline about adults with diffuse glioma. It is not eligible for inclusion in the review as it did not meet study design criteria.
Kabbouche 2010	This is a discussion paper about the management of children and adolescents presenting with headache in an acute setting. It is not eligible for inclusion in the review as it did not meet study design criteria.
Kahn 2014	This is a review and commentary about the management of headache. It is not eligible for inclusion in the review as it did not meet study design criteria.
Kernick 2009	This is a historical cohort study using data from the UK GP research database for children aged 5 to 17 years presenting with headache in primary care. The study compared children with headache to matched controls to explore management, e.g. number of consultations. It is not eligible for inclusion in the review as it did not meet study design criteria.
Knox 2012	This is a description of a case series of people admitted to an acute medical unit due to acute headache, between January and December 2011. The study aimed to better characterise people referred to acute care with headache, by taking a sample and looking at investigations undertaken. It is not eligible for inclusion in the review as it did not meet study design criteria.
Langdon 2017	This is a commentary and overview about paediatric headache. It is not eligible for inclusion in the review as it did not meet study design criteria.
Lange 2011	This is a comparison of the characteristics and diagnoses of people attending the emergency department with neurological symptoms. There was no intervention, and the study had no control group. It is not eligible for inclusion in the review as it did not meet study design criteria.
Langen 2008	This is a review of imaging techniques for people with glioma. It is not eligible for inclusion in the review as it did not meet study design criteria.

Study	Reason for exclusion
Langen 2011	This is a review and guidance for imaging techniques for people with glioma. It is not eligible for inclusion in the review as it did not meet study design criteria.
Langen 2017	This is a review of neuro-oncology imaging techniques for people with brain tumours. It is not eligible for inclusion in the review as it did not meet study design criteria.
Langen 2018	This is an article giving an update on amino acid PET for brain tumours. It is not eligible for inclusion in the review as it did not meet study design criteria.
Larner 2006	This is a discussion article about referral guidelines for suspected brain tumour. It is not eligible for inclusion in the review as it did not meet study design criteria.
Laursen 2012	This is a descriptive case series using a local clinical database and retrospective review of patient records and radiology reports to explore the implementation of the Integrated Brain Cancer Pathway. There is no control group, and it is not eligible for inclusion in the review as it did not meet study design criteria.
Laursen 2012a	This is a descriptive case series using a local clinical database and retrospective review of patient records and radiology reports to explore the implementation of the Integrated Brain Cancer Pathway. The study looked at the diagnostic process over eight quarters following the implementation of the pathway. It is not eligible for inclusion in the review as it did not meet study design criteria.
Le Bas 2005	This is a commentary on the use of perfusion MR imaging in people with brain tumours. It is not eligible for inclusion in the review as it did not meet study design criteria.
Leal 2019	This is a discussion about people with acute stroke in the emergency unit. It is not eligible for inclusion in the review as it did not meet study design criteria.
Lee 2018	This abstract describes a retrospective audit examining compliance with the two-week wait guideline. It is not eligible for inclusion in the review as it did not meet study design criteria.
Llewellyn 2018	This is a qualitative study of the experiences of people with brain tumours, their families, and healthcare professionals. It is not eligible for inclusion in the review as it did not meet study design criteria.
Long 2017	This is a review looking at the management of people with transient ischaemic attack in the emergency department. It is not eligible for inclusion in the review as it did not meet study design criteria.
McCrea 2013	This is a commentary using a scenario of new referral to an outpatient clinical, to give a practical overview of management of children under 5 years of age with headache. It is not eligible for inclusion in the review as it did not meet study design criteria.
Medina 2002	This is a discussion paper about imaging in paediatric headache. It is not eligible for inclusion in the review as it did not meet study design criteria.
Mirsky 2017	This is an expert consensus on diagnosis and management of suspected stroke in children. It is not eligible for inclusion in the review as it did not meet study design or participant criteria.
Mohammad 2016	This is a retrospective study assessing the NICE 'two-week wait' guidelines for CNS cancer. There is no control group and it is not eligible for inclusion in the review as it did not meet study design criteria.
Molassiotis 2010	This is a qualitative study of 75 people with cancer, exploring their experience of cancer diagnosis. It is not eligible for inclusion in the review as it did not meet study design criteria.
Moller-Hartmann 2002	This is a retrospective case review of use of MRI versus proton MRI in the differentiation of brain mass lesions. It is not eligible for inclusion in the review as it did not meet study design criteria.
Munoz-Ceron 2019	This is an evaluative study of the ICHD-3 criteria for differentiating between primary and non-primary headaches in all people with headache at a triage unit in an emergency department. There was no control group. It is not eligible for inclusion in the review as it did not meet study design criteria.
Nahab 2012	This is a before-after cohort study, comparing before and after the implementation of an accelerated diagnostic protocol for all people presenting with transient ischaemic stroke to an emergency department's observation unit, over an 18month period. It was not a controlled study and it is not eligible for inclusion in the review as it did not meet study design or participant criteria.
Penfold 2017	This is a discussion article about diagnosing adult primary brain tumours. It is not eligible for inclusion in the review as it did not meet study design criteria.

Study	Reason for exclusion
Pengiran 2003	This is a case review of people referred to three hospitals, with suspected neurological cancers, via a two-week wait referral system for brain tumours. There was no control group and it is not eligible for inclusion in the review as it did not meet study design criteria.
Pitfield 2012	This is a commentary piece about the management of raised intracranial pressure in children. It is not eligible for inclusion in the review as it did not meet study design criteria.
Richards 2009	Not a research study but a supplement bringing together research on England's National Awareness and Early Diagnosis Initiative.
Rittman 2012	This is a before-after study assessing the implementation and impact of NICE guidelines for the referral of any suspected brain tumour to MDT. It was not controlled, and the focus was not on time-to-diagnosis. It is not eligible for inclusion in the review as it did not meet study design criteria.
Scharl 2017	Not a study but a German commentary on the European Association for Neuro-Oncology guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas.
Shack 2016	This is a before-after study evaluating whether an institutional acute stroke protocol could accelerate the diagnosis and secondary treatment of paediatric stroke. It is not eligible for inclusion in the review as it did not meet study design or participant criteria.
Shanmugavadivel 2016	This is a review of the HeadSmart campaign. It is not eligible for inclusion in the review as it did not meet study design criteria.
Shanmugavadivel 2020	This is a further publication of the HeadSmart study, which did not meet the review study design criteria, as it lacked a concurrent control group.
Simpson 2010	This is a retrospective study exploring the impact of GP direct-access computerised tomography for the investigation of chronic daily headache. It is not eligible for inclusion in the review as it did not meet study design criteria.
Stupp 2009	This is a guideline, clinical recommendation for the management of malignant glioma. It is not an intervention study, and it is not eligible for inclusion in the review as it did not meet study design criteria.
Tatencloux 2017	This is a retrospective case review of people under 25 years of age, in Institut Curie, during one year. It looked at the treatment of children and adolescents, and aimed to describe care pathways between symptoms and consultation. It is not eligible for inclusion in the review as it did not meet study design criteria.
Thust 2018	This is a survey, distributed to the European Society of Neuroradiology members about glioma imaging. It is not eligible for inclusion in the review as it did not meet study design criteria.
Titlic 2008	This is a test accuracy study of clinical assessment in diagnosing various brain conditions. It is excluded because it does not meet study design and participant criteria.
Umotong 2017	This abstract describes a retrospective audit of time from referral for diagnostic imaging to treatment. It is not eligible for inclusion in the review as it did not meet study design criteria.
Vedelo 2018	This is a qualitative study of four people with brain tumour, looking at their experience. It is not eligible for inclusion in the review as it did not meet study design criteria.
Walker 2015	This is a conference paper in neuro-oncology, outlining the HeadSmart campaign, as also detailed in the HeadSmart 2016 paper. It is not eligible for inclusion in the review as it did not meet study design criteria.
Walker 2016	This is a before-after study exploring the impact of the *HeadSmart: Be Brain Tumour Aware* campaign, which was launched in June 2011 across the UK, and aimed to reduce the total diagnostic interval from a pre-campaign time point in 2006. The study also sought to improve professional and public awareness of paediatric CNS tumours. It was not a controlled study, and it is not eligible for inclusion in the review as it did not meet study design criteria.
Wan 2017	This abstract describes a systematic review examining the impact of hospital and surgeon characteristics on outcomes for people with brain tumour. It is not eligible for inclusion in the review as it did not meet study design criteria.

Study	Reason for exclusion
Webb 2015	This is a retrospective case review of people who had urgent brain cancer referrals to the neurology service at a British district general hospital, between January 2009 and September 2013. The study evaluated the brain cancer referral pathway, and sought to identify the determinants of referrals resulting in significant neurological diagnoses after specialist review. There was no control group. It is not eligible for inclusion in the review as it did not meet study design criteria.
Weddell 2017	This abstract describes a retrospective audit examining the time to diagnosis for 50 people. It is not eligible for inclusion in the review as it did not meet study design criteria.
Weller 2014	This is a guideline for anaplastic glioma and glioblastoma. It is not eligible for inclusion in the review as it did not meet study design criteria.
Weller 2017	This is a guideline, and not a research study. It is not eligible for inclusion in the review as it did not meet study design criteria.
Williams 2007	This is an audit of radiotherapy dose fractionation, access, and waiting times for people with cancer in the UK, in 2005. It is not eligible for inclusion in the review as it did not meet study design criteria.
Wilne 2007	This is a review of presenting symptoms for children with intracranial tumours. It is not eligible for inclusion in the review as it did not meet study design criteria.
Wilne 2010	This is guidance, a review, and results of a Delphi process workshop about referral and management of children with brain tumours, and recommendations for practice. It is not eligible for inclusion in the review as it did not meet study design criteria.
Zhou 2018	This is a retrospective analysis of route to diagnosis data for 66,9220 people with 35 cancers, diagnosed between 2006 and 2010, following either fast track or routine primary to secondary care referral. This was not a controlled study. It is not eligible for inclusion in the review as it did not meet study design criteria.
Zienius 2019	This retrospective study identified 2938 referrals for direct-access CT scans between 2010 and 2015, to explore the predictive value of the Kernick and NICE 2005 referral guidelines. It is not eligible for inclusion as it did not meet the study design criteria.

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. (2000* or 2001* or 2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).ed.
32. 30 and 31
33. (protocol* adj5 (referral* or algorithm* or strateg* or diagnos*)).mp.
34. 29 and 33
35. exp Stroke/
36. (transient ischaemic attack* or TIA* or stroke* or cerebrovascular accident* or CVA*).mp.
37. exp Epilepsy/
38. (seizure* or epilep*).mp.
39. exp Headache/
40. ((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.
41. 35 or 36 or 37 or 38 or 39 or 40
42. 34 and 41
43. 32 or 42

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 for effectiveness evidence

1. exp brain tumor/
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. practice guideline/
6. exp clinical pathway/
7. ((clinical* or treatment* or diagnos* or practice or critical or care or cancer) adj5 (guideline* or guidance* or pathway*)).ti,ab.
8. clinical decision making/
9. (care adj (map* or plan* or interval*)).ti,ab.
10. exp health care planning/
11. public health/
12. professional standard*.tw.
13. protocol compliance/
14. health promotion/
15. clinical protocol/
16. exp consensus development/
17. (consensus adj3 (develop* or conference*)).mp.
18. 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
19. exp early diagnosis/
20. "Referral and Consultation"/
21. ((primary or patient or doctor or secondary* or system or total or diagnostic or pre-diagnostic or treatment or time) adj3 interval*).ti,ab.
22. (cancer waiting time* or total pre-therapy interval* or TPTI).mp.
23. ((direct access* or direct-access* or open access* or open-access* or OACT) adj5 (diagnos* or detect* or interven* or investigat* or refer*)).mp.
24. diagnostic procedure/
25. diagnos*.ti,ab.
26. 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 4 and 18 and 26
28. (2000* or 2001* or 2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).dd.
29. 27 and 28
30. (protocol* adj5 (referral* or algorithm* or strateg* or diagnos*)).mp.
31. 26 and 30
32. exp cerebrovascular accident/
33. (transient ischaemic attack* or TIA* or stroke* or cerebrovascular accident* or CVA*).mp.
34. exp epilepsy/
35. (seizure* or epilep*).mp.
36. exp headache/
37. ((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.
38. 32 or 33 or 34 or 35 or 36 or 37
39. 31 and 38
40. 29 or 39

CENTRAL strategy for effectiveness evidence

#1 MeSH descriptor: [Brain Neoplasms] explode all trees
#2 (brain or intracranial or intra-cranial or cerebr*) near/5 (cancer* or tumor* or tumour*

or neoplas* or carcinoma* or metastat* or malignan*)
#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*)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Practice Guidelines as Topic] explode all trees
#6 MeSH descriptor: [Critical Pathways] explode all trees
#7 ((clinical* or treatment* or diagnos* or practice or critical or care or cancer) near/5 (guideline* or guidance* or pathway*))
#8 MeSH descriptor: [Clinical Decision-Making] this term only
#9 (care near (map* or plan* or interval*))
#10 MeSH descriptor: [Health Planning Guidelines] this term only
#11 MeSH descriptor: [Health Plan Implementation] this term only
#12 MeSH descriptor: [Public Health] this term only
#13 professional standard
#14 MeSH descriptor: [Guideline Adherence] this term only
#15 MeSH descriptor: [Practice Guidelines as Topic] explode all trees
#16 MeSH descriptor: [Health Promotion] this term only
#17 MeSH descriptor: [Clinical Protocols] this term only
#18 MeSH descriptor: [Consensus Development Conferences as Topic] explode all trees
#19 (consensus near/3 (develop* or conference*))
#20 #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
#21 MeSH descriptor: [Early Diagnosis] explode all trees
#22 MeSH descriptor: [Referral and Consultation] explode all trees
#23 ((primary or patient or doctor or secondary* or system or total or diagnostic or pre-diagnostic or treatment or time) near/3 interval*)
#24 (cancer waiting time* or total pre-therapy interval* or TPTI)
#25 ((direct access* or direct-access* or open access* or open-access* or OACT) near/5 (diagnos* or detect* or interven* or investigat* or refer*))
#26 MeSH descriptor: [Diagnostic Techniques and Procedures] this term only
#27 diagnos*
#28 #21 or #22 or #23 or #24 or #25 or #26 or #27
#29 #4 and #20 and #28
#30 MeSH descriptor: [Stroke] explode all trees
#31 transient ischaemic attack* or TIA* or stroke* or cerebrovascular accident* or CVA*
#32 MeSH descriptor: [Epilepsy] explode all trees
#33 seizure* or epilep*
#34 MeSH descriptor: [Headache] explode all trees
#35 headache*
#36 (headache* or seizure* or epilep* or transient ischaemic attack* or TIA* or stroke* or cerebrovascular accident* or CVA*) near/5 (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)
#37 #30 or #31 or #32 or #33 or #34 or #35 or #36
#38 protocol* near/5 (referral* or algorithm* or strateg* or diagnos*)
#39 #28 and #38
#40 #39 and #37
#41 #29 or #40

MEDLINE search strategy for economic 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. (2000* or 2001* or 2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).ed.
32. 30 and 31
33. (protocol* adj5 (referral* or algorithm* or strateg* or diagnos*)).mp.
34. 29 and 33
35. exp Stroke/
36. (transient ischaemic attack* or TIA* or stroke* or cerebrovascular accident* or CVA*).mp.
37. exp Epilepsy/
38. (seizure* or epilep*).mp.
39. exp Headache/
40. ((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.
41. 35 or 36 or 37 or 38 or 39 or 40
42. 34 and 41
43. 32 or 42
44. economics/
45. exp "costs and cost analysis"/
46. economics, dental/
47. exp "economics, hospital"/
48. economics, medical/
49. economics, nursing/
50. economics, pharmaceutical/
51. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
52. (expenditure$ not energy).ti,ab.
53. (value adj1 money).ti,ab.
54. budget$.ti,ab.
55. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56. ((energy or oxygen) adj cost).ti,ab.
57. (metabolic adj cost).ti,ab.
58. ((energy or oxygen) adj expenditure).ti,ab.
59. 56 or 57 or 58
60. 55 not 59
61. letter.pt.
62. editorial.pt.
63. historical article.pt.
64. 61 or 62 or 63
65. 60 not 64
66. Animals/
67. Humans/
68. 66 not (66 and 67)
69. 65 not 68
70. 43 and 69

Key

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
ab=abstract
sh=subject heading
ti=title pt=publication type

Embase strategy for economic evidence

1. exp brain tumor/
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. practice guideline/
6. exp clinical pathway/

7. ((clinical* or treatment* or diagnos* or practice or critical or care or cancer) adj5 (guideline* or guidance* or pathway*)).ti,ab.
8. clinical decision making/
9. (care adj (map* or plan* or interval*)).ti,ab.
10. exp health care planning/
11. public health/
12. professional standard*.tw.
13. protocol compliance/
14. health promotion/
15. clinical protocol/
16. exp consensus development/
17. (consensus adj3 (develop* or conference*)).mp.
18. 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
19. exp early diagnosis/
20. "Referral and Consultation"/
21. ((primary or patient or doctor or secondary* or system or total or diagnostic or pre-diagnostic or treatment or time) adj3 interval*).ti,ab.
22. (cancer waiting time* or total pre-therapy interval* or TPTI).mp.
23. ((direct access* or direct-access* or open access* or open-access* or OACT) adj5 (diagnos* or detect* or interven* or investigat* or refer*)).mp.
24. diagnostic procedure/
25. diagnos*.ti,ab.
26. 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 4 and 18 and 26
28. (2000* or 2001* or 2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).dd.
29. 27 and 28
30. (protocol* adj5 (referral* or algorithm* or strateg* or diagnos*)).mp.
31. 26 and 30
32. exp cerebrovascular accident/
33. (transient ischaemic attack* or TIA* or stroke* or cerebrovascular accident* or CVA*).mp.
34. exp epilepsy/
35. (seizure* or epilep*).mp.
36. exp headache/
37. ((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.
38. 32 or 33 or 34 or 35 or 36 or 37
39. 31 and 38
40. 29 or 39
41. Health Economics/
42. exp Economic Evaluation/
43. exp Health Care Cost/
44. pharmacoeconomics/
45. 41 or 42 or 43 or 44
46. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
47. (expenditure$ not energy).ti,ab.
48. (value adj2 money).ti,ab.
49. budget$.ti,ab.

50. 46 or 47 or 48 or 49
51. 45 or 50
52. letter.pt.
53. editorial.pt.
54. note.pt.
55. 52 or 53 or 54
56. 51 not 55
57. (metabolic adj cost).ti,ab.
58. ((energy or oxygen) adj cost).ti,ab.
59. ((energy or oxygen) adj expenditure).ti,ab.
60. 57 or 58 or 59
61. 56 not 60
62. 40 and 61

Key

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
ab=abstract
sh=subject heading
ti=title pt=publication type

Appendix 2. ‘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 were selectively reported
- Unclear risk of bias, e.g. it is unclear whether outcomes were 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, we will record 'no information' as the judgement.

1. Possible confounding

We will assess baseline differences, possible post-baseline differences in prognostic factors, or switching interventions.

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

We will assess whether, and the extent to which deviations from the protocol or intervention/s allocated occur.

5. Bias due to missing data

We will assess differential loss to follow-up that may relate to prognostic factors.

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

We will assess how investigators select and report results.

References

References to studies excluded from this review

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Figures and tables

Figure 1

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

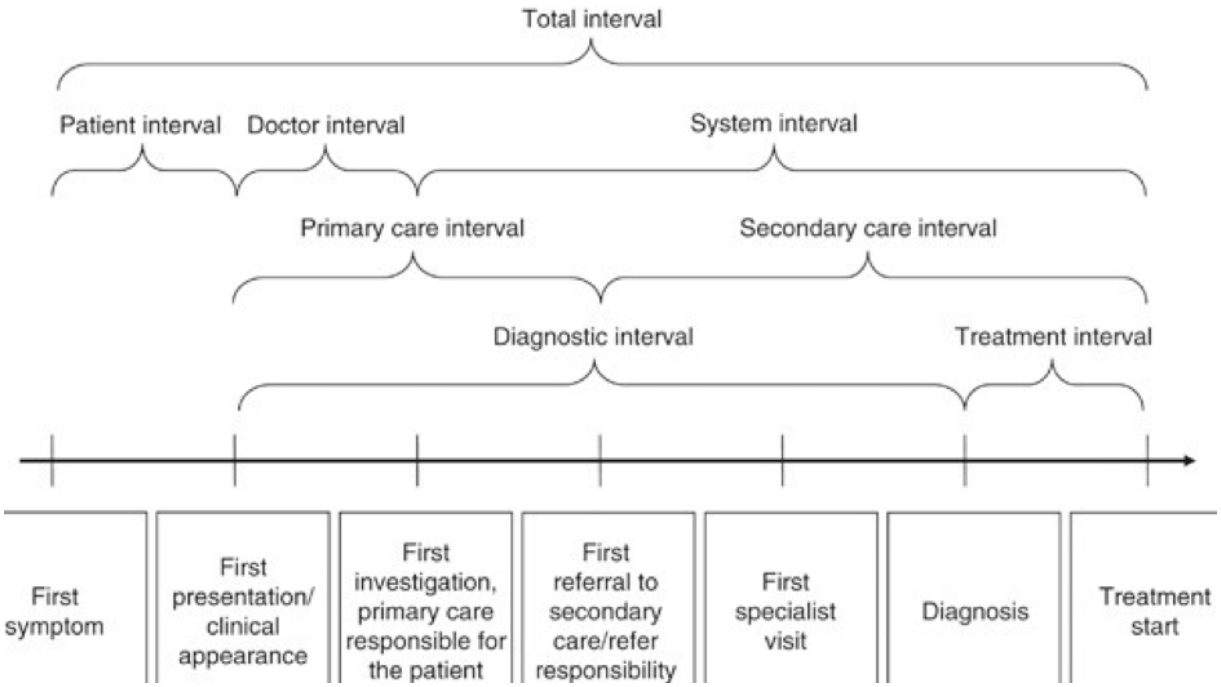
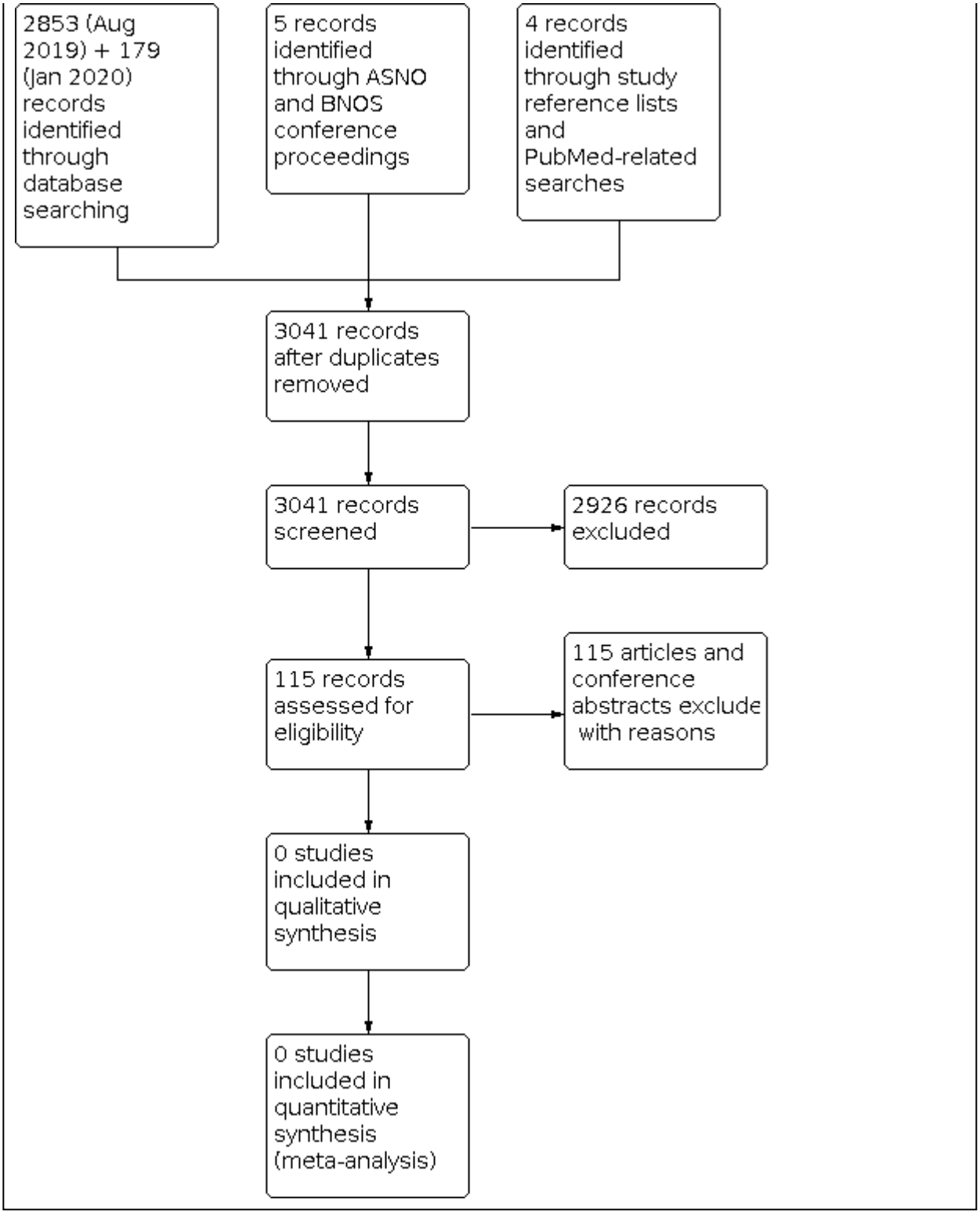


Figure 2

PRISMA flow diagram of studies identified for the review


2853 (Aug 2019) + 179 (Jan 2020) records identified through database searching
5 records identified through ASNO and BNOS conference proceedings
4 records identified through study reference lists and PubMed-related searches
3041 records after duplicates removed
3041 records screened
2926 records excluded
115 records assessed for eligibility
115 articles and conference abstracts exclude with reasons
0 studies included in qualitative synthesis
0 studies included in quantitative synthesis (meta-analysis)