Brain tumours (primary) and brain metastases in adults
Consultation on draft guideline - Stakeholder comments table
12/01/2018 to 23/02/2018

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Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Association of British Neurologists	ER A	23	8	The guideline is based on clinical experience of the committee, yet no research recommendations were made on this topic, despite the level of evidence at best being low. Surely this is an area where further higher quality research is necessary?	Thank you for your comment. Although the evidence was limited, the committee was satisfied that it was sufficient to justify recommending MR imaging in the investigation of a suspected brain tumour. The committee did not prioritise this topic for a research recommendation as they believed that various different advanced imaging techniques are already so incorporated into clinical practice that no one will obtain funding for conducting such research. Additionally, they were not convinced the potential gains from a marginal trial on advanced techniques were sufficient to justify recommending research in this area at the expense of any of their other prioritised recommendations.
Association of British Neurologists	ER A	23	26	Is there evidence that early identification confers benefit beyond lead-time bias? Should this not be an area for further research – e.g. randomisation to a treatment approach of intervention vs further imaging and treatment if findings confirmed at 3 months.	Thank you for your comment. Research recommendations can only be prioritised for those questions that were searched in the guideline, therefore the research recommendation that is suggested in this comment cannot be included.
Association of British Neurologists	ER A	24	15	The committee believed the evidence was robust? This is not reflected in the expert discussion or the level of evidence.	Thank you for your comment. This has been rephrased to make it clearer that the committee considered the evidence an adequate basis on which to make recommendations given the difficulty of conducting more definitive research.
Association of British Neurologists	GL	5	1.2.2	"Consider maximal safe resection at first radiological diagnosis" Consider changing this statement to "consider early maximal safe resection" rather than at "first radiological diagnosis". For low grade glioma (LGG) there is not the same urgency to operate immediately (unlike High Grade Glioma). Though initial radiological diagnosis may be suggestive of a LGG a subsequent follow up scan (eg at 3 months) can clarify the situation further and on occasion change the initial diagnosis.	Thank you for your comment. This has been changed to 'as part of initial management (within 6 months of radiological diagnosis)' to allow time to clarify the situation if appropriate.
Association of British Neurologists	GL	6	1.2.8	"Consider active monitoring for people who are aged around 40 and under with IDH-mutated low-grade glioma and have no residual tumour on postoperative MRI." Is the word "consider" correct in this context given that LGG are likely to recur? This could be changed to "Commence active monitoring for people who are aged around 40 and under with IDH-mutated low-grade glioma and have no residual tumour on postoperative MRI."	Thank you for your comment. The words 'consider' and 'offer' are used to denote different strengths of evidence underpinning recommendations. In this case the committee did not have high quality evidence that active monitoring was the optimal management strategy, but did have a high degree of consensus on the issue. They therefore used the weaker of the two recommendation forms ('consider') as they believed it was a good idea but did not have trial evidence to support this.
Association of British Neurologists	GL	6	1.2.6 and 1.2.7	Regarding radiotherapy and PCV treatment for LGG patients the evidence states less than 40 years with residual tumour or 40 years and over therefore is the word "around" required?	Thank you for your comment. The committee considered that the evidence did not support differential treatment for those, for example, aged 39.9 years and those aged 40.1 years, since the trial was not designed to detect such a difference. The committee therefore concluded a hard age cut-off could be an equality issue. Consequently the word 'around' allows clinicians to make a judgement based on the specific clinical presentation of the individual.
Association of British Neurologists	GL	9	1.2.19	The is a small typographical error with 2 commas "have a Karnofsky performance status greater than or equal to 70,, and"	Thank you, this has been corrected.
Association of British Neurologists	GL	9, 10	1.11.19 - 1.2.23	This could be clarified with a flow diagram	Thank you for your comment. A flow diagram is being produced for these recommendations and will be published alongside the guideline.
Association of British Neurologists	GL	10	1.2.27	We assume 1.2.27 should read "Advise people who have an initial diagnosis of grade IV glioma (glioblastoma) …" rather than "Advise people who have an initial diagnosis of grade III …"	Thank you for your comment. This has been corrected.
Association of British Neurologists	GL	12	1.2.36	"If a person has a radiologically-suspected enhancing high-grade glioma, ---- offer 5-amino-levulinic acid --- an adjunct to maximise resection at initial surgery." The studies were where the operator thought "complete resection" was possible. "Maximal" is in the eye of the beholder – 20% might be maximal in some. (If using maximal perhaps a definition e.g. (>90%) and why is 5-ALA "offer" and other two (ioMRI and ioUS 1.2.40 and 1.2.41 are only consider. Have the other two been shown to be less effective?	Thank you for your comment. This recommendation has been edited to say that 5-ALA should be offered if the surgical resection of all enhancing tumours is possible. Given the low quality of evidence, the committee chose to make weak recommendations with the exception of the recommendation for 5-ALA where an economic model developed for the guideline allowed them to make stronger recommendations.

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Association of British Neurologists	GL	12	12	The section on “Techniques for resection of glioma” does not mention the use of functional MRI to localise eloquent cortex and preserve function. This can be a useful addition to presurgery planning.	Thank you for your comment. No evidence for functional MRI was identified in the systematic review of the literature, and so the committee did not make recommendations on this topic.
Association of British Neurologists	GL	15	7-9	Table 3 Clarification would be welcomed regarding interval scanning for grade II 1p/19q non-codeleted, IDH mutated (astrocytoma) The table states “Grade II and Grade III 1p/19q codeleted, IDH mutated (oligodendroglioma)” and “Grade III 1p/19q non-codeleted, IDH-mutated (astrocytoma) and Grade IV (glioblastoma)” Does “Grade II and Grade III 1p/19q codeleted, IDH mutated (oligodendroglioma)” refer to all grade II LGG or just grade II oligodendroglioma? Given the shortened transformation time to a HGG for grade II 1p/19q non-codeleted, IDH mutated (astrocytoma) it could be argued that these should be included in the “Grade III 1p/19q non-codeleted, IDH-mutated (astrocytoma) and Grade IV (glioblastoma)” group.	Thank you for your comment. The table has been lengthened to include recommendations on grade II 1p/19q non-codeleted, IDH mutated glioma.
Association of British Neurologists	GL	15	7	“Table 3 Possible regular clinical review schedule for glioma depending on grade of tumour” Table 3 is a very useful addition to the guidelines. Should the table however be renamed as it is suggestion for follow up interval scanning rather than clinical review.	Thank you for your comment, and we are glad you believe Table 3 is a useful addition to the guideline. Recommendation 1.3.1 states that the scan should be discussed with the patient in the context of any changes to symptoms or goals, and therefore Table 3 is titled to highlight that these reviews should take place at around the same time as the interval scans.
Association of British Neurologists	GL	22	1	As per table 3 Table 7 is a very useful addition to the guidelines but again should the table be renamed as it is suggestions for follow up interval scanning rather than clinical review.	Thank you for your comment. It is the intent of the committee that clinical review would happen shortly after interval scanning, and therefore the table has been named to make this explicit.
Association of British Neurologists	GL	30	4.1.4	80% of LGG and 30-40% HGG (and many with meningioma and cerebral metastasis) develop epilepsy. On-going seizures and anti-epileptic medication can cause significant morbidity for patients with brain tumours. We note that there is a reference to the generic NICE epilepsy guidelines but feel that there are issues specific to the diagnosis and management of seizures in this patient group not covered in the guidelines e.g. avoiding enzyme inducing anti-epileptic drugs. We would welcome the inclusion of a recommendation for consideration of early referral to a neurologist for prompt diagnosis and management of seizures, including referral to an epilepsy specialist nurse.	Thank you for your comment. The evidence on brain-tumour specific interactions with epilepsy medication was not systematically searched, and therefore the committee are unable to make recommendations on this topic.
Association of British Neurologists	GL	30	4.1.7	“Explain to the person the implications of having a brain tumour on driving and any relevant legal consequences (for example if the person with the brain tumour has a responsibility to inform the DVLA).” The need to take into account the presence of on-going focal seizures or planned anti-epileptic drug reductions when providing their DVLA advice needs also to be considered.	Thank you for your comment. The committee believe the recommendation already encompasses the need to take into account the presence of on-going focal seizures and planned anti-epileptic drug reductions as part of explaining the implications on driving, and have amended the full guideline to make it explicit that this information should be discussed.
Brain and Spine Foundation	General	General	General	The Brain and Spine Foundation welcome the NICE Guideline Brain tumours (primary) and brain metastases in adults. The recognition of the unique challenges this group of people face when diagnosed with any type of brain tumour, is very welcome. Including them in the decision making and the person’s preference to treatments is also welcome. We cannot comment on the time line for follow up scans and appointments, but are concerned with the increasing number of people being diagnosed with brain tumours and metastases if the current services will be able to manage.	Thank you for your comment. The aim of NICE guidelines is to act as a guide regarding the services that should be commissioned and delivered for people with brain tumours. The committee therefore made recommendations relating to follow up scans and appointments, as well as other aspects of care, to ensure that a good standard of care is given to people with brain tumours. The committee always consider the health economic impact when making recommendations, even when no economic evidence has been identified or de novo analysis performed, as is the case for this recommendation. Consideration of cost effectiveness and resource use are documented in the Evidence Reports.
Brain and Spine Foundation	GL	30	22	4.1.5 The physical and psychological needs of both the person and carer will not remain static, so ongoing accessible support from a key worker or health professional is essential as many people have to travel considerable distances to the specialist centres.	Thank you for your comment. We are pleased you support the recommendation to make a key worker available.
Brain and Spine Foundation	GL	30	27	4.1.6 Identifying the appropriate time to give a person information written or spoken is very individual, as some will want information immediately on diagnosis and some will want to wait until further into their treatment. Also the quality of information must be taken into consideration, several organisations	Thank you for your comment. The full guideline has been updated with explanation that individualising information provision also includes considering the appropriate time to give a person information.

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				produce information on brain tumours through the NHS England Information Standard quality marker.	
Brain and Spine Foundation	GL	31	17	4.2 The neurorehabilitation assessment to identify the needs of the individual also needs to take into consideration the considerable distances people may need to travel to access these specialists.	Thank you for your comment. The committee believed that by recommending that assessment be consistent with the person's rehabilitation goals that distance from specialists would be taken into account. However to make this explicit the rationale and impact section has been amended to read that neurological rehabilitation is especially time consuming if the person with a tumour lives a long way from the rehabilitation centre, and that this should explicitly be considered.
Brain Tumour Research	GL	1	5	Whilst individual clinical roles are not identified in the guideline, we feel there should be a reference to Neuro-Oncology Clinical Nurse Specialists as this role is essential to the care of brain tumour patients. Currently brain tumour patients do not always have access to a CNS and this is a distinct contributing factor in their poor patient experience.	Thank you for your comment. The guideline has been amended to state that the key worker is often a clinical nurse specialist.
Brain Tumour Research	GL	33	8	Before finalising this guideline, we would ask the guideline committee to request a copy of the Department of Health and Social Care Task and Finish Working Group report on Brain Tumour Research and consider the recommendations set out. If any are found to be relevant to putting this guideline into practice, and promoting the research opportunities and responsibilities within clinical services, we would be happy to help bring the committee and relevant Working Group contacts together.	Thank you for your comment. NICE have a specific process for generating research recommendations, which ensures impartiality and that they are generated from the research evidence. This means that the committee cannot officially consider the Department of Health and Social Care Task and Finish Working Group report on Brain Tumour Research in drafting the guideline.
Brain Tumour Research	GL	33	22	Brain Tumour Research is pleased to see the consideration of new treatment combinations as without new innovative technologies, neuro-oncology teams are constantly relying on decades old treatments that fail to deliver the same outcomes as experienced by other site-specific cancer patient groups. Given that IDH wildtype gliomas are considered prognostically heterogeneous and do not have uniformly poor prognosis, we would suggest that this recommendation be amended to include grade II and grade III IDH wildtype gliomas. This would better allow the delineation of discrete favourable and unfavourable prognostic groups against the treatment outcomes within a single investigation. Clinicans in particular are presently struggling with those patients, unsure where the balance between over-treating and under-treating lies. A trial would enrol patient in situations of real equipoise and be highly legitimate and valuable.	Thank you for your comment. Research recommendations are drafted where there is an inability of the reviewed literature to answer the research question posed. Since evidence on the primary treatment for grade III glioma was not sought (since it was argued that it would very often be surgery) a research recommendation cannot be made for this group.
Brain Tumour Research	GL	36	12	Brain Tumour Research welcomes all efforts to research specific brain tumour types as many have been overlooked by multi-disciplinary research fields for decades, supporting the lack of progress in survival rates. After consulting with our own research and clinical contacts, we have received some feedback on the efficacy of clinical trials in radiotherapy for patients with grade 1 meningioma. As stated in the guideline, grade 1 meningioma have a slow-growth characteristic and the incidences of reoccurrence following partial resection is negligible. Factoring in these realities, would it even be practical to assemble a trial group of incompletely excised grade 1 meningioma patients within a feasible trial window? We suggest the committee review this recommendation, considering the biggest impact that could be achieved and any challenges involved in developing a trial of this nature. Feedback received included queries as to whether the fulfilment of this research question could be resource-heavy and very prolonged for limited patient gain – is there a good prospect of survival being increased? A more detailed rationale within the guideline is needed for all stakeholders to consider.	Thank you for your comment. The committee believe historic trials of the timing of radiotherapy in grade 1 meningioma have suffered from a lack of clinical equipoise. They also believe that radiotherapy and surgical techniques have advanced far enough that equipoise is now a realistic expectation. Therefore the committee believes that the trial they describe is feasible in a reasonable trial window, and that the historic inabilities of such trials to recruit should not be a reason to prevent investigation of this question now. The committee believe that because of the slow-growing characteristics of grade 1 meningioma there is a good chance of finding evidence of significant quality of life improvements (sufficient to justify the research) and at least a nontrivial chance of finding evidence of increase overall survival. More detail has been added to the section describing the importance of this research to help explain the committee's decision making.
Brain Tumour Research	GL	39	8	We welcome the reference to the standard practice to save tissue samples for biopsy, this has been an important development for pathological and molecular diagnoses and the development of personalised cancer treatments. However, we would have liked to see a focus on tissue samples for research	Thank you for your comment. The committee did not seek evidence on whether storing tissue for research (or participating in research more generally) was beneficial for specific patients, and so cannot make a recommendation on this topic.

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				purposes also. The guideline rightly sets out the poor survival rate for patients with malignant brain tumours and ultimately this can only be improved through pre-clinical studies and greater access to clinical trials. Secure access to viable brain tumour tissue samples is a critical component to this process and we know through our own research Centres of Excellence that by having clinical and research teams working closely with one another is this achieved. Whilst not all neuro-oncology clinical teams operate with close proximity to their research counterparts, a recommendation to establish a research tissue sample protocol nationally would be immensely helpful. If this is coincided with current clinical biopsy protocols then there would be little additional disruption to patients or healthcare professionals. Brain Tumour Research supports BRAIN UK, a network of 26 NHS and Academic Centres working together to provide CNS tissue for vital research. They provide a matching service for researchers requiring human tissue from disorders affecting the brain and neuromuscular system. They are happy to consider all types of studies from anywhere in the world. Rolled out integration between clinical teams across NHS England and networks such as this would no doubt accelerate our progress towards developing new treatments for brain tumour patients.	
Brain Tumour Research	GL	40	13	Following consultation with our own clinical and research contacts, it was felt that radiotherapy treatment protocols for low-grade gliomas had merit for further investigation and clinical research. There is currently too much uncertainty around radiotherapy techniques, doses and fraction size design. This needs to be explored in a trial setting whereby practices can be harmonised, increasing patient outcomes across all clinical teams.	Thank you for your comment. The committee was satisfied that there was evidence of benefit in the treatment protocols they recommended, and recommended further research in areas where they were uncertain of any treatment protocol's ability to improve outcomes (particularly IDH-wildtype grade II glioma).
Brain Tumour Research	GL	55	11	Whilst there are references to concerns over the delivery of clinical services to older patient cohorts, there is little mention of the barriers to optimal care quality for Teenagers and Young Adults. Line 11 signposts concerns over the transition from paediatric to adult services but fails to offer any practical solutions to improving this key pathway junction. The fact that the issue of service transition, experienced in many pathways is mentioned only on the penultimate page of the guidelines gives the impression of it being an afterthought. Brain tumours continue to kill more children and adults under the age of 40 than any other cancer. Whilst the mortality rates of key childhood cancers are improving, progress has continued to be much slower for many paediatric brain tumour types. It is vital that the patient experience for vulnerable young people and concerned families is not worsened through service transition and that clinical handover of any treatments or long-term therapy are seamless and patient-centered. Brain tumour patients have a significantly lower experience of cancer care than the average patient. According to research carried out by the 2014 National Cancer Patient Experience Survey, they have one of the worst experiences of cancer care in general. The areas that are particularly problematic are the level of support patients have felt they have had, with 11% fewer brain tumour patients experiencing good support from clinicians and nurses during treatment than average patients for example. The nature of paediatric patients and the concerns of parents and guardians make the need for quality care transition even more important.	Thank you for your comment. The committee agreed the most appropriate way to address this issue was to add a specific recommendation (1.10.10) referring to the existing NICE guidance for the care of people aged 16-24 in cancer services.
British HIV Associations (BHIVA)]	General	General	General	Prior to treatment all patients should have an HIV test	Thank you for your comment. NICE has published guidance on HIV testing: increasing uptake among people who may have undiagnosed HIV (NG60) and a further quality standard on HIV testing: encouraging uptake (QS157). Therefore the committee believed that HIV testing was already covered by NICE guidance and no change has been made to recommendations.

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British HIV Associations (BHIVA)]	General	General	General	Careful attention must be paid to potential drug interactions between antiretrovirals and chemotherapy.	Thank you for your comment. The committee believed that being aware of interactions between drugs - including chemotherapy drugs - was part of good general clinical practice, and therefore did not require a specific recommendation. Consequently no change has been made to recommendations.
British Neuro-Oncology Society	GL	General	General	We are pleased to see access to intra-operative MRI is in there for high as well as low grade gliomas but this is a significant resource implication and lacks any high quality evidence base.	Thank you for your comment. The committee agreed that the evidence for intraoperative MRI was not high quality, although they did emphasise that intraoperative MRI did have some evidence that suggested a possible benefit. Consequently, the committee made a weak recommendation for intraoperative MRI which will allow centres to continue to use their preferred intraoperative visualisation techniques, and the recommendation is therefore not expected to have a significant resource impact.
British Neuro-Oncology Society	GL	4 and 5	1.1.3	We feel that the section on molecular biomarkers is vague, which reflects a lack of robust evidence, we are not sure this guidance will push standards up in the UK. We need a Cochrane prognostic reviews of best technique for MGMT testing and Cochrane diagnostic review of best test for 1p19q testing (these are on-going). It would be helpful to recommend a minimum testing time, by which results should be available, so as not to delay treatment.	Thank you for your comment. NICE guidelines are developed to robust standards of evidence, and therefore the abilities of recommendations to push up standards is conditional on the evidence uncovered. As no robust evidence was uncovered on this topic, the committee was unable to make recommendations on a definitive minimum testing time standard.
British Neuro-Oncology Society	GL	5	1.2.3	We are concerned that there is no specific mention of MDT discussion prior to surgery for patients with high grade tumours, although this is part of current IOG. Particularly for patients in whom subsequent oncology treatment may not be appropriate this is often valuable. This could be included as 'If maximal safe resection is not possible, consider a biopsy to obtain diagnosis, only in patients with a performance score sufficient to allow further oncological treatment or if there is doubt about the diagnosis or if a patient does not want to undergo resective surgery.'	Thank you for your comment. A recommendation has been added recommending referral to MDT as soon as the tumour (of any grade) is diagnosed, to help plan management.
British Neuro-Oncology Society	GL	5	1.2	We feel that the surgical expertise should include - access to intra-operative image guidance - access to 5-ALA - access to awake craniotomy - intra-operative neurophysiological monitoring - experience with insertion of Carmustine wafers With additional Neuroradiological support: - post-operative MRI access within 48 hours may be an advantage, although within 72 hours is acceptable - pre-operative fMRI and/or DTI may be an advantage in selected cases.	Thank you for your comment. The committee did not identify enough evidence to specify what imaging is required and therefore are unable to fully amend the recommendation as you suggested. Carmustine wafers are covered in recommendation 1.2.18 and 5 ALA in 1.2.36. The guideline has also been amended to add 'access to intraoperative image guidance' as a key part of surgical expertise, which the committee agreed encompasses the points in the second suggested recommendation you made.
British Neuro-Oncology Society	GL	15	Table 3	Guidelines for grade II, 1p/19q non-co-deleted IDH1-mutated astrocytoma appear to be missing.	Thank you for your comment. The table has been lengthened to include recommendations on grade II 1p/19q non-codeleted, IDH mutated glioma.
British Neuro-Oncology Society	GL	16		We would encourage the committee to consider the difficult question of pre-operative steroids in meningiomas. There is legal precedent for this and consequently most of us do try to give pre-operative steroids but I am not aware of any overwhelming medical evidence in support of this practice – a statement clarifying the evidence for steroids prior to surgery on meningiomas would be most welcome.	Thank you for your comment. The committee reviewed evidence only on meningioma which was not successfully treated with surgery, and therefore cannot address this issue in the guideline.
British Neuro-Oncology Society	GL	20	2.3.1 and 1.3.7	We feel that the recommended follow up protocol for meningioma is rather prescriptive. The variation between groups makes it difficult to remember and therefore unlikely to be followed. It may be preferable to get a single protocol for imaging of grade 1 and grade 2 meningiomas whether completely resected or not – it would be a more pragmatic, if a less scientific compromise. Likewise the glioma follow up is also somewhat prescriptive given lack of evidence base. This is a contentious area and could have significant resource implications regarding scanning time.	Thank you for your comment. The committee were unable to uncover any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example table might be helpful to clinicians and Trusts in planning the timing and extent of follow-up scans. Since the table is not intended to be prescriptive, no change has been made to the recommendations regarding pragmatism or scanning time as a resource.
British Neuro-Oncology Society	GL	26	3.2.5	We note that SRS to surgical cavities is recommended for patients with brain metastases although this is not currently commissioned. We also note it is not fully supported by high quality evidence of benefit in terms of survival.	Thank you for your comment. NICE recommends treatments based on an assessment of the available evidence and cost-effectiveness of those treatments, but not on the basis of existing commissioning structures. It will be a matter for local implementation to commission services to enable the recommendations in this guideline to be delivered.

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					With respect to your second comment, the committee found weak evidence that surgical cavity irradiation reduced both local recurrence rates and time to local recurrence, but no evidence that it improved overall survival. Although the evidence on recurrence was not statistically significant, the committee argued that it was plausible that irradiation of the cavity could delay recurrence, and so were persuaded by it on the basis that reduced or delayed recurrence should improve quality of life.
British Neuro-Oncology Society	GL	31	4.2	The section on Neuro-rehabilitation is quite short. Is it worth mentioning that rehab for high grade glioma patients is different from Neuro-rehab in general ie time-critical treatments maybe required e.g. post-op chemo and radio need to balanced against prolonged in-patient rehab. Rehab maybe crucial in improving a post-op patients performance score and therefore increase the likelihood of adjuvant therapy.	Thank you for your comment. A decision was taken at scoping that the content of neurological rehabilitation was sufficiently complex that separate guidance was required rather than including it as a question in this guideline. Therefore more detailed recommendations on neuro-rehabilitation are outside the scope of this guideline, and may be included in the scope of future NICE guidance.
British Neuro-Oncology Society	GL	32	4.3.2	We feel that to "Assess the person's individual risk of developing late effects when they finish treatment. Record these in the written treatment summary and explain them to the person (and their relatives and carers, as appropriate)." – is challenging in routine practice.	Thank you for your comment. The committee agrees that it is challenging to create an individualised prediction of the risk of developing specific late effects, but believe that it is current practice to identify broad categories of potential late effect and that this is what they are recommending. Consequently no change to the recommendations has been made.
British Neuro-Oncology Society	GL	33-37	General	No research recommendations are made for imaging. These should be included in view of limited large scale evidence (see evidence report A) for impact of frequency of imaging follow-up; use of advanced techniques for treatment stratification in non-enhancing glioma, methods for distinguishing treatment-related effects from tumour progression; that inform clinical decision-making and design of clinical trials.	Thank you for your comment. Although the evidence was limited, the committee was satisfied that it was sufficient to justify recommending MR imaging in the investigation of a suspected brain tumour. The committee did not prioritise this topic for a research recommendation as they believed that various different advanced imaging techniques are already so incorporated into clinical practice that no one will obtain funding for conducting such research. Additionally, they were not convinced the potential gains from a marginal trial on advanced techniques were sufficient to justify recommending research in this area at the expense of any of their other prioritised recommendations**,** but agree that the impact of frequency of imaging in follow-up is a high priority for research. Consequently, research recommendation 4 has been amended to include an explicit reference to the frequency of imaging.
British Neuro-Oncology Society	GL and ref to evidence report A	37 23	1.2.8	Conclusion that there is no evidence that more advanced techniques is incorrect. Whilst evidence must be graded, papers quoted in evidence report A are very limited and do not fully capture the literature; there is for example evidence based on limited series that techniques such as DCS-MRI and amino acid PET improve diagnostic accuracy.	Thank you for your comment. This review question assessed whether the addition of advanced MRI to standard MRI had a better diagnostic accuracy than advanced MRI alone. For this reason, only studies that compared standard MRI in combination with advanced MRI with advanced MRI only were included, and single centre series were not eligible for inclusion. No evidence meeting this criteria was found for PET-CT and PET-MRI.
British Society of Neuroradiologists	GL	General	General	While we support the use of intraoperative MRI in selected cases it should be emphasised that here is currently no high quality evidence for it's benefit in adult neurooncology; very few UK centres currently have this facility, which requires high levels of capital investment and radiologist and radiographer time.	Thank you for your comment. The committee agreed that the evidence for intraoperative MRI was not high quality, although they did emphasise that intraoperative MRI did have some evidence that suggested a possible benefit. Consequently, the committee made a weak recommendation for intraoperative MRI which will allow centres to continue to use their preferred intraoperative visualisation techniques, and the recommendation is therefore not expected to have a significant resource impact.
British Society of Neuroradiologists	GL	5	1.2.3	We are concerned that MDT discussion of suspected high grade glioma is not mandated. Extensive experience of our membership across UK neuroscience centres, indicates the importance of expert neuroradiology review for consideration of differential diagnosis and surgical and other treatment planning. This is included in current Improving Outcomes Guidance, and forms part of widespread UK practice.	Thank you for your comment. A recommendation has been added recommending referral to MDT as soon as the tumour (of any grade) is diagnosed, to help plan management.
British Society of Neuroradiologists	GL	15	Table 3	Guidelines for grade II, 1p/19q non-codeleted IDH1-mutated astrocytoma appear to be missing. This is an important group.	Thank you for your comment. The table has been lengthened to include recommendations on grade II 1p/19q non-codeleted, IDH mutated glioma.

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British Society of Neuroradiologists	GL	23	3.1.2	Symptoms from a brain metastasis may be the first presentation of a systemic malignancy. This section (or an additional one) needs to detail that if an identified brain mass is suspected to be a metastasis in a patient without a known systemic malignancy, then appropriate investigation, including body CT, biopsy of the primary site (if possible), for tissue diagnosis, and management through the appropriate cancer MDT is likely to need to be undertaken before further treatment of the brain tumour is considered.	Thank you for your comment. The guideline recommends that extracranial imaging appropriate to the tumour type (and biopsy, if possible) be carried out before treatment of a brain metastasis, which would include the investigations you describe.
British Society of Neuroradiologists	GL	33 - 37	General	We are concerned that no research recommendations are made for imaging, and that this is an important omission. There is clearly a clinical need due to the paucity of high quality evidence (reference evidence report A, and conclusions reported in GL) to inform best clinical practice in key areas, for example: Schedules for imaging follow-up/surveillance and their clinical impact . Clinical utility of advanced MRI and PET (Positron Emission Tomography) techniques for prognosis and treatment stratification; with specific reference to added value in the presence of molecular tissue characterisation (and in accord with WHO 2016 guidelines). Advanced methods for distinguishing treatment-related effects from tumour progression; that inform clinical decision-making and design of clinical trials. Some aspects of the above are within the James Lind Alliance top ten priorities for Brain tumour. Multicentre platform studies based and further Cochrane reviews are needed.	Thank you for your comment. Although the evidence was limited, the committee was satisfied that it was sufficient to justify recommending MR imaging in the investigation of a suspected brain tumour. The committee did not prioritise this topic for a research recommendation as they believed that various different advanced imaging techniques are already so incorporated into clinical practice that no one will obtain funding for conducting such research. Additionally, they were not convinced the potential gains from a marginal trial on advanced techniques were sufficient to justify recommending research in this area at the expense of any of their other prioritised recommendations.
British Society of Neuroradiologists	GL (and with reference to evidence report A)	37 23	1.2.8	The statement that there is no evidence for the utility of more advanced techniques in tumour grading/stratification is misleading. Although there is a paucity of evidence base from large scale multicentre studies, and existing evidence grade reflects this, The papers quoted in evidence report A are, however, very limited and do not reflect the literature; multiple limited single centre series indicate techniques such as perfusion MRI and amino acid PET improve diagnostic accuracy. Moreover clinical experience from several centres represented by BSNR supports selective clinical application of such methods.	Thank you for your comment. This review question assessed whether the addition of advanced MRI to standard MRI had a better diagnostic accuracy than advanced MRI alone. For this reason, only studies that compared standard MRI in combination with advanced MRI with advanced MRI were included, and single centre series were not eligible for inclusion. No evidence meeting this criteria was found for PET-CT and PET-MRI. However as advanced techniques are recommended where the radiologist considers them necessary this should not contradict the clinical experience of the BSNR centres you refer to. Consequently no change has been made to the statement that no evidence was uncovered on this topic.
Compassion in Dying	GL	General	General	Compassion in Dying is a national charity working to inform and empower people to exercise their rights and choices around their treatment and care at the end of life and in advance of a potential loss of capacity.We do this by: providing information and support over our free phone Information Line; supplying free Advance Decision to Refuse Treatment (ADRT) and Advance Statement forms and publications which inform people how they can plan ahead for the end of their lives; supplying a free resource www.mydecisions.org.uk so that people can make an Advance Decision to Refuse Treatment online; running information sessions and training for professionals, community groups and volunteers on a range of end-of-life topics, including accredited Continuing Professional Development (CPD) modules; and conducting and reviewing research into end-of-life issues to inform policy makers and promote person-centred care. As such, our comments focus on strategies we believe are needed to ensure that people have the information and support they need to plan ahead and receive the care that is right for them.	Thank you for your comments and for providing information about Compassion in Dying.
Compassion in Dying	GL	7	23 - 24	“Make the decision after discussing these factors.” – this removes agency from the individual, who must be central to the decision-making process. If the decision being made is purely clinical based on the person’s condition, as opposed to one that can be influenced by the individual’s values and preferences, then this should be made clear. However, given the nature of the factors to consider, particularly fertility preservation and planning around important life events, the individual’s own views are seem central. The current	Thank you for your comment. We have slightly amended the wording of your suggestion to be consistent with the NICE style guide to read: ‘discussing the potential advantages and disadvantages of each option with them.’

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				wording suggests that this decision is owned by the clinician, though that does not appear to be the case. We recommend this sentence be re-phrased as "A decision should be made with the person after discussion of these factors. The person's values and preferences should be given priority in the decision and be documented accordingly."	
Compassion in Dying	GL	12	20 - 21	As with the above comment, it is not clear who is making the choice in regards to awake craniotomy. If the person is eligible for it and the decision is solely influenced by their preferences according to the potential benefits and risks, then it is that person's decision to make, not the clinician's. We recommend this sentence be re-phrased as "Discuss awake craniotomy and its potential benefits and risks with the person and their relatives and carers (as appropriate). Once the person has made a decision then document this and their reasoning for the decision."	Thank you for your comment. The recommendation has been rephrased, 'Discuss awake craniotomy and its potential benefits and risks with the person and their relatives and carers (as appropriate) so that they can make an informed choice about whether to have it. Only consider the procedure if the person is likely not to be significantly distressed by it' to clarify that the person with the tumour must make the final decision, but significant distress would be a contraindication.
Compassion in Dying	GL	17	3	We recommend this be re-phrased as "Before a decision is made on radiotherapy for meningioma, take into account:" While such changes in language may seem small they offer huge potential benefit in ensuring the person feels involved in decisions about their care. Incorporating a person's preferences is a key aspect of this, but there is a risk the impact of this is nullified if the person feels the weight of their preferences in the decision is minimal.	Thank you for your comment. The language used in guidelines is extremely important, and your close reading of the text extremely valuable. We have made the change you suggested.
Compassion in Dying	GL	20	1	See comment 5	Thank you for your comment. We aim to address every comment we receive.
Compassion in Dying	GL	29	15	We note that in the section 'Supporting people living with a brain tumour', there is a focus on the care needs of people with a brain tumour but there is nothing in these guidelines which establishes how the person can make their wishes for care and treatment known to those involved in their care. While some may be able to communicate their wishes for treatment now, healthcare professionals should explain how people can document their wishes for future care with emphasis on the fact that a brain tumour may cause difficulty in communicating and potentially a future loss of capacity, temporarily or permanently, to make healthcare decisions for themselves. We therefore think it is important that this section includes guidance on how people can make their wishes known and the unique benefits of advance care planning for people living with a brain tumour. This is particularly important as we know that 68% of Britons would like more control over decisions about their health1 and when care preferences are recorded people are much more likely to "die well".2 In 2016 we commissioned the International Longevity Centre UK (ILC) to conduct a literature review of existing evidence on the economic and social impact of Advance Care Planning. Evidence indicates that Advance Care Planning can lead to cost savings for care providers, fewer unplanned or inappropriate hospital admissions, more people dying in their preferred place of care and improved communication between patients, healthcare staff and families.3 We believe everyone should be made aware of their legal rights and choices when making decisions about their treatment, including how to plan their treatment in advance in a legally binding way, for example by making an Advance Decision to Refuse Treatment or Lasting Power of Attorney for Health and Welfare. Discussing and recording care and treatment preferences is of vital importance for ensuring that people with brain tumours receive the care that is right for them. Care plans made are reviewed regularly, whenever new symptoms, treatments or their side effects arise so that people can make informed decisions about their treatment. New symptoms and new treatment options may prompt an individual to change their mind about their care plan, such as refusing certain life-sustaining treatments. We therefore recommend including a section on advance care	Thank you for your comment, and for the detailed information on advanced care planning for consideration by the committee. Advanced care planning was not prioritised for investigation by the guideline as the committee believed many aspects of advanced care planning would be similar in brain tumours as other kinds of condition. Consequently it is not possible to include a recommendation on this issue.

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				planning, which highlights the particular benefits for those living with a brain tumour and explains the various ways someone may choose to plan ahead. This section could also include bullet point or sentence encouraging healthcare professionals to make referrals to other organisations for further support. For example, both the healthcare professional and/or the patient could contact charities such as Compassion in Dying to receive specific guidance on how to fill out an advance decision to refuse treatment or advance statements, order forms or publications from us, or speak to our Specialist Information and Support Nurse. 1 Ipsos Mori, Global Trends – Health, 2017 2 'Plan Well, Die Well', Compassion in Dying, 2015 3 ILC findings are summarised in 'My Life, My Decision: Planning for the End of Life, A new approach to engaging people and communities' Compassion in Dying, 2016	
Freeman Hospital	GL	GENERAL COMMENT	General	I am very surprised that this document on brain tumours does not include sections on any other than gliomas, mets and meningiomas. Firstly ependymomas are classified as gliomas and are not mentioned at all and are a rare but complex entity to manage. I believe ependymoma should be included. Secondly there are a number of other tumour entities eg cerebral lymphoma, pineal parenchymal tumours, germ cell tumours, cranial nerve tumours and pituitary adenomata that have not been mentioned. Even if there is mention of a further pending document or very short sections on each I feel the document will look more complete with this in.It is certainly not acceptable to progress this guidance without mentioning these areas at all.	Thank you for your comment. The specific tumour areas to be focussed on were decided in consultation with stakeholders during the scoping phase of the guideline. The decision to focus mainly on three tumour types was made to ensure a good balance between publishing the guideline in time to make a difference in clinical practice and covering the clinical management of the largest segment of the population possible. Consequently it will not be possible to review the evidence on tumours which are out of scope.
Freeman Hospital	GL	12	General	Very helpful that what is not recommended is pointed out eg cannabis and TTF – this is helpful support when discussing these matters with patients	Thank you for your kind comments.
Freeman Hospital	GL	15	TABLE 3	I think the follow up table for oligodendroglioma needs amendment as it suggest post year 10 scan follow up for oligodendroglioma is optional, in reality median survival is 12-15 years and this is a more important time for attention to scan follow up as relapse treatment options are usually wide	Thank you for your comment. The recommendations contained in this table are just suggestions based on the clinical consensus of the committee and intended to be modified in respect to individual clinical characteristics of a tumour and the person's preferences. Stakeholder feedback is mixed over whether the recommendations are recommending scans too frequently or too infrequently, and therefore the committee does not believe there is clinical consensus on amending the table. Consequently the table has not been amended.
Freeman Hospital	GL	METS SECTION 27	3.3.2	I would like to see the imaging guidance for follow up of SRS / surgery patients being more firmly recommended in stable patients from systemic disease point of view. The brain mets commissioning document recommends 3 monthly MRI surveillance in these patients with the view that further SRS will be facilitated if further mets develop and hence supports avoidance of WBRT	Thank you for your comment. The committee did not uncover evidence on the optimal follow-up schedule for people with brain metastases, and were therefore unable to make firm recommendations in this section.
Freeman Hospital	GL	METS SECTION 28	3.2.4	I am not satisfied that WBRT in the brain mets section has been commented on in broad sense to not offer this as a adjuvant to surgey or SRS. In reality this a legitimate option for younger patients of good PS who have good survival prospect after careful consent. It is a relevant discussion in those that have had more than 1 met managed and of course we can extrapolate what we know about lung cancer to all primaries – I believe that this section would benefit from rewording	Thank you for your comment. The committee considered several trials showing no evidence that whole brain radiotherapy improved overall survival in making their recommendations, while still exposing patients to risk. In addition the Brown et al (2017) trial which was included in the evidence review demonstrated weak evidence in favour of postoperative stereotactic radiosurgery. The committee believe that three-fraction stereotactic radiotherapy can be delivered to moderately large volumes and therefore the evidence is stronger that stereotactic radiosurgery/radiotherapy should be considered before whole-brain radiotherapy in this group of people, and therefore the committee does not believe it is appropriate to alter the recommendation except to clarify that both stereotactic radiotherapy and radiosurgery should be considered in this role.
Freeman Hospital	GL	METS SECTION 28	3.2.5	Delighted to see that cavity SRS is being advocated post surgical resection – evidence supports this and we strongly approve of this in Newcastle – obviously technical suitability allowing. There will be tariffs attracted to srs	Thank you for your comment.

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				units with this change but this will likely be made up for from lower local control failure rates.	
Headway – the brain injury association	GL	4	4	We recommend providing information to patients about the imaging tools they have been referred to, as some patients can be quite apprehensive about being referred for a scan and not knowing anything about how the scan will look/ how it works/ what it will show etc. Headway has recently published a factsheet on scans and tests after brain injury, which includes information about MRI in accessible-language, among other commonly employed tests used in the diagnosis and monitoring of brain tumours. Please consider signposting readers of this guideline to the factsheet, which is available at www.headway.org.uk/information-library. This information might sit better elsewhere in these guidelines, for instance in an appendix.	Thank you for your comment. NICE policy is not to link to information which is not NICE accredited, and therefore we cannot link to the Headway factsheet.
Headway – the brain injury association	GL	21	8	Provide guidance on approximate timescales of receiving results, as this can reduce apprehension felt by patients/families, who may otherwise feel anxious about not knowing when to expect these.	Thank you for your comment. The committee did not uncover any evidence on the appropriate timescale for receiving results, and believed it could differ depending on individual features of the tumour or the person with the tumour. Consequently they could not make a recommendation providing guidance on the approximate timescale for receiving results.
Headway – the brain injury association	GL	25	2 – table: planning treatment around important life event	Provide clear guidance on a case-by-case basis on patient's ability to carry out activities such as air travel and sports as patients and families are often concerned about this and require guidance that it is difficult for other services to offer. This is a frequent enquiry received by our helpline, and not an issue that we can provide individual guidance on; this must come from consultants involved in patient's care.	Thank you for your comment. In the opinion of the committee it is difficult to provide routine information on the ability carry out activities that might be disrupted by a brain tumour, since situations will be so individualised (for example some people might not care about air travel, and some might care a very great amount). The committee therefore wrote recommendations to very greatly increase the empowerment of patients to ask specific questions of their consultant about activities which matter to them. In addition, recommendations on routine follow-up should also help with this information transfer. Consequently no change has been made to the recommendations, as the committee believes the existing recommendations should help address the underlying issue this comment raises.
Headway – the brain injury association	GL	27	2 – table: no who brain radiotherapy, side effects	Potential for physical, emotional, behavioural and psychological difficulties, as well as cognitive loss because of disease progression. Please consider including these categories as well.	Thank you for your comment. The potential side effects are based on trial evidence and therefore we could not include non evidence-based side effects in this table without making the quality of evidence potentially ambiguous. We have therefore included these factors in the discussion of care needs, where there is no ambiguity about how important addressing them is.
Headway – the brain injury association	GL	27	10	Invite family members to offer information on changes in physical, psychological and cognitive wellbeing as well, as patient may underreport effects or may lack insight into their issues, which only family members can accurately comment on.	Thank you for your comment. The recommendations include a recommendation to 'Discuss health and social care support needs with the person with a brain tumour and their relatives and carers (as appropriate)' and therefore family members should be given an opportunity to discuss changing needs of the person with the tumour if this is appropriate.
Headway – the brain injury association	GL	30	1	Please include emotional well-being at the end of this list as well, since some people may have emotional/psychological effects but this may not necessarily manifest as personality, cognitive or behavioural issues but nevertheless be just as detrimental to patient's wellbeing. Physical effects should also be noted here.	Thank you for your comments. The intent of this recommendation is to highlight the ways in which management of brain tumours is entirely distinct from other types of cancers. Consequently physical effects and certain emotional effects are covered in the subsequent three recommendations. The committee discussed how changes in emotion could also be brought about as a physiological response to the tumour's effect on the brain, but believed this was covered by the list of cognition / personality / behaviour and could be ambiguous if otherwise specified. Consequently the committee did not amend the guideline.
Headway – the brain injury association	GL	30	9	Consider asking relatives and carers about this separately as well, as there may be things that a relative feels they cannot talk about in front of the patient such as issues with managing anger or lacking insight, and vice versa (i.e. talk to patient separately)	Thank you for your comment. In the absence of indications of any lack of capacity, discussing a person's condition without that person present would be a very exceptional thing to do. The committee therefore cannot recommend inviting relatives and carers to comment on this separately.
Headway – the brain injury association	GL	30	17	Include loss of ability to return to work in this list	Thank you for your comment. While the loss of ability to return to work is an important theme emerging from the evidence in respect to this question, it is

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					not something the NHS can directly address as a care need. Consequently the committee cannot highlight this need in the guideline.
Headway – the brain injury association	GL	30	19	Include potential for change in sexual functioning in this list	Thank you for your comment. The guideline has been amended to read "potential for change in personal and sexual relationships".
Headway – the brain injury association	GL	31	1	We would emphasise the importance of always providing this information written down, as many brain injury survivors develop memory problems that can cause them to experience difficulties with retaining information, unless available in an alternative format (such as written down) and to take away with them	Thank you for your comment. In response to your comment we have removed the phrase 'usually meaning' and instead clarified that this means written and spoken every time.
Headway – the brain injury association	GL	31	6	Headway' booklet Driving after brain injury offers general information on this topic, which can be referred to here.	Thank you for your comment. It is not possible to refer to information materials developed by external organisations within the recommendations unless those information materials are NICE-accredited.
Headway – the brain injury association	GL	31	12	Headway has a network of support groups and branches across the country that can offer supportive care to people affected by acquired brain injury (including tumours). Please consider mentioning this in these guidelines as it would be beneficial to patients/ families and clinicians alike to have guidance on where they can access support from in their local area throughout their treatment and care pathway.	Thank you for your comment. NICE guidelines are based on the best available evidence and therefore it is not possible to refer to specific support groups within the recommendations as no evidence was reviewed to assess their effectiveness in improving the experience of care. Once the guideline has been published there will be an 'Information for the public' page on the NICE website to signpost relevant organisations that can give support to people with brain tumours.
Headway – the brain injury association	GL	31	23	Offer information on accessing rehabilitation written down. Many brain injury survivors and families may struggle with processing information in early days and it would be useful for them to have this information to take away with them to read when they are able to process them.	Thank you for your comment. The recommendation has been amended to make the provision of written information more explicit.
Headway – the brain injury association	GL	32	4	As well as cognitive decline, people can develop a range of behavioural, emotional and psychological issues following a brain tumour. This must be included in this list, which is otherwise largely focused on physical long-term impact.	Thank you for your comment. This section of the guideline prioritised reviewing evidence on monitoring for physical effects, since monitoring for behavioural, emotional and psychological issues is covered in the sections on regular clinical review for each type of tumour. However to make this more explicit, more detail has been added to the rationale and impact section of the relevant sections.
Headway – the brain injury association	GL	33	1	We would suggest removing 'high risk' here as some people may not be seen as being 'high risk' at the time but nevertheless require neuropsychological support later on.	Thank you for your comment. Section 1.10 outlines the neurorehabilitation support needs of people with brain tumours, including the need for referral for neurological rehabilitation assessment at diagnosis and every stage of follow up (see recommendation 1.10.1). Therefore the committee did not think it necessary to amend this recommendation as you have suggested.
Headway – the brain injury association	GL	50	25	We welcome this as many brain injury survivors do indeed require some level of rehabilitation to address the myriad of effects that brain injury can cause.	Thank you for your comment. We are pleased you are satisfied with this section.
Headway – the brain injury association	GL	54	21	Referrals may not be coming from GPs due to GPs not recognising the symptoms of brain tumours and therefore not providing referrals in a timely manner. Patients may report symptoms many times but fail to get a referral, until the tumour develops to the point of A&E admission. Indeed, a 2017 report from the Neurological Alliance discussed how 42% of patients saw their GP more than five times before seeing a neurological specialist. Headway has produced a factsheet for GPs to support them with the management of ABI, which could be referred to here.	Thank you for your comment. The recognition and referral of brain cancers is discussed in existing NICE guidance on suspected cancer: recognition and referral (NG12)
Hull and East Yorkshire Hospitals NHS Trust (HQ)	GL	6	9 and 15	1.2.6-8 It would be useful if the committee specify the number of cycles and the type of regimen used in this study of Buckner et al, NEJM 2016. In this study a median of 4 of planned 6 cycles could be given as the PCV regimen used was of 8 –weekly regimen. The PCV regimen currently used in GBM is 6 –weekly that is more toxic and in practice the patients usually could receive a median of 2-3 cycles. If appropriate number of cycles could not be given then the patient may not derive the benefit shown in the Buckner trial. Thus the committee should be more specific in suggesting to use PCV- 8 weekly regimen to a total of 6 cycles.	Thank you for your comment. The number of cycles and regimen have been added.

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Hull and East Yorkshire Hospitals NHS Trust (HQ)	GL	7	8	1.2.11 GII IDH wild type: The guidance is ambigious -' prognosis similar to GBM'. The committee should be very clear about this group patients where significant uncertainties exist. Presently, there is no evidence and no study has been conducted (to my knowledge) to treat GII wild type similar to the treatment regimen for the GBM. The closest evidence lies in the same study of Buckner et al (NEJM 2016).I suggest, based on this study, IDH wild type should also be treated as IDH mutated until we get more evidence otherwise. The reason being that the IDH was tested only in 45% of the study population. There were only 42 (of total 250) patients with wild type thus this group was not analysed in the Buckner study. As IDH wild type most likely to occur in pure astrocytoma histology, and the survival curve of astrocytoma is presented, thus, this astrocytoma group may work as a surrogate to IDH wild type. Due to, again, very low number of pure astrocytoma in this study (52/250) p level for the PFS was 0.06 . However, HR which was 0.58 cannot be ignored indicating a clinical significance but not statistically significance observed in this study for the astrocytoma group could be due to inadequate power. Thus, indirectly, it could be inferred (in the absence of any other evidence otherwise) that pure astrocytoma (mostly are IDH wild type) also get clinically meaningful benefit with radiotherapy followed by PCV chemotherapy , but not as great as is observed in the IDH mutated type.	Thank you for your comment. The committee acknowledged that there are still some areas of uncertainty for the management IDH- wildtype grade II gliomas, and they decided to make a research recommendation about this. According to the committee's experience, IDH- wildtype grade II gliomas have a worse prognosis than IDH1 and IDH2, and the behaviour of these tumours may be similar to that of glioblastomas. Therefore, they recommended to take this into consideration when thinking about management options. As it is suggested, the trial conducted by Buckner 2016, identified 62.8% patients with IDH1 R132H mutation present, and there were not enough patients with events in the group without the IDH1 R132H mutation to establish any association with the interventions. However, subgroup exploratory analyses conducted by this same trial, showed that those with IDH1 R132H had significantly longer progression free survival and overall survival than those without the IDH1 R132H mutation (p< 0.005 in both cases). In the absence of available evidence addressing the optimal management of IDH- wildtype grade II gliomas, the committee preferred to make only a research recommendation.
Hull and East Yorkshire Hospitals NHS Trust (HQ)	GL	7	17	1.2.13 To avoid ambiguity, it would be great if the number of cycles (4 cycles of PCV) is specified as was given in both the studies (RTOG and EORTC) Similarly, the option of 8 cycles of temozolomide should be kept open as in practice many patients cannot tolerate or not fit for PCV chemotherapy. In NOA -4 study, a German study , (JCO December 10, 2009) 4 cycles of 8-weekly PCV regimen or 8 cycles of 4 -weekly temozolomide before radiotherapy or after radiotherapy were equally effective.	Thank you for your comment. The number of cycles, 4-6 based on the protocol of the trial, and not 4, as it is suggested in the comment has been added. However, the option of TMZ has not as the committee did not find any evidence to support TMZ over PCV. The committee were aware of clinical opinion that temozolomide could be effective, however they decided not to recommend temozolomide in low grade tumours as the only evidence they uncovered on temozolomide alone in this population demonstrated no effect versus radiotherapy alone and therefore the committee could not recommend TMZ+radiotherapy on the basis of the existing evidence, especially as there was direct evidence of improved overall survival for PCV+radiotherapy. Consequently these recommendations have not been amended.
International Brain Tumour Alliance	GL	General	General	Thank you for this opportunity to comment on the draft guideline for "Brain Tumours (Primary) and Brain Metastases in Adults". Our suggested additional words are indicated in green font in this table.	Thank you for your comment. We will respond to each point individually.
International Brain Tumour Alliance	GL	5	43287	Should MGMT testing be a "given" and not a matter that might, on consideration, be thought of as unnecessary? MGMT promoter methylation status could be critical in accessing some clinical trials, especially for patients with un-methylated MGMT tumours. In general, we also feel that clinicians should stress to brain tumour patients scheduled for surgery the vital importance of tumour tissue banking or at least reserving frozen tissue for possible future therapies such as tumour-lysate pulsed dendritic cell vaccine therapy, or other future molecular analyses.	Thank you for your comment. The wording of the recommendation for MGMT status has been strengthened from 'consider' to 'test'.
International Brain Tumour Alliance	GL	6	21 - 23	We feel that the term "active monitoring", which we assume replaces the term "watch and wait", should be specifically defined for the sake of clarity and consistency in how different clinicians approach this and explain it to patients and caregivers.	Thank you for your comment. We have revised the definition of 'active monitoring' in the 'Terms used in this guideline' section to clarify that active monitoring occurs when a person is not currently having treatment for their cancer.
International Brain Tumour Alliance	GL	7	22	We realise that there is a desire not to identify or refer to people as their disease or as the "patient". However, using the word "people" in certain parts of this document results in unclear guidance. For example, on page 7, line 22 it says: "Discuss with people the order of PCV and radiotherapy and the potential benefits and risks of each option…" Which people? Members of the MDT? The patient? The caregiver? Others? We recommend that the descriptive word "patient" is retained to avoid confusion as a result of possibly awkward wording. These guidelines should not sacrifice clarity and precision	Thank you for your comment. The term 'person' always refers to the person with the condition unless otherwise stated, in order to remain consistent with other NICE guidelines and products. The guideline has been amended to make this explicit in any place where ambiguity might remain.

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				based on the use of an imprecise, much wider term ("people") where the context demands the precision of identification of those individuals as "patients". Confusion could lead to potential liability because the guidelines could become inherently misleading. We feel that there is also lack of clarity in the use of the word "people" on page 1 at line 5, the first bullet point. We recommend that this is changed to "Patients and caregivers using services for the diagnosis, management and care of a primary brain tumour or brain metastases"	
International Brain Tumour Alliance	GL	8 and 9	11 - 18 and overleaf line 1	Suggest the addition of the following words in green font: "Advise patients people who have an initial diagnosis of grade III glioma (and their relatives and carers, as appropriate) that the available evidence does not support the use of the following. However, patients should be made aware that research into some of these potential treatments is on-going and be encouraged to enter into dialogue with their clinicians at any time if they have further questions about these."	Thank you for your comment. Recommendation 4.1.6 highlights that information requirements might change throughout a person's care pathway (including follow-up) and that regular communication should be established to allow a person to ask questions of their clinician if they have further questions. The committee therefore believed that updating a person on changes in research on treatments potentially relevant to their condition (not just those for which there is currently no high-quality evidence) was already covered by these recommendations. The discussion section has been expanded to explain this, but no further change to the recommendations has been made.
International Brain Tumour Alliance	GL	8	1-3	We think that this table is a useful decision aid and wonder if it could be provided to the patient and caregiver as part of a newly-diagnosed information pack.	Thank you for your comment. The information in this guideline will be available to various groups who may wish to subsequently produce patient information packs. Additionally, NICE are currently working with 'Braintrust' to develop materials to support people with brain tumours to access the guideline.
International Brain Tumour Alliance	GL	10	19 - 27	Suggest the addition of the following words: "Advise patients people who have an initial diagnosis of grade IV III glioma (and their relatives and carers, as appropriate) that the available evidence does not support the use of the following. However, patients should be made aware that research into some of these potential treatments is on-going and be encouraged to enter into dialogue with their clinicians at any time if they have further questions.	Thank you for your comment. Recommendation 4.1.6 highlights that information requirements might change throughout a person's care pathway (including follow-up) and that regular communication should be established to allow a person to ask questions of their clinician if they have further questions. The committee therefore believed that updating a person on changes in research on treatments potentially relevant to their condition (not just those for which there is currently no high-quality evidence) was already covered by these recommendations. The discussion section has been expanded to explain this, but no further change to the recommendations has been made. Thank you also for highlighting the duplication between Grade III and IV sections.
International Brain Tumour Alliance	GL	10	17 - 18	There is robust evidence that TTF plus temozolomide results in increased progression-free survival and overall survival in patients with newly diagnosed glioblastoma (Stupp et al, Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma A Randomized Clinical Trial, JAMA 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718). The EF14 trial concluded that: "In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival." It is clear that questions of cost/availability remain, but patients should always be made aware of all possible treatment options that are backed by strong evidence so they can have all of the relevant information and make informed decisions. Patients have the right to receive this information and it should not be for clinicians to decide to omit, at their discretion, communication on available treatments based, for example, on the clinician's view as to the financial resources of the patient. We further understand that it is not without precedent that the level of evidence deemed acceptable in relation to a particular treatment may comprise one large randomised clinical trial. That, we understand, was the position in relation to the approval and recommendation of temozolomide as it is in the case of	Thank you for your comment. While many recommendations in this guideline may apply in a variety of settings (for example; NHS, private, international), the principle focus of the guideline is the NHS setting. The recommendation not to offer tumour treating fields was not based on clinical evidence, but on published cost-effectiveness evidence. Clinical evidence for this treatment was reviewed, and recorded in Evidence Report A. However the decision to not recommend was on the basis of cost-effectiveness. Although there was some evidence that tumour treating fields improved overall survival and progression free survival, the committee concluded that the effect size of the study did not justify the additional cost of this intervention in either those with MGMT methylated or unmethylated status. A more complete discussion of the cost-effectiveness considerations that led to this recommendation can be found in the associated discussion section of Evidence Report A. Of the two specific studies you cite, the Stupp et al (2017) paper was included but the Taphoorn et al (2018) paper was not as it was published after the cut-off date for inclusion in this guideline. However the inclusion of the Taphoorn et al (2018) paper would not have changed recommendations, as the paper states ""health-related quality of life did not differ significantly between

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				tumour treating fields. Moreover, we understand that the level of evidence in respect of tumour treating fields is Level IIB, which we believe corresponds to the level of evidence which was available in 2005-2006 when recommending the use of temozolomide for first line therapy of glioblastoma. In addition, there is further evidence available in relation to tumour treating fields in a recent secondary analysis of quality of life using tumour treating fields (Taphoorn et al, Influence of Treatment with Tumor-Treating Fields on Health-Related Quality of Life Patients with Newly Diagnosed Glioblastoma, doi:10.101/jamaoncol.2017.5082) which has demonstrated that improved quality of life and independence in activities of daily living was maintained for a longer period of time in patients receiving tumour treating fields. During that period of improved quality of life, we understand that the patients in question required less supportive care, fewer second line therapies, etc. Finally, we understand that there has been some criticism of the design of the EF14 trial for tumour treating fields in that it did not incorporate a trial arm of patients receiving a sham device (in effect, a placebo). However, it is of note that some newly-designed drug trials do not include a placebo. We believe that this is acceptable with a trial that is looking at overall survival as an endpoint.	treatment arms"" and the significant difference in deterioration-free survival was still insufficient to make the intervention cost-effective at a threshold of £20,000 to £30,000 per QALY.
International Brain Tumour Alliance	GL	10	19	Is there an error in this line? Shouldn't it read: "Advise people [or preferably "patients"] who have an initial diagnosis of grade IV glioma" and not grade III glioma as this statement is in the section on grade IV glioma?	Thank you for your comment. This has been corrected.
International Brain Tumour Alliance	GL	11	21	Would the use of carmustine wafers exclude a patient with glioblastoma from enrolling in some potential later trials? If so, this must be clearly explained to the patient in advance.	Thank you for your comment. The reference to carmustine wafers has now been removed from this recommendation as the committee could not determine whether there was sufficient benefit to justify the risk of this intervention.
International Brain Tumour Alliance	GL	12	43407	Suggest the addition of the following words: "Advise patients people who have an initial diagnosis of a recurrent high grade glioma (and their relatives and carers, as appropriate) that the available evidence does not support the use of the following. However, patients should be made aware that research into some of these potential treatments is on-going and be encouraged to enter into dialogue with their clinicians at any time if they have further questions.	Thank you for your comment. Recommendation 4.1.6 highlights that information requirements might change throughout a person's care pathway (including follow-up) and that regular communication should be established to allow a person to ask questions of their clinician if they have further questions. The committee therefore believed that updating a person on changes in research on treatments potentially relevant to their condition (not just those for which there is currently no high-quality evidence) was already covered by these recommendations. The discussion section has been expanded to explain this, but no further change to the recommendations has been made.
International Brain Tumour Alliance	GL	13	9	There is no mention of referral to palliative/supportive care specialists.	Thank you for your comment. While there is no mention of these specialists in the section you highlight on follow-up of the physical activity of the tumour, palliation and supportive care are mentioned in recommendations 1.2.31 and 1.10.12. Consequently no change will be made to recommendations, as these specialists are covered elsewhere in the guideline.
International Brain Tumour Alliance	GL	14	13 - 16	We note that in some institutions in the UK and abroad, MRI results are known relatively quickly, sometimes even within the same day or within a day or two of the MRI appointment. Every effort should be made to significantly reduce waiting times for MRI results as the wait for these results can cause intense stress for the patient and their family.	Thank you for your comment. While the committee did not review evidence on what the maximum appropriate wait was, recommendation 1.10.8 emphasises the committee's view that delays should be kept to an absolute minimum. Consequently no change to the recommendations has been made, as the guideline already recommends reducing waiting times to the minimum practical.
International Brain Tumour Alliance	GL	14	1 - 2 (Table 2)	Suggest that the contents of this table are discussed fully with patients and caregivers at an appropriate time so that they can fully understand and appreciate the pros and cons of more frequent follow-up.	Thank you for your comment. These tables should be discussed fully with patients as the timing of regular clinical reviews is based on them.
International Brain Tumour Alliance	GL	21	43351	See comment 13	Thank you for your comment. We will address this comment directly in our response to comment 13.
International Brain Tumour Alliance	GL	29	11	We are disappointed to see that there is no mention of the role of brain tumour-specific not-for-profits and charities and the crucial role they can play in providing additional care and support to brain tumour patients, their caregivers and families. We feel that reference should be made to these	Thank you for your comment. NICE publish contact details of condition-specific charities and not-for-profits in the 'Information for the public' section of their website associated with each guideline. Consequently the guideline itself does not contain reference to such organisations.

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				organisations in the guidance document under “Supporting people living with a brain tumour”.	
International Brain Tumour Alliance	GL	29	11	In this section there is no reference made to supporting the patient with information on fertility preservation and as this is a time-critical challenge, we think it is important to flag this area of support in this section. However, infertility is mentioned on page 8 (Table 1) and on page 32 as a late-onset side effect.	Thank you for your comment. We have added a recommendation that fertility be discussed with the person with the tumour, and that recommendation in existing NICE guidance on fertility problems: assessment and treatment (CG156) be followed if appropriate.
International Brain Tumour Alliance	GL	30	13 - 21	Care needs of people with brain tumours also include dealing with stigmatisation relating to possible negative perceptions of friends, family, employers, colleagues, etc. We believe that mention of this aspect should be included in this section because of its impact on social care support needs.	Thank you for your comment. The committee did not find any evidence in the literature they reviewed that brain tumours carried a greater stigma than other types of cancer, and therefore did not make a specific recommendation on this topic.
International Brain Tumour Alliance	GL	30	13 - 21	Brain tumour patients (and their caregivers) can be affected by depression yet there is no mention of this in the section on supporting people living with a brain tumour.	Thank you for your comment. The intent of this section is to highlight ways in which the care needs of a person with a brain tumour might differ from the care needs of a person with another type of cancer. Consequently, as depression, on which there is already NICE guidance (see Depression CG90), is not a unique feature of brain tumours, it would not be appropriate to mention in this section.
International Brain Tumour Alliance	GL	30	13 - 21	We feel that the words “loss of employment and resulting financial hardship” should also be added to this bullet list as being part of the complex needs of and challenges faced by brain tumour patients.	Thank you for your comment. While the loss of employment and resultant financial hardship is an important theme emerging from the evidence in respect to this question, it is not something the NHS can directly address as a care need. Consequently the committee cannot highlight this need in the guideline and therefore no change has been made to recommendations.
International Brain Tumour Alliance	GL	30	22 - 26	There is no mention in this section of the crucial importance of the clinical nurse specialist (CNS) in the brain tumour setting. The CNS is often the lynchpin holding together the patient/caregiver journey and could be the key worker. We realise that this may be covered by the reference in NICE guidance on “improving outcomes for people with brain and other central nervous system tumours” but we feel the role of the CNS merits specific mention in this document.	Thank you for your comment. The guideline has been amended to state that the key worker is often a clinical nurse specialist.
International Brain Tumour Alliance	GL	30	43350	There is no mention of the need for healthcare professionals, particularly those breaking bad news, to have a thorough set of adequate communication skills with which to discuss the impact of a brain tumour on the patient and his/her family. We feel that reference should be made in these guidelines to this in order to encourage clinicians to seek professional training in this regard if they do not already possess these skills or sufficient experience.	Thank you for your comment. While there are brain-tumour specific issues to do with communication (such as the importance of realism in giving a prognosis), general communication skills such as breaking bad news are part of ordinary clinical practice and consequently not prioritised for inclusion in the guideline.
International Brain Tumour Alliance	GL	31	17 - 23	This section is disappointing in its brevity and we feel it should be expanded to include references to such things as the settings in which neuro-rehab can be delivered (ie hospitals, community healthcare centres, schools, etc); referral to any existing NICE guidance on the role of neuro-rehabilitation and its effects; quality of life; palliative care; etc. Neuro-rehabilitation is a vital area of concern to brain tumour patients and their families and we feel that it is not sufficiently covered in this short section on the topic.	Thank you for your comment. A decision was taken at scoping that the content of neurological rehabilitation was sufficiently complex that separate guidance was required rather than including it as a question in this guideline. Therefore more detailed recommendations on neuro-rehabilitation are outside the scope of this guideline, and may be included in the scope of future NICE guidance.
International Brain Tumour Alliance	GL	31	1-4	A suitable format would also include a recording of appointments (ie for example recorded on a mobile phone). Sometimes news is so shocking for a brain tumour patient and caregiver that they do not take in the spoken word at the time. A recording of an appointment can be very useful in recalling exact information later.	Thank you for your comment. The committee believes the recommendation is sufficiently explicit that any suitable format should be considered, and therefore recording would be covered by this recommendation if it is appropriate. Consequently they have not amended the recommendations.
International Brain Tumour Alliance	GL	31	6-8	Suggest adding the words: “Losing the ability or legal right to drive can have a profound effect on the patient’s independence, employment status and self-esteem. Therefore, it is important to explain to the patient the implications of having a brain tumour on driving.”	Thank you for your comment. This text has been added to the rationale and impact section of the guideline.
International Brain Tumour Alliance	GL	33	1-11	See comment 16 above. Perhaps this would be a good place to insert a statement to the effect of “Consider referral to fertility counselling for people who are at risk of treatment-related infertility”	Thank you for your comment. We have added a recommendation that fertility be discussed with the person with the tumour, and that recommendation in

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					existing NICE guidance on fertility problems: assessment and treatment (CG156) be followed if appropriate.
International Brain Tumour Alliance	GL	33	12	See comment 2. See Perhaps a definition of “active monitoring” could be included here.	Thank you for your comment. A definition of 'active monitoring' has been added to the guideline.
International Brain Tumour Alliance	GL	33	17	We agree – all of these research questions are very important and we are pleased to see them formally included here as “Recommendations for research”.	Thank you for your kind comments.
International Brain Tumour Alliance	GL	35	16 - 17	The use of the terms “informal caregivers” and “carers” in the same sentence is confusing. The use of the term ``informal” to describe brain tumour caregivers is, in our opinion, inappropriate as there is nothing really “informal” about the role. It is often necessary to be involved as a brain tumour caregiver 24/7. Brain tumour caregivers often also become highly skilled at caring for the patient, especially towards the patient’s end of life. We feel that the term “informal caregivers” detracts from the crucial role that caregivers play in the brain tumour journey and suggest that they simply be called “caregivers” or “carers” throughout the guidance document. This will also avoid confusion and inconsistency.	Thank you for your comment. This wording was intended to differentiate carers who were paid and unpaid for their care, but the guideline has been updated with your suggestion as it is a clear improvement in terms of both clarity and consistency.
NCRI-ACP-RCP-RCR	ER A	23	8	The guideline is based on clinical experience of the committee, yet - No research recommendations were made on this topic, despite the level of evidence at best being low. Surely this is an area where further higher quality research is necessary	Thank you for your comment. Although the evidence was limited, the committee was satisfied that it was sufficient to justify recommending MR imaging in the investigation of a suspected brain tumour. The committee did not prioritise this topic for a research recommendation as they believed that various different advanced imaging techniques are already so incorporated into clinical practice that no one will obtain funding for conducting such research. Additionally, they were not convinced the potential gains from a marginal trial on advanced techniques were sufficient to justify recommending research in this area at the expense of any of their other prioritised recommendations.
NCRI-ACP-RCP-RCR	ER A	23	26	Is there evidence that early identification confers benefit beyond lead time bias? Should this not be an area for further research –e.g. randomisation to a treatment approach of intervention vs further imaging and treatment if findings confirmed at 3 months.	Thank you for your comment. Research recommendations can only be prioritised for those questions that were searched in the guideline, therefore the research recommendation that is suggested in this comment cannot be included.
NCRI-ACP-RCP-RCR	ER A	24	15	The fact that the committee believed the evidence ‘was robust’ is not reflected in the expert discussion or the level of evidence.	Thank you for your comment. This has been rephrased to make it clearer that the committee considered the evidence an adequate basis on which to make recommendations given the difficulty of conducting more definitive research.
NCRI-ACP-RCP-RCR	General	General	General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.	Thank you for your comment. We will respond to each point individually.
NCRI-ACP-RCP-RCR	GL	General	General	Recommendation not to offer Tumour Treating Fields is at odds with RCT showing survival benefit in patients with newly diagnosed GBM, especially in MGMT methylated patients.	Thank you for your comment. Clinical evidence for this treatment was reviewed, and recorded in Evidence Report A. Published cost- effectiveness evidence was identified around Tumour Treating Fields and it was on this basis the committee concluded that they could not recommend tumour treating fields. Although there was some evidence that tumour treating fields improved overall survival and progression free survival, the committee concluded that the effect size of the study did not justify the additional cost of this intervention in either those with MGMT methylated or unmethylated status. A more complete discussion of the cost-effectiveness considerations that led to this recommendation can be found in the associated discussion section of Evidence Report A.
NCRI-ACP-RCP-RCR	GL	6	8	one has to be very careful with wide adoption of 54 in 30 with pcv early on for low grade gliomas. Only one study and significant morbidity possible	The trial this recommendation is based on is significantly powered to detect differences across treatment arms and has enough follow-up to detect any major morbidity (median follow-up was 11.9 years). For this reason, the committee considered that people have oligodendrogliomas would benefit of this specific intervention. The trial did not indicate significant morbidity and additional trials assessing the cognitive function of patients who received

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					radiotherapy concluded that cognitive function remains stable after having received radiotherapy. Consequently the committee believe their recommendations are justifiable in relation to the evidence, and therefore have not amended the guideline.
NCRI-ACP-RCP-RCR	GL	8	13	Rephrase as: support the 'routine' use of	Thank you for your comment. The committee consider the statement is accurate, as the available evidence does not support any use of these therapies and techniques (routine or otherwise). All NICE guidance is an aid to clinical decision making (that is, it does not overrule good clinical judgement) and so in the case of a patient with specific characteristics making a treatment in this list suitable the recommendation does not prevent that treatment being offered.
NCRI-ACP-RCP-RCR	GL	8	13	No statement about use of metformic, statins etc. in brain metastasis and meningioma – this may imply that they can be used.	Thank you for your comment. Evidence on these therapies was not sought in evidence reviews of brain metastases and meningioma, so the committee cannot state with certainty that there is or is not an evidence base supporting the use of these therapies. Therefore no change has been made to recommendations.
NCRI-ACP-RCP-RCR	GL	10	1.2.23	This could be clarified with a flow diagram	Thank you for your comment. A flow diagram is being produced for these recommendations and will be published alongside the guideline.
NCRI-ACP-RCP-RCR	GL	10	19	Typo – should be grade IV glioma	Thank you for your comment. This has been corrected.
NCRI-ACP-RCP-RCR	GL	12	1.2.36	'If a person has a radiologically-suspected enhancing high-grade glioma, ---- offer 5-amino-levulinic acid --- an adjunct to maximise resection at initial surgery.' The studies were where the operator thought 'complete resection' was possible. The term 'maximal' is subjective – 20% might be maximal in some. If using maximal a definition e.g. (>90%) would be helpful. Our experts question why 5-ALA should be 'offer' and other two (ioMRI and ioUS 1.2.40 and 1.2.41 are only 'consider'. Our experts question whether the other two have been shown to be less effective?	Thank you for your comment. This recommendation has been edited to say that 5-ALA should be offered if the surgical resection of all enhancing tumours is possible. Given the low quality of evidence, the committee chose to make weak recommendations with the exception of the recommendation for 5-ALA where an economic model developed for the guideline allowed them to make stronger recommendations.
NCRI-ACP-RCP-RCR	GL	17	Table 4	Definition of complete resection (Simpson 1-2) and subtotal (Simpson 3-5) are different to those adopted in clinical trials and endorsed by EORTC and NRG. Gross total resection = Simpson 1-3. Subtotal resection = Simpson 4-5. The baseline MRI at 3 months can often show florid changes due to surgery and may not be suitable to assess residual. Recall the Simpson criteria were produced in 1957 and pre-date any imaging, therefore the surgeon's assessment is more useful than the MRI. An MRI within 72 hours would be better (as per glioma practice).	Thank you for your comment. The Simpson criteria have been adjusted to fit your recommendation. As the recommendations are relevant only following surgery (or if surgery is not possible), a recommendation cannot be made as to whether an MRI should take place 72 hours following surgery. However the table headings have been amended to make it clear that if surgery has not taken place imaging should be undertaken.
NCRI-ACP-RCP-RCR	GL	19	1.2.21	GBM over 70 non-methylated - 40 in 15 with tmz. Non significant benefit in CE6. Agree that tmz should be available in methylated.	Thank you for your comment. The committee believed that the evidence was suggestive in non-methylated although not significant, and so made a weak 'consider' recommendation to allow for clinical judgement of the point.
NCRI-ACP-RCP-RCR	GL	20	2.3	Concern from patients that meningioma discharge after 10 years may cause more anxiety that continued periodic review.	Thank you for your comment. The committee were unable to uncover any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example table might be helpful to clinicians and Trusts in planning the timing and extent of follow-up scans. Since the table is not intended to be prescriptive, clinicians with patients who might be anxious about discharge need not follow that aspect of the schedule.
NCRI-ACP-RCP-RCR	GL	20	Section 2.3	The MRI sequences will be challenging in practice and would have an impact on already time pressed resources within many radiology departments. Some services follow-up meningioma with just a T1+gad volume only, or omit the T1+gad completely e.g. resected convexity meningioma may just need T2 (if it was easily seen on T2 before)	Thank you for your comment. In follow up (as opposed to diagnosis) the recommendation for standard structural MRI is a weak 'consider' recommendation rather than a strong 'offer' recommendation. This is because there are some tumours and tumour characteristics that can be adequately detected without the complete set of imaging protocols. Therefore if a radiology department believes that a particular patient does not need T1+gad, the recommendations allow for this clinical judgement. Therefore no change has been made to recommendations.

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NCRI-ACP-RCP-RCR	GL	22	Table 7	Meningioma recurrence in grade II is such that follow-up should be lifelong.	Thank you for your comment. The committee were unable to uncover any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example table might be helpful to clinicians and Trusts in planning the timing and extent of follow-up scans. Since the table is not intended to be prescriptive, no change has been made to the recommendations as clinicians are not expected to follow the table if it is not appropriate for their practice: the table states that discharge should be considered, but is not necessarily expected and therefore the option of lifelong follow up is still available.
NCRI-ACP-RCP-RCR	GL	23	3.2	Wbrt - the strong wording of not using it should be limited to areas with evidence. That is Quartz population only. The rest remains a decision based upon risk and merit. The way it is worded at present may lead to detrimental outcomes through prejudice against use. For example: Wbrt has no role in poor prognosis lung cancer - accepted widely For pts suitable for srs - discussion of risks. For patients not suitable for srs then wbrt may have a role (outside poor PS lung ca). Cavity srs - local control inferior for large cavities due to dose reduction. Fractionated rads gives higher lc as can allow for uncertainty. Defining cavity can be challenge. Small targets normally treated with primary srs. These issues should be discussed and considered before any decisions.	Thank you for your comment. The committee considered several trials showing no evidence that whole brain radiotherapy improved overall survival in making their recommendations, while still exposing patients to risk. In addition the Brown et al (2017) trial which was included in the evidence review demonstrated weak evidence in favour of postoperative stereotactic radiosurgery. The committee believe that three-fraction stereotactic radiotherapy can be delivered to moderately large volumes and therefore the evidence is stronger that stereotactic radiosurgery/radiotherapy should be considered before whole-brain radiotherapy in this group of people, and therefore the committee does not believe it is appropriate to alter the recommendation except to clarify that both stereotactic radiotherapy and radiosurgery should be considered in this role.
NCRI-ACP-RCP-RCR	GL	29	1	Considering 80% of LGG and 30-40% HGG and many with meningioma and cerebral metastasis have develop epilepsy, our experts were surprised there is absolutely nothing on the requirement to have a neurologist and epilepsy specialist nurse. All other people with epilepsy should see a neurologist and have an epilepsy specialist nurse, (see NICE Guideline https://www.nice.org.uk/guidance/cg137)	Thank you for your comment. The committee believed that the NICE guidance on epilepsies: diagnosis and management (CG137 that you link to) was sufficient to ensure good management of the condition. Consequently they included a link to the guideline, but no other reference to the management of epilepsy in brain tumours.
NCRI-ACP-RCP-RCR	GL	36	11	Meningioma research question. EORTC had a failed trial to answer this question. Poor recruitment due to lack of equipoise by neurosurgeons	Thank you for your comment. The committee believes that radiotherapy technique has moved on sufficiently from EORTC that equipoise may now be possible, and the research recommendation has been updated to explain this.
Neuroanaesthesia & Critical Care Society of Great Britain & Ireland]	GL	General	General	Surgery should take place in a department of Neuroanaesthesia which complies with GPAS standards	Thank you for your comment. The committee did not review evidence on particular standards for neuroanaesthesia departments, and consequently cannot recommend any particular standard for these departments.
Royal College of General Practitioners	GL	4 General	1.1.1	The initial pathway of investigating of a patient with suspected brain tumour or metastases happens in Primary Care and this document would be improved by including a reference to the NG12 NICE Guidelines Page 25 Paragraph 1.9.1 “Urgent direct access within two weeks for MRI, or CT if MRI not possible for adults with progressive, sub-acute loss of central nervous system function”. Provision of direct access to MRI within two weeks will improve the time to diagnosis of brain tumours, has implications for the stage of diagnosis and hence the management options available to the patient once the diagnosis is confirmed. However, provision of prompt direct access will have an impact on local MRI services with human resource and cost implications. Clearly a secondary care oriented guideline	Thank you for your comment. You are correct that this guideline is significantly oriented to secondary care, although there are some recommendations with implications for primary care providers. Reference to NG12 will be made through the NICE Pathway team (for example on the NICE website) and therefore the link between this guideline and NG12 will be made explicit at publication.
Royal College of Occupational Therapists	GL	General	General	There are clear prescriptive guidelines for treatment planning to support oncologists / MDT members in diagnosis and deciding the best form of treatment.	Thank you for your comment. We are pleased you are satisfied with these sections of the guideline.
Royal College of Occupational Therapists	GL	29	4.1	There is no mention of using the holistic needs assessment that could be used to support personalised care planning and supporting the person. https://www.macmillan.org.uk/about-us/health-professionals/programmes-and-services/recovery-package	Thank you for your comment. NICE policy is not to link to information which is not NICE accredited, and therefore we cannot link to the holistic needs assessment.

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Royal College of Occupational Therapists	GL	30	4.1.4	It is important to acknowledge the loss of occupation roles /employment.	Thank you for your comment. While the loss of occupation role / employment is an important theme emerging from the evidence in respect to this question, it is not something the NHS can directly address as a care need.
Royal College of Occupational Therapists	GL	31	4.2.2	This recommendation may be challenging- not due to the health professional recommending or advising on neurorehabilitation, but due to the huge variation of neuro-rehab services across the geographical regions.	Thank you for your comment. A decision was taken at scoping that the content of neurological rehabilitation was sufficiently complex that separate guidance was required rather than including it as a question in this guideline. Therefore variation in facilities across health geographies is outside the scope of this guideline, and may be included in the scope of future NICE guidance.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	General	General	If there is a change, risks (infection, swelling etc) should also be highlighted	Thank you for your comment. The section on the committee's discussion of the evidence has been updated to explain that part of the purpose of the review would be to update the patient on how their risk might change as a result.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	5	16	MGMT testing Pg 5, line 6, point 1.1.4 states only to 'consider testing ... for MGMT promoter methylation' – it is not included as a mandatory requirement of neuropathology reporting of high grade gliomas. We feel strongly that it ought to be included as mandatory and the wording strengthened beyond just 'consider' (we accept that it is slightly different from the diagnostic-markers list under 1.1.3; but we do feel it ought to be mandated as standard for the reasons set out below). Although MGMT testing does not aid diagnosis, it unquestionably falls into the category of a molecular marker which determines prognosis and guides treatment and feel its inclusion as a mandatory part of neuropathology reports for high-grade gliomas is warranted for the following reasons: MGMT is a very important prognostic marker which indicates patients' chances of responding to chemotherapy treatment. While it may not lead clinicians to withhold chemo in all unmethylated patients (outside of clinical trials) it does help inform how to weigh decisions in terms of prioritising quality of life vs active treatment and how much to encourage patients struggling with chemo toxicity to persevere. It is very important in helping to support patients in making informed decisions about their treatment and future care planning at all stages from diagnosis onwards. MGMT testing is integral to the EANO guidelines (Lancet Oncology 2017). To omit this from the UK guideline list of standard, mandatory molecular tests puts us out of step with the rest of the Europe and with the USA, significantly adversely affecting our ability to compare outcomes with international centres. This type of international comparison is a key central tenet of NHSe's assessment of effectiveness of cancer care; failure to routinely test all patients for MGMT methylation status renders future meaningful comparison impossible. Many UK centres already test for this routinely; to make it only advisory opens the opportunity for services to be cut back as a cost-saving exercise. While this may seem improbable, many hospitals' management follow NICE guidance to the letter and 'consider' implies an 'expendable luxury'. It also provides hospital seeking to improve their service by introducing testing for MGMT for the reasons given above with no support to do so. The draft guidance states on page 9, section 1.2.20, line 17 to offer chemo to patients over 70 who are MGMT methylated; similarly in section 1.2.23, using TMZ alone in elderly patients MGMT methylated is suggested, and on page 42 line 12, where the impact of using TMZ in MGMT methylated patients over 70 is discussed. This is not consistent with the initial advice to only 'consider' testing for MGMT; it would be consistent with inclusion of MGMT testing as mandatory. Testing for MGMT is integral to the conduct of clinical trials where many study designs investigating novel therapies seek to replace concurrent TMZ with the novel agent in unmethylated patients and add it to XRT and TMZ	Thank you for your comment, and for the strong rationale you present for the change. The wording of the recommendation for MGMT status has been strengthened from 'consider' to 'test'.

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				in methylated patients. To not have MGMT testing as a routine part of care for UK patients risks making us a less attractive place to open trials (initial study site selection questionnaires almost always include the question 'is MGMT testing standard care at your centre?'). While I accept that the phrasing ('…Consider testing…') used does not prevent centres testing for MGMT, its omission from national guidance may be viewed unfavourably and reduce the chances of international studies opening in the UK because omission of MGMT status from routine histology reports may be seen as a surrogate of a lower standard of neuropathological reporting. Pharmaceutical companies use such surrogates, and while I accept that that thinking may be flawed, the fact that it is routine and standard in other countries may well adversely affect their perception of UK standards. When costing clinical trials it is also helpful if as many procedures as possible are 'standard care' as procedures above standard care add additional costs and barriers to study opening. Although most commercial trials would test MGMT centrally, knowledge of participants' MGMT is these days vital for any series, even retrospective, submitted for publication or abstracts at American or European meetings. If this guidance does lead to reduction in MGMT testing, which in the current financial climate it might, only 'considering' MGMT testing will significantly detract from the considerable clinical utility of these guidelines. If this guidance does lead to reduction in MGMT testing, which in the current financial climate it might, only 'considering' MGMT testing will significantly detract from the considerable clinical utility of these guidelines.	
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	6	General	Management of newly diagnosed Low Grade Glioma Page 6. PCV mentioned as only option. No consideration of temozolomide. While the evidence is for PCV, many clinicians do consider temozolomide as an alternative. I think the guideline committee should at least consider the option of temzolomide where there are specific considerations such as fertility. The comparison of adjuvant PCV versus temozolomide should be a priority for research. Page 6 and 7. Adjuvant PCV is only considered an option for IDH-mutated low grade glioma. To implement this will require IDH-sequencing to be available in all centres with a turn around time of around 6 weeks for tumours which do not have the commonest IDH-1 mutation. This is not uniformly available at present. Also, although Buckner (2016) confirmed benefit in IDH-1 mutant low grade gliomas, in fact only around 60% of the trial patients tumours tested were IDH-1 mutant. The non-mutated group was too small to draw a definitive conclusion. Therefore the overall result of the trial should stand according to histopathological label (oligodendrogliomas more benefit than "oligoastrocytomas" more benefit than astrocytomas), without IDH-wildtype patients being excluded from adjuvant PCV until there is better evidence for this subgroup specifically. Page 7. Point 1.2.10. Do not give more than 54 Gy for IDH mutated Grade II glioma – does not allow for suspicion of Grade III. 1.2.10, page 7, line 6: Consider inserting: unless radiological characteristics suggest sampling errors and the overall tumour morphology is more in keeping with grade 3 disease. For grade 3 disease, 59.4Gy in 33# or 60Gy in 30# may be indicated.	Thank you for your comment. The trial this recommendation is based on (Buckner 2016) showed a benefit in overall survival and progression-free survival for those who received radiation therapy in combination with PCV. This overall effect appeared to be larger in those with oligodendroglia, oligoastrocytoma, and in those with IDH1 R132H mutations. The committee were aware of clinical opinion that temozolomide could be effective, however they decided not to recommend temozolomide in low grade tumours as the only evidence they uncovered on temozolomide alone in this population demonstrated no effect versus radiotherapy alone and therefore the committee could not recommend TMZ+radiotherapy on the basis of the existing evidence, especially as there was direct evidence of improved overall survival for PCV+radiotherapy. The comparison of concurrent and adjuvant temozolomide to radiotherapy in patient with IDH-wildtype tumour has been prioritised for research. With regard to the IDH mutated grade II glioma recommendations; these aim to standardise practice and to reduce geographical variations across the country, not only with regard to treatment, but also to molecular pathogenesis and biologic behaviour. As it is suggested, the trial conducted by Buckner 2016, identified 62.8% patients with IDH1 R132H mutation present, and there were not enough patients with events in the group without the IDH1 R132H mutation to establish any association with the interventions. However, subgroup exploratory analyses conducted by this same trial, showed that those with IDH1 R132H had significantly longer progression free survival and overall survival than those without the IDH1 R132H mutation ($p< 0.005$ in both cases). Currently, there is no available evidence supporting the use of a specific intervention for IDH-wildtype grade II glioma, for this reason, the committee prioritised a research recommendations in this setting. With regards to Page 7. Point 1.2.10, if there is a suspicion of Grade III then this would fall outside the recommendations of this section (which are for

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					confirmed Grade II). The committee agreed through a process of consensus that clinical judgement is more clinically appropriate than recommendations in such a presentation-specific situation, and consequently the committee have not made recommendations on this topic elsewhere in the guideline.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	10	19	Management of High Grade Gliomas Page 10, 1.2.27, line 19: typo - should read grade IV, not grade III.	Thank you for your comment. This has been corrected.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	11	General	Page 11: 1.2.32: Further surgery with or without carmustine wafers. It was not our understanding that carmustine at relapse was either of proven benefit, or funded?	Thank you for your comment. The reference to carmustine wafers has now been removed from this recommendation as the committee could not determine whether there was sufficient benefit to justify the risk of this intervention.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	11	General	Page 11, section 1.2.32, line 22: An expansion of the statement 'consider radiotherapy' would be welcome, especially to suggest a minimum time from initial treatment.	Thank you for your comment. The committee understands there are ongoing trials in this area and therefore were unwilling to make recommendations which could be contradicted by trials which are reporting shortly. Consequently they have not amended the recommendations.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	12	17	Page 12, section 1.2.37, line 17: "consider awake craniotomy"… we support the use of awake craniotomy as a surgical strategy to increase the extent of resection of gliomas in eloquent areas. However, awake craniotomy is not the only strategy, as for motor function, an available option is surgery under GA with neurophysiological mapping and monitoring. This is mentioned in the current guideline on page 5, section 1.2.1, line 17, where "expertise in intraoperative neurophysiological monitoring" is recommended for low grade gliomas. We believe the same option should be mentioned for high grade glioma. Finally, while awake craniotomy and intraoperative neurophysiological monitoring are usually employed for gliomas, the current guidelines mention these surgical strategies only in the context of gliomas, which is not reflective of current neurosurgical practice. Metastases in eloquent areas, for example, can be operated with the use of these surgical strategies and this should be included.	Thank you for your comments. The committee made recommendations only where there was evidence to support such recommendations, or where the evidence could be easily extrapolated to cover similar technology. However no evidence was uncovered on neurophysiological mapping. Consequently the committee were unable to make a recommendation on neurophysiological mapping and monitoring as an alternative to intraoperative imaging. The prioritisation for the evidence review is slightly different for low- and high-grade glioma in this guideline, which is the reason why only low-grade glioma recommends the qualifications for the surgical team. The low-grade glioma recommendations are for initial management, whereas the high-grade glioma recommendations are for initial management following surgery. Consequently, comment on the expertise of the surgeons in high grade glioma was not prioritised for an evidence review and the committee were unable to make recommendations on this topic. Resection techniques are not mentioned in meningioma or metastases because resection techniques in these conditions were not prioritised for an evidence review and therefore the committee were unable to make recommendations on this topic.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	General	13	1	Page 13, Section 1.2.40 line 1: 'consider intraoperative MR' –we think this statement requires revision. The recent Cochrane review found no evidence to support the use of intra-operative MR imaging. Furthermore we do not agree that the use of intraoperative MRI enhances preservation of function.This can be better assessed with intraoperative mapping& monitoring . Also, this technique is available in only a few sites in the UK;We are concerned that this statement gives it more kudos that it deserves and risks jeopardising patient care if they feel they have to seek second opinions at intra-operative-MR-equipped centres at a time when time is of the essence and prompt maximal resection is indicated. We believe this section ought to be reviewed to recommend intraoperative real-time imaging of some kind, to include USS or MR but focus on functional neuroanatomy. In addition, we question the	Thank you for your comment. The committee believed the evidence for intraoperative MRI was indicative of beneficial outcomes for patients, and therefore recommended it as an imaging option. However both intraoperative MRI and intraoperative ultrasound are merely options to be 'considered', and therefore doing neither intraoperative ultrasound nor MRI may be a reasonable option in some situations. The reference to 'maximal safe resection' has been removed as the committee agreed that this could be confusing.

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				terminology used to describe the role and contribution of intraoperative real-time imaging. In the current draft, it is suggested that both intraop-MRI and ultrasoundd can help to “achieve maximal safe resection”. We question this, as intraoperative imaging does not tell anything about the safety of resection, which can be assessed only with the techniques of awake craniotomy or neurophysiological monitoring previously discussed. We therefore suggest to simply say that intraoperative real-time imaging (MRI or ultrasound) can only help to “achieve maximal resection”.	
Royal Salford NHS Foundation Trust (Manchester) King’s College Hospital NHS Foundation Trust	GL	15	General	Follow-up for glioma Page 15, table 3: we do not agree that discharging patients with completely resected grade 1 gliomas after just 1 annual follow-up scan is advisable. Late recurrence of pilocytic astrocytomas can occur in adults; we would follow annually to 5-10 years. Our practice would not usually be to reduce imaging frequency in a grade 3 glioma, even if co-deleted, to annual after just 2 years. I would continue to image as per grade 3 & 4, although we accept that this view may not be shared and may be over-cautious. Table 3 omits to offer guidance on grade II and grade III IDH wild type tumours (only IDH mutant are listed). Grade III IDH wt should sit with Grade III IDH mutant and grade IV. Grade II wt should perhaps sit with that group as well, but with a comment to image 6 monthly out to 5 years, rather than 3 monthly? This needs to be addressed and added.	Thank you for your comments, we have addressed them in order: We have added a specific reference to pilocytic astrocytomas, specifically that they should be followed up for 15 years 'at increasing intervals' i) We have added a specific reference to pilocytic astrocytomas, specifically that they should be followed up for 15 years 'at increasing intervals' ii) The recommendations contained in this table are just suggestions, therefore we do not believe the table is in conflict with your current practice iii) Reference to IDH wildtype tumours has been added to the table.
Royal Salford NHS Foundation Trust (Manchester) King’s College Hospital NHS Foundation Trust	GL	16	General	Meningiomas Page 16, 2.1.2 add: consider dedicated skull base sequences eg Fat Saturated post-contrast T1 to assist in determining disease extent and in planning surgical and radiotherapy treatment. There is no comment on PET imaging in meningiomas. The group may wish to considering adding this, or mentioning it in some form? The utility of this is, in my view, more investigated and proven than intraoperative MR, which has been included under gliomas (see comments above)	Thank you for your comment. In response to your comment, the committee agreed that this wording merely duplicated the general considerations applicable to any meningioma (discussed in the following recommendations) and so have cut this line from the guideline.
Royal Salford NHS Foundation Trust (Manchester) King’s College Hospital NHS Foundation Trust	GL	17	General	Page 17, Table 4: grade II, Simpson's 1-2: add 'or consider clinical trial entry'. The ROAM study will be recruiting for some years to come and is undoubtedly clinically appropriate in the situation of equipoise implied by the guidance.	Thank you for your comment. It is the understanding of the committee that the ROAM trial is for the same treatment options as recommended in the table, and that therefore trial entry would be automatically considered if the clinician was in equipoise. Therefore no change has been made to recommendations
Royal Salford NHS Foundation Trust (Manchester) King’s College Hospital NHS Foundation Trust	GL	20	General	Page 20. Point 2.2.3. “From the suitable radiotherapy techniques, choose the one which minimises the dose to normal brain tissue.” I strongly disagree with this statement. This could often mean SRS is preferred over a fractionated course, or proton therapy would be preferred over photon therapy. There are other important considerations, as well as convenience which has already been mentioned, importantly risk of severe acute effects (such as symptomatic cerebral oedema which is an increased risk with SRS), and cost effectiveness considerations / cost per QALY (e.g. proton versus photon). For young people aged under 16-24, total integral dose is a consideration which is less relevant in older individuals. There is no specific mention of SRS. Should it be made explicit that the guidance covers SRS for meningiomas? We assume it does? The comments and recommendations hold true for all XRT modalities? Page 20, section 2.2.3, Line 8: considering adding at the end '…..while maximising the chances of local tumour control'... as the technique which minimises dose to normal brain is not necessarily the most clinically appropriate.	Thank you for your comment. In response, we have changed the recommendation to read, '...choose the one which maximises the chances of local tumour control while minimising the dose to normal brain tissue' The immediately preceding recommendation (now 1.4.4) deals with the need to consider radiotherapy morbidity before a decision is made on radiotherapy for meningioma. All recommendations in the guideline are made with consideration to health economic issues and these are documented in the ‘Cost effectiveness and resource use’ sections of the Evidence Reports.
Royal Salford NHS Foundation Trust (Manchester) King’s College Hospital	GL	22	General	Page 22, table 7 grade I meningioma: for some grade 1 tumours treated with XRT, e.g. skull base meningiomas where there are potentially significant clinical sequelae if tumour recurs, continuation of annual imaging out to 5 years should be considered. Page 22, table 7: Grade II meningiomas: no differentiation is made between completely and incompletely resected. It may	Thank you for your comment. The committee were unable to uncover any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example table might be helpful to clinicians and Trusts in planning the timing and extent

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NHS Foundation Trust				be clinically indicated to continue annual surveillance out to 9 years in some patient subgroups. Page 22, table 7: Asymptomatic incidental meningiomas. We favour a longer follow up, particularly in young patients . An option should be given to rescan yearly for a period of time. p22 We wonder why among the recommendations regarding surveillance for patients with meningiomas, the Lancet paper published in 2016 has not been taken into account (EANO guidelines for the diagnosis and treatment of meningiomas. Lancet Oncol. 2016 Sep;17(9):e383-91. doi: 10.1016/S1470-2045(16)30321-7).	of follow-up scans. Since the table is not intended to be prescriptive, annual imaging out to five years is not ruled out in these tumour types. The Lancet paper you reference was excluded from the guideline since it was a guideline and therefore not admissible as evidence for NICE guidelines unless it contains details of the systematic reviews undertaken. This paper did not, and so NICE conducted its own systematic review.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	23	General	Brain metastases Page 23, section 3.1.3, line 10: I applaud and support this statement, and the statement on page 48, line 1-5: 'performing all imaging before neuroMDT referral will reduce delays to local intracranial treatment if it is appropriate and give clarity to people with brain tumours, their family and carers'. However, I wonder if there needs to be a caveat e.g. 'unless in patients with solitary brain lesions and signs of raised ICP / situations of clinical emergency? ' or a statement to say that those people should be referred to neurosurgical on call?	Thank you for your comment. Emergency management of tumours (for example raised ICP or situations of clinical emergency) is outside the scope of the guideline, since very radical intervention may be required in a very short timeframe at any point of management, and this could depend on idiosyncratic features of the tumour or person with the tumour.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	26	General	Page 26, 3.2.4 and 3.2.5 These are practice-changing but welcome statements. However, no mention is made of how to manage someone whose surgical cavity is too large for SRS. Statement 3.2.5 should at least include a caveat e.g. 'when possible' - the studies limited the cavity size / volume. While I accept that the evidence base is purely for SRS, by stating that WBRT should not be offered but SRS considered, this form of words risks excluding patients with cavities too large for SRS from having any adjuvant XRT at all. Might 3.2.5 be revised to include or '…. other targeted focal Radiotherapy'? At least we need some acknowledgement that 'traditional' SRS will not be possible for many patients.	Thank you for your comment. The guideline has been updated with a recommendation to consider surgical cavity size before deciding on treatment, and to consider both stereotactic radiotherapy and stereotactic radiosurgery when irradiating the cavity.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	26	5	Page 26: 3.2.6, line 5: commissioning guidance uses 'controlled or controllable', not just 'controlled'. The distinction between these 2 is important and I suggest adding in the word 'controllable' as well, as the evidence base is there for e.g. treatable but as yet untreated primary lung cancers.	Thank you for your comment. The guideline has been updated with your suggestion.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	29	General	Page 29, table 11. We welcome the guidance on follow-up imaging for brain metastases but wonder if it should be made more explicit that this implies only to patients who would remain candidates for further treatment. E.g. expand the title of the table to say .....'.... for Brain metastases patients treated with surgery or SRS who remain candidates for further active treatment'	Thank you for your comment. The committee were unable to uncover any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example table might be helpful to clinicians and Trusts in planning the timing and extent of follow-up scans. Since the table is not intended to be prescriptive, clinicians may or may not wish to restrict further follow up imaging to those who remain candidates for further active treatment and this decision is not precluded by the recommendation.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	31	General	Ÿ Neuro-rehabilitation Page 31, section 4.2.2: consider adding: 'Neurorehabilitation with the aim of reversal of disability and restoration of function is often not possible in patients with brain tumours. In order to manage expectations and maintain engagement and motivation, staff should explain to patients and carers that the aims of neurorehabilitation include to: Maintain function and prevent / slow future deterioration Optimise functioning in the face of disability Come to terms with disability Reduce impact of treatment toxicity e.g. long-term steroid use.	Thank you for your comment. A decision was taken at scoping that the content of neurological rehabilitation was sufficiently complex that separate guidance was required rather than including it as a question in this guideline. Therefore the content of information delivered about neuro-rehabilitation is outside the scope of this guideline, and may be included in the scope of future NICE guidance.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	31	General	Similarly, Page 51, line 16 and perhaps on page 31 as above, consider adding in a sentence to say 'Good communication between Neuro-oncology teams and Neuro-rehabilitation teams is essential to ensure that the purpose of referrals and the goals of rehabilitation are clear, taking into account diagnosis and prognosis. This can be a very difficult area for neuro-rehab teams who, in our experience, often welcome this type of guidance. Mis-match between the	Thank you for your comment. A decision was taken at scoping that the content of neurological rehabilitation was sufficiently complex that separate guidance was required rather than including it as a question in this guideline. Therefore communication between the neuro-oncology and neuro-rehab teams is outside the scope of this guideline, and may be included in the scope of future NICE guidance.

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				understanding of rehabilitation teams and patients / carers / oncology teams regarding prognosis and goals can be a source of anxiety and distress; good communication about expectations and prognosis can help to overcome this.	
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	33	General	Recommendations for research Research questions 1-4: I support the recommendations for research numbers 1-4, pages 33-36. My only comment pertains to research question 3, page 35, as detailed above. We do feel, however, that the recommendations for research fail to reflect the fact that less progress has been made in improving survival from high grade glioma than virtually any other cancer type; for most patients, the outlook remains grim. While the evidence base for first line treatment for tumours of different grades & subtypes is strong and growing, despite the recommendations in section 1.2.28, page 11, there is little consensus and few effective treatment options at relapse, especially second relapse. Therefore, could consider adding something like: Does the addition of novel agents / repurposed drugs at diagnosis or relapse improve outcomes? Or What is the most appropriate treatment for gliomas of any grade which have recurred after first or subsequent lines of treatment? Pease see further comments below, on comments made on page 43, 'Why the committee made its recommendations' Research question 5: Page 36, line 12: while I accept the presented rationale, I am unconvinced that this (timing of XRT in incompletely resected grade 1 meningioma) is a pressing research priority. In my opinion, it is an area which requires complex individualised decision-making. While difficulty of question should not provide a barrier per se, this would be an incredibly difficult question to address given the natural history of this disease. I feel the treatment recommendations are strong and an unconvinced that this is a pressing or feasible question. No research questions are suggested on the topic of metastases. This may be beyond the scope of this guidance and fall under disease-specific teams – breast, lung, etc. However, further to my comments above, consideration could be given to including something like: 'Is conventional radiotherapy delivered as a targeted cavity-boost effective in patients not suitable for SRS following resection of a brain metastasis?'	Thank you for your comment. The committee was aware of trials in this area which were due to report after the publication of the guideline such as the EORTC 26101 trial. They therefore did not believe another marginal trial in this area would be of significant benefit to patients in the absence of new evidence suggesting likely positive outcomes using novel agents for people with recurrent glioma. The committee believe historic trials of the timing of XRT in grade 1 meningioma have suffered from a lack of clinical equipoise. They also believe that radiotherapy and surgical techniques have advanced far enough that equipoise is now a realistic expectation. Therefore they believe that a trial in this area could be valuable, especially as an aid to the sort of complex individualised decision making you describe. The committee considered the suggested research recommendation. They believed that without expert guidance on the treatment of various primaries (for example breast and lung as you describe) they would be unable to design a trial that would be of certain value. Consequently they did not make a research recommendation in this area.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	35	General	Page 35, Line 22, Research is important ... consider adding ... '… because earlier and timely supportive care interventions and care plans may help reduce unplanned and / or emergency contact with secondary and tertiary providers'. This is very real – a meaningful proportion of acute admissions / A&E attendances would be avoidable with adequate supportive care with pre-planning. This provides a further tangible reason to support this type of research – unplanned admissions expose patients to both distress and the risks of being in hospital – falls, infection etc. and can be frustrating and distressing for patients and carers and clinically inappropriate and burdensome for staff.	Thank you for your comment. Your suggestion has been incorporated into the final guideline.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	42	General	Management of high grade gliomas: Why the committee made its recommendations Page 42, lines 12-14: while we concur with the recommendation that the use of tumour treating fields, bevacizumab, elotinib and cediramib cannot be supported for recurrent high grade glioma, I do not understand or support the inclusion of the statement on page 42, lines 13-15 that these recommendations are 'likely to lead to potential resource saving for the NHS ... which will free up resources elsewhere'. The NHS is not presently funding (nor about to fund) any of these treatments; to state that not using them will lead to will lead to potential resource saving for the NHS and will free up resources elsewhere seems to be to be erroneous. It risks raising hopes in managers less-closely engaged in the field that this guidance will be cost-saving, which in my opinion it will not.	Thank you for your comment. The section has been substantially updated to reflect that the recommendations are unlikely to create a change in practice.

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Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	43	General	Page 43, Line 15-16: 'these recommendations might lead to research into newer interventions such as a ketogenic diet. This could change practice in the future'. We welcome this statement, but would like to see other areas of potential interest included in that list including cannabis oil, immunotherapy and even metformin. I do not believe the evidence for the ketogenic diet is any stronger than for any other novel intervention and that it therefore deserves special mention, while inclusion of other potential treatments in that list might serve as a meaningful catalyst for research in those areas. Overall, the section on management of recurrent high grade glioma fails to convey just how bleak the prognosis in that situation is, how low the response rates to the standard treatments are and the profound depth of need for better treatments in this area. While We accept that this document is not a research agenda, I do feel that such a thorough review and setting out of the evidence ought to reflect the above, as this will be a powerful and much-cited, much referenced document for years to come.	Thank you for your comment. Ketogenic diet is picked out as an example, and not the only treatment which could be researched in the future, however the reference to ketogenic diet has been cut to avoid prejudicing future researchers. It is not possible to amend the short guideline document to better convey the prognosis of recurrent high-grade glioma, as discussing prognosis is part of standard clinical practice (and therefore outside the scope of the guideline) and not therefore suitable for a recommendation. However some sense of the prognosis is conveyed in the full guideline document, where the committee can expand on the reasons behind their decisions.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	43	General	Page 43, line 23-24: 'there was evidence that intraoperative MRI could improve the extent of maximal resection'. This statement is in direct contravention of the recent Cochrane review. We are surprised by its inclusion in the same sentence as 5-ALA, with the implication that the evidence is of the same strength. This is not the case (there is strong RCT evidence to support the use of 5-ALA). Although the document does go on to say that the evidence on intra-operative MR could be generalised to ultrasound, we would like the sentence to be revised to reflect the disparity in the evidence base for 5-ALA, and consider replacing 'intraoperative MR' with a more generic term 'intra-operative real time imaging ' with, intraoperative MR and ultrasound listed in parenthesis afterwards.	Thank you for your comment. The difference in the strength of evidence is reflected in the strength of the recommendations - to 'offer' 5-ALA while merely 'considering' intraoperative MR or ultrasound. Intraoperative MR was recommended since there was some evidence that suggested a possible benefit, although this evidence was not statistically significant and therefore the committee could not make a strong recommendation.
Royal Salford NHS Foundation Trust (Manchester) King's College Hospital NHS Foundation Trust	GL	49	General	Page 49, lines 14-17: I concur that the imaging follow-up schedule for brain mets may have resource implications for some units where it represents an increase above current practice. It should also be recognised that reviewing follow-up MR scans in patients who have had several episodes of SRS to different lesions becomes more complex and time consuming. The committee may want to consider adding this.	Thank you for your comment. The rationale and impact section associated with the follow-up sections has been updated in line with your suggestion.
Salford Royal NHS Foundation Trust	GL	OVERALL	General	Also, importantly: This guideline covers anyone diagnosed aged 18 or over, but no mention is made of TYA services who would be responsible for patients aged 18-24. Consideration should be given to adding some acknowledgment of this.	Thank you for your suggestion. The committee agreed to add a recommendation (1.9.10) cross referring to the existing NICE guidance for the care of people aged 16-24 in cancer services as this contains relevant recommendations for this group.
Salford Royal NHS Foundation Trust	GL	5	line 6, point 1.1.4	Pg 5, states only to 'consider testing ... for MGMT promoter methylation' – it is not included as a mandatory requirement of neuropathology reporting of high grade gliomas. We feel strongly that it ought to be included as mandatory and the wording strengthened beyond just 'consider' (we accept that it is slightly different from the diagnostic-markers list under 1.1.3; but we do feel it ought to be mandated as standard for the reasons set out below). Although MGMT testing does not aid diagnosis, it unquestionably falls into the category of a molecular marker which determines prognosis and guides treatment and feel its inclusion as a mandatory part of neuropathology reports for high-grade gliomas is warranted for the following reasons: i) MGMT is a very important prognostic marker which indicates patients' chances of responding to chemotherapy treatment. While it may not lead clinicians to withhold chemo in all unmethylated patients (outside of clinical trials) it does help inform how to weigh decisions in terms of prioritising quality of life vs active treatment and how much to encourage patients struggling with chemo toxicity to persevere. It is very important in helping to support patients in making informed decisions about their treatment and future care planning at all stages from diagnosis	Thank you for your comment, and for the strong rationale you present for the change. The wording of the recommendation for MGMT status has been strengthened from 'consider' to 'test'.

				onwards. ii) MGMT testing is integral to the EANO guidelines (Lancet Oncology 2017). To omit this from the UK guideline list of standard, mandatory molecular tests puts us out of step with the rest of the Europe and with the USA, significantly adversely affecting our ability to compare outcomes with international centres. This type of international comparison is a key central tenet of NHSe's assessment of effectiveness of cancer care; failure to routinely test all patients for MGMT methylation status renders future meaningful comparison impossible. iii) Many UK centres already test for this routinely; to make it only advisory opens the opportunity for services to be cut back as a cost-saving exercise. While this may seem improbable, many hospitals' management follow NICE guidance to the letter and 'consider' implies an 'expendable luxury'. It also provides hospital seeking to improve their service by introducing testing for MGMT for the reasons given above with no support to do so. iv) The draft guidance states on page 9, section 1.2.20, line 17 to offer chemo to patients over 70 who are MGMT methylated; similarly in section 1.2.23, using TMZ alone in elderly patients MGMT methylated is suggested, and on page 42 line 12, where the impact of using TMZ in MGMT methylated patients over 70 is discussed. This is not consistent with the initial advice to only 'consider' testing for MGMT; it would be consistent with inclusion of MGMT testing as mandatory. v) Testing for MGMT is integral to the conduct of clinical trials where many study designs investigating novel therapies seek to replace concurrent TMZ with the novel agent in unmethylated patients and add it to XRT and TMZ in methylated patients. To not have MGMT testing as a routine part of care for UK patients risks making us a less attractive place to open trials (initial study site selection questionnaires almost always include the question 'is MGMT testing standard care at your centre?'). While I accept that the phrasing ('…Consider testing…') used does not prevent centres testing for MGMT, its omission from national guidance may be viewed unfavourably and reduce the chances of international studies opening in the UK because omission of MGMT status from routine histology reports may be seen as a surrogate of a lower standard of neuropathological reporting. Pharmaceutical companies use such surrogates, and while I accept that that thinking may be flawed, the fact that it is routine and standard in other countries may well adversely affect their perception of UK standards. vi) When costing clinical trials it is also helpful if as many procedures as possible are 'standard care' as procedures above standard care add additional costs and barriers to study opening. Although most commercial trials would test MGMT centrally, knowledge of participants' MGMT is these days vital for any series, even retrospective, submitted for publication or abstracts at American or European meetings. vii) If this guidance does lead to reduction in MGMT testing, which in the current financial climate it might, only 'considering' MGMT testing will significantly detract from the considerable clinical utility of these guidelines. We were surprised that MGMT was omitted from Table 18 in Evidence Review A, page 27, line 24, under the heading 'What are the most useful molecular markers to determine prognosis / guide treatment in glioma?', yet MGMT is listed in table 19, page 28, line 15. While we concur that there is a dirth of RCT evidence on this issue and MGMT testing does not aid diagnosis, it unquestionably informs prognosis and management decisions as outlined below and I feel strongly should be We have read Evidence Review A and the other supporting documentation and understand why the committee reached their recommendation on this question. However, on various matters elsewhere in the guidance the committee comments that the evidence base is weak and the guidelines draw on clinical experience and opinion. We suggest that extension of this model to the question of routine MGMT testing is warranted.	

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Salford Royal NHS Foundation Trust	GL	6, 7	General	Page 6. PCV mentioned as only option. No consideration of temozolomide. While the evidence is for PCV, many clinicians do consider temozolomide as an alternative. I think the guideline committee should at least consider the option of temzolomide where there are specific considerations such as fertility. The comparison of adjuvant PCV versus temozolomide should be a priority for research. Page 6 and 7. Adjuvant PCV is only considered an option for IDH-mutated low grade glioma. To implement this will require IDH-sequencing to be available in all centres with a turn around time of around 6 weeks for tumours which do not have the commonest IDH-1 mutation. This is not uniformly available at present. Also, although Buckner (2016) confirmed benefit in IDH-1 mutant low grade gliomas, in fact only around 60% of the trial patients tumours tested were IDH-1 mutant. The non-mutated group was too small to draw a definitive conclusion. Therefore the overall result of the trial should stand according to histopathological label (oligodendrogliomas more benefit than “oligoastrocytomas” more benefit than astrocytomas), without IDH-wildtype patients being excluded from adjuvant PCV until there is better evidence for this subgroup specifically.	Thank you for your comment. The trial this recommendation is based on (Buckner 2016) showed a benefit in overall survival and progression-free survival for those who received radiation therapy in combination with PCV. This overall effect appeared to be larger in those with oligodendroglia, oligoastrocytoma, and in those with IDH1 R132H mutations. The committee were aware of clinical opinion that temozolomide could be effective, however they decided not to recommend temozolomide in low grade tumours as the only evidence they uncovered on temozolomide alone in this population demonstrated no effect versus radiotherapy alone and therefore the committee could not recommend TMZ+radiotherapy on the basis of the existing evidence, especially as there was direct evidence of improved overall survival for PCV+radiotherapy. The comparison of concurrent and adjuvant temozolomide to radiotherapy in patient with IDH-wildtype tumour has been prioritised for research. With regard to the IDH mutated grade II glioma recommendations; these aim to standardise practice and to reduce geographical variations across the country, not only with regard to treatment, but also to molecular pathogenesis and biologic behaviour. As it is suggested, the trial conducted by Buckner 2016, identified 62.8% patients with IDH1 R132H mutation present, and there were not enough patients with events in the group without the IDH1 R132H mutation to establish any association with the interventions. However, subgroup exploratory analyses conducted by this same trial, showed that those with IDH1 R132H had significantly longer progression free survival and overall survival than those without the IDH1 R132H mutation (p< 0.005 in both cases). Currently, there is no available evidence supporting the use of a specific intervention for IDH-wildtype grade II glioma, for this reason, the committee prioritised a research recommendations in this setting.
Salford Royal NHS Foundation Trust	GL	7	Point 1.2.10.	Do not give more than 54 Gy for IDH mutated Grade II glioma – does not allow for suspicion of Grade III.	Thank you for your comment. If there is a suspicion of Grade III then this would fall outside the recommendations of this section (which are for confirmed Grade II). The committee agreed through a process of consensus that clinical judgement is more clinically appropriate than recommendations in such a presentation-specific situation, and consequently the committee have not made recommendations on this topic elsewhere in the guideline.
Salford Royal NHS Foundation Trust	GL	7	1.2.10 LINE 6	1.2.10, page 7, line 6: Consider inserting: unless radiological characteristics suggest sampling errors and the overall tumour morphology is more in keeping with grade 3 disease. For grade 3 disease, 59.4Gy in 33# or 60Gy in 30# may be indicated.	Thank you for your comment. If there is a suspicion of Grade III then this would fall outside the recommendations of this section (which are for confirmed Grade II). The committee agreed through a process of consensus that clinical judgement is more clinically appropriate than recommendations in such a presentation-specific situation, and consequently the committee have not made recommendations on this topic elsewhere in the guideline.
Salford Royal NHS Foundation Trust	GL	10	1.2.27, line 19	Page 10,: typo - should read grade IV, not grade III.	Thank you for your comment. This has been corrected.
Salford Royal NHS Foundation Trust	GL	11	1.2.32	Further surgery with or without carmustine wafers. It was not our understanding that carmustine at relapse was either of proven benefit, or funded? If there is a change, risks (infection, swelling etc) should also be highlighted	Thank you for your comment. The reference to carmustine wafers has now been removed from this recommendation as the committee could not determine whether there was sufficient benefit to justify the risk of this intervention.
Salford Royal NHS Foundation Trust	GL	11	section 1.2.32, line 22	: An expansion of the statement 'consider radiotherapy' would be welcome, especially to suggest a minimum time from initial treatment.	Thank you for your comment. The committee understands there are ongoing trials in this area and therefore were unwilling to make recommendations which could be contradicted by trials which are reporting shortly. Consequently they have not amended the recommendations.
Salford Royal NHS Foundation Trust	GL	13	Section 1.2.40 line 1	consider intraoperative MR' –we think this statement requires revision. The recent Cochrane review found no evidence to support the use of intra-operative MR imaging. Furthermore we do not agree that the use of intraoperative MRI enhances preservation of function.This can be better	Thank you for your comment. This has now been amended to read: 'Consider intraoperative MRI to help achieve surgical resection of both low-grade and high-grade glioma while preserving neurological function, unless MRI is contraindicated'.

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				assessed with intraoperative mapping& monitoring . Also, this technique is available in only a few sites in the UK;We are concerned that this statement gives it more kudos that it deserves and risks jeopardising patient care if they feel they have to seek second opinions at intra-operative-MR-equipped centres at a time when time is of the essence and prompt maximal resection is indicated. We believe this section ought to be reviewed to recommend intraoperative real-time imaging of some kind, to include USS or MR but focus on functional neuroanatomy	The committee supported the use of iMRI to because the evidence showed that this technique achieves a higher rate of tumour resection without compromising areas of the brain implicated in language. The committee acknowledged the lack of high quality evidence in this field, and were aware of the limitations of the trial this recommendation is based on (Senft 2011), however they agreed that it would not have been possible to conduct a trial comparing surgical techniques masking surgeons and patients.". As the recommendation is only that MRI be 'considered', doing neither intraoperative ultrasound nor MRI is a reasonable option and therefore patient safety should not be jeopardised if time is of the essence. Consequently the committee have not amended the recommendations.
Salford Royal NHS Foundation Trust	GL	15	General	i) Page 15, table 3: we do not agree that discharging patients with completely resected grade 1 gliomas after just 1 annual follow-up scan is advisable. Late recurrence of pilocytic astrocytomas can occur in adults; we would follow annually to 5-10 years. ii) Our practice would not usually be to reduce imaging frequency in a grade 3 glioma, even if co-deleted, to annual after just 2 years. I would continue to image as per grade 3 & 4, although we accept that this view may not be shared and may be over-cautious. iii) Table 3 omits to offer guidance on grade II and grade III IDH wild type tumours (only IDH mutant are listed). Grade III IDH wt should sit with Grade III IDH mutant and grade IV. Grade II wt should perhaps sit with that group aswell, but with a comment to image 6 monthly out to 5 years, rather than 3 monthly? This needs to be addressed and added.	Thank you for your comments, we have addressed them in order: i) We have added a specific reference to pilocytic astrocytomas, specifically that they should be followed up for 15 years 'at increasing intervals' ii) The recommendations contained in this table are just suggestions, therefore we do not believe the table is in conflict with your current practice iii) Reference to IDH wildtype tumours has been added to the table.
Salford Royal NHS Foundation Trust	GL	16	General	i) Page 16, 2.1.2 add: consider dedicated skull base sequences eg Fat Saturated post-contrast T1 to assist in determining disease extent and in planning surgical and radiotherapy treatment. ii) There is no comment on PET imaging in meningiomas. The group may wish to considering adding this, or mentioning it in some form? The utility of this is, in my view, more investigated and proven than intraoperative MR, which has been included under gliomas (see comments above)	Thank you for your comment. The guideline has not been amended to include comment on dedicated skull base sequences or PET as the committee did not uncover any evidence on these topics and they were viewed as too detailed to make recommendations based purely on the committee's consensus.
Salford Royal NHS Foundation Trust	GL	17	Table 4	iii) Page 17, Table 4: grade II, Simpson's 1-2: add 'or consider clinical trial entry'. The ROAM study will be recruiting for some years to come and is undoubtedly clinically appropriate in the situation of equipoise implied by the guidance.	Thank you for your comment. It is the understanding of the committee that the ROAM trial is for the same treatment options as recommended in the table, and that therefore trial entry would be automatically considered if the clinician was in equipoise. Therefore no change has been made to recommendations.
Salford Royal NHS Foundation Trust	GL	20	Point 2.2.3.	iv) Page 20. "From the suitable radiotherapy techniques, choose the one which minimises the dose to normal brain tissue." I strongly disagree with this statement. This could often mean SRS is preferred over a fractionated course, or proton therapy would be preferred over photon therapy. There are other important considerations, as well as convenience which has already been mentioned, importantly risk of severe acute effects (such as symptomatic cerebral oedema which is an increased risk with SRS), and cost effectiveness considerations / cost per QALY (e.g. proton versus photon). For young people aged under 16-24, total integral dose is a consideration which is less relevant in older individuals. v) There is no specific mention of SRS. Should it be made explicit that the guidance covers SRS for meningiomas? We assume it does? The comments and recommendations hold true for all XRT modalities? vi) Page 20, section 2.2.3, Line 8: considering adding at the end '…..while maximising the chances of local tumour control'... as the technique which minimises dose to normal brain is not necessarily the most clinically appropriate. vii)	Thank you for your comment. In response, we have changed the recommendation to read, '...choose the one which maximises the chances of local tumour control while minimising the dose to normal brain tissue' The immediately preceding recommendation (now 1.4.4) deals with the need to consider radiotherapy morbidity before a decision is made on radiotherapy for meningioma. All recommendations in the guideline are made with consideration to health economic issues and these are documented in the 'Cost effectiveness and resource use' sections of the Evidence Reports.
Salford Royal NHS Foundation Trust	GL	22	Table 7	Page 22, table 7 grade I meningioma: for some grade 1 tumours treated with XRT, e.g. skull base meningiomas where there are potentially significant clinical sequelae if tumour recurs, continuation of annual imaging out to 5	Thank you for your comment. The committee were unable to uncover any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example

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				years should be considered. viii) Page 22, table 7: Grade II meningiomas: no differentiation is made between completely and incompletely resected. It may be clinically indicated to continue annual surveillance out to 9 years in some patient subgroups. p22 We wonder why among the recommendations regarding surveillance for patients with meningiomas, the Lancet paper published in 2016 has not been taken into account (EANO guidelines for the diagnosis and treatment of meningiomas. Lancet Oncol. 2016 Sep;17(9):e383-91. doi: 10.1016/S1470-2045(16)30321-7).	table might be helpful to clinicians and Trusts in planning the timing and extent of follow-up scans. Since the table is not intended to be prescriptive, annual imaging out to five years is not ruled out in these tumour types. The Lancet paper you reference was excluded from the guideline since it was a guideline and therefore not admissible as evidence for NICE guidelines unless it contains details of the systematic reviews undertaken. This paper did not, and so NICE conducted its own systematic review.
Salford Royal NHS Foundation Trust	GL	26	3.2.4 and 3.2.5	• Page 26, 3.2.4 and 3.2.5 These are practice-changing but welcome statements. However, no mention is made of how to manage someone whose surgical cavity is too large for SRS. Statement 3.2.5 should at least include a caveat e.g. 'when possible' - the studies limited the cavity size / volume. While I accept that the evidence base is purely for SRS, by stating that WBRT should not be offered but SRS considered, this form of words risks excluding patients with cavities too large for SRS from having any adjuvant XRT at all. Might 3.2.5 be revised to include or '…. other targeted focal Radiotherapy'? At least we need some acknowledgement that 'traditional' SRS will not be possible for many patients. • Point 3.2.5 – page 26 –Also there is no mention of pre-operative stereotactic radiotherapy – there are several studies advocating this approach over post operative cavity (Patel KR1 vComparing pre-operative stereotactic radiosurgery (SRS) to post-operative whole brain radiation therapy (WBRT) for resectable brain metastases: a multi-institutional analysis. J Neurooncol. 2017 Feb;131(3):611-618. doi: 10.1007/s11060-016-2334-3. Epub 2016 Dec 20. There needs to be clear guidance on this as pre-op SRS has been shown to reduce radiation necrosis and allow more precise targeting	Thank you for your comment. The guideline has been updated with a recommendation to consider surgical cavity size before deciding on treatment, and to consider both stereotactic radiotherapy and stereotactic radiosurgery when irradiating the cavity. The focus of this section of the guideline was on post-operative management, or where an operation was not possible. Consequently evidence on pre-operative stereotactic radiotherapy was not sought or included (including the J Neurooncol article you cite) and the recommendations cannot be altered.
Salford Royal NHS Foundation Trust	GL	26	3.2.6, line 5	• Page 26:: commissioning guidance uses 'controlled or controllable', not just 'controlled'. The distinction between these 2 is important and I suggest adding in the word 'controllable' as well, as the evidence base is there for e.g. treatable but as yet untreated primary lung cancers.	Thank you for your comment. The guideline has been updated with your suggestion.
Salford Royal NHS Foundation Trust	GL	29	Table 11	• Page 29, table 11. We welcome the guidance on follow-up imaging for brain metastases but wonder if it should be made more explicit that this implies only to patients who would remain candidates for further treatment. E.g. expand the title of the table to say .....'.... for Brain metastases patients treated with surgery or SRS who remain candidates for further active treatment'	Thank you for your comment. The committee were unable to uncover any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example table might be helpful to clinicians and Trusts in planning the timing and extent of follow-up scans. Since the table is not intended to be prescriptive, clinicians may or may not wish to restrict further follow up imaging to those who remain candidates for further active treatment and this decision is not precluded by the recommendation.
Salford Royal NHS Foundation Trust	GL	31	section 4.2.2	i) Page 31,: consider adding: 'Neurorehabilitation with the aim of reversal of disability and restoration of function is often not possible in patients with brain tumours. In order to manage expectations and maintain engagement and motivation, staff should explain to patients and carers that the aims of neurorehabilitation include to: • Maintain function and prevent / slow future deterioration • Optimise functioning in the face of disability • Come to terms with disability • Reduce impact of treatment toxicity e.g. long-term steroid use.	Thank you for your comment. Section 1.10 addresses the care needs for people with a brain tumour, including the impact of having a brain tumour on the person (1.10.3) and the complex challenges they are likely to face (1.10.4). Therefore the committee decided to make no further recommendations in this area.
Salford Royal NHS Foundation Trust	GL	35	22	iii) Page 35, Line 22, Research is important ... consider adding ... '… because earlier and timely supportive care interventions and care plans may help reduce unplanned and / or emergency contact with secondary and tertiary providers'. This is very real – a meaningful proportion of acute admissions / A&E attendances would be avoidable with adequate supportive care with pre-planning. This provides a further tangible reason to support this type of research – unplanned admissions expose patients to both distress and the risks of being in hospital – falls, infection etc. and can be frustrating and	Thank you for your comment. Your suggestion has been incorporated into the final guideline.

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				distressing for patients and carers and clinically inappropriate and burdensome for staff.	
Salford Royal NHS Foundation Trust	GL	36	12	Page 36, line 12: while I accept the presented rationale, I am unconvinced that this (timing of XRT in incompletely resected grade 1 meningioma) is a pressing research priority. In my opinion, it is an area which requires complex individualised decision-making. While difficulty of question should not provide a barrier per se, this would be an incredibly difficult question to address given the natural history of this disease. I feel the treatment recommendations are strong and an unconvinced that this is a pressing or feasible question. iii) No research questions are suggested on the topic of metastases. This may be beyond the scope of this guidance and fall under disease-specific teams – breast, lung, etc. However, further to my comments above, consideration could be given to including something like: 'Is conventional radiotherapy delivered as a targeted cavity-boost effective in patients not suitable for SRS following resection of a brain metastasis?'	Thank you for your comment. The committee believe historic trials of the timing of XRT in grade 1 meningioma have suffered from a lack of clinical equipoise. They also believe that radiotherapy and surgical techniques have advanced far enough that equipoise is now a realistic expectation. Therefore they believe that a trial in this area could be valuable, especially as an aid to the sort of complex individualised decision making you describe. The committee considered the suggested research recommendation. They believed that without expert guidance on the treatment of various primaries (for example breast and lung as you describe) they would be unable to design a trial that would be of guaranteed value. Consequently they did not make a research recommendation in this area.
Salford Royal NHS Foundation Trust	GL	42	12-14	i) Page 42,: while we concur with the recommendation that the use of tumour treating fields, bevacizumab, elotinib and cediramib cannot be supported for recurrent high grade glioma, I do not understand or support the inclusion of the statement on page 42, lines 13-15 that these recommendations are 'likely to lead to potential resource saving for the NHS ... which will free up resources elsewhere'. The NHS is not presently funding (nor about to fund) any of these treatments; to state that not using them will lead to will lead to potential resource saving for the NHS and will free up resources elsewhere seems to be to be erroneous. It risks raising hopes in managers less-closely engaged in the field that this guidance will be cost-saving, which in my opinion it will not.	Thank you for your comment. The section has been substantially updated to reflect that the recommendations are unlikely to create a change in practice.
Salford Royal NHS Foundation Trust	GL	43	15 - 16	ii) Page 43, Line 15-16: 'these recommendations might lead to research into newer interventions such as a ketogenic diet. This could change practice in the future'. We welcome this statement, but would like to see other areas of potential interest included in that list including cannabis oil, immunotherapy and even metformin. I do not believe the evidence for the ketogenic diet is any stronger than for any other novel intervention and that it therefore deserves special mention, while inclusion of other potential treatments in that list might serve as a meaningful catalyst for research in those areas. Overall, the section on management of recurrent high grade glioma fails to convey just how bleak the prognosis in that situation is, how low the response rates to the standard treatments are and the profound depth of need for better treatments in this area. While We accept that this document is not a research agenda, I do feel that such a thorough review and setting out of the evidence ought to reflect the above, as this will be a powerful and much-cited, much referenced document for years to come.	Thank you for your comment. The section has been updated with other newer interventions mentioned in your comment, such as cannabis oil, immunotherapy and metmorfin.
Salford Royal NHS Foundation Trust	GL	43	23 - 24	iii) Page 43,: 'there was evidence that intraoperative MRI could improve the extent of maximal resection'. This statement is in direct contravention of the recent Cochrane review. We are surprised by its inclusion in the same sentence as 5-ALA, with the implication that the evidence is of the same strength. This is not the case (there is strong RCT evidence to support the use of 5-ALA). Although the document does go on to say that the evidence on intra-operative MR could be generalised to ultrasound, we would like the sentence to be revised to reflect the disparity in the evidence base for 5-ALA, and consider replacing 'intraoperative MR' with a more generic term 'intra-operative real time imaging ' with, intraoperative MR and ultrasound listed in parenthesis afterwards	Thank you for your comment. The section has been updated with other newer interventions mentioned in your comment, such as cannabis oil, immunotherapy and metmorfin.
Salford Royal NHS Foundation Trust	GL	49	14 - 17	iv) Page 49, lines 14-17: I concur that the imaging follow-up schedule for brain mets may have resource implications for some units where it represents an increase above current practice. It should also be recognised that reviewing	Thank you for your comment. The rationale and impact section associated with the follow-up sections has been updated in line with your suggestion.

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				follow-up MR scans in patients who have had several episodes of SRS to different lesions becomes more complex and time consuming. The committee may want to consider adding this.	
Salford Royal NHS Foundation Trust	GL	54	15	i) Page 54, Line 15: I am very pleased to see the use of the term 'pre-malignant low grade gliomas' - the previous use of the word 'benign' in respect of this diagnosis mis-represents the natural history of this diagnosis. Pre-malignant is a much more appropriate term.	Thank you for your comment. We are pleased you are satisfied with the wording of this recommendation.
Scottish Adult Neuro-Oncology Network	GL	5	1.2.1	All patients should have access to neuropsychological assessment and support prior to surgery.	Thank you for your comment. Recommendation 1.2.1 (in the consultation version of the guideline) is only about surgical expertise, not surgical support. However recommendation 1.2.39 (in the consultation version of the guideline) does recommend the involvement of a neuropsychologist prior to surgery. Consequently the guideline has not been amended, as there is already a discussion of support for surgical intervention.
Scottish Adult Neuro-Oncology Network	GL	5	1.2.2	At present there is little evidence that early surgery confers prognostic benefit and further research is needed to evaluate the benefits of surgery at first radiological diagnosis. In this area of personalised medicine and as per CRUK audit of the role of oncology MDT, all options of management should be openly discussed with the patient from surveillance with radiological imaging including perfusion imaging, to biopsy and surgical resection. Patients need to be involved in the decision making progress and the first consultation with a Neurosurgeon can be overwhelming in terms of information. Patient preferences need to be taking into account and the stage of life a patient is in can influence their decision on what management pathway they would like. It would not be unreasonable to give patients time to reflect on the information they have been given at first consultation, whilst they are placed under clinical and radiological surveillance. Equally there may be patients who are very keen for surgery at first consultation and they should be.	Thank you for your comment. The committee were persuaded by evidence that obtaining a biopsy early returned vital prognostic information and information on treatment options, and also persuaded that resection had benefit over biopsy alone. Consequently they believed that there was enough evidence to make a weaker 'consider' recommendation about early surgery. However the committee considered your comment that the timing should be based on patient preference, and therefore amended the recommendation to read 'within 6 months of radiological diagnosis' (rather than 'on first radiological diagnosis') to account for the fact that people with tumours may need a period of consideration of their options. Also to allow for the possibility of a second imaging sequence to be undertaken at a later time point to look for progression and to assess for symptom change, as the committee also recognised that a proportion of low-grade gliomas harbours unfavourable gene profiles (e.g., IDH wild-type) that make them more like high grade tumours from a prognostic perspective.
Scottish Adult Neuro-Oncology Network	GL	6	45170	1. Should have the option of Temozolomide as well as PCV. 2. It should be noted that the criteria given for immediate oncological treatment are based on no more evidence than those for inclusion in the clinical trial which demonstrated additional benefit to combined treatment. This trial did not however address upfront treatment vs surveillance. The clinical factors chosen for entry are entirely reasonable as factors long identified as putting patients at risk of early progression, but there is no guarantee that such early intervention with oncological therapy in these circumstances is more beneficial than watch and wait and treat on progression. The only randomised study to address this was with XRT alone and shows no OS benefit. The significant cognitive morbidity of early radiotherapy in patients dependent on their executive function for employment should not be downplayed. It is a presumption that the morbidity and consequences of XRT +/- chemo are outweighed by survival benefits of early intervention which has no support in the literature provided, only the opinion of your expert panel. We respectfully offer an alternative opinion, and our understanding is there remains such uncertainty that a randomised trial of surveillance vs intervention (with modern oncological therapy guided by molecular data) in newly diagnosed LGG is planned. Until then there should remain a level of equipoise. There seems a concern that patients may not be managed in specialist units, and this may be guiding the recommendation, but the really important recommendation should be that all LGG should be under the care of a specialist team. Survival can be in excess of 10 years so the long-term effects of radiotherapy become an important issue. 3. Should not be so specific in the order of radiotherapy and chemotherapy treatment in co-deleted oligos. Giving chemotherapy first in a	Thank you for your comments. In the order that you raise them: 1) The committee were aware of clinical opinion that temozolomide could be effective, however they decided not to recommend temozolomide in low grade tumours as the only evidence they uncovered on temozolomide alone in this population demonstrated no effect versus radiotherapy alone and therefore the committee could not recommend TMZ+radiotherapy on the basis of the existing evidence, especially as there was direct evidence of improved overall survival for PCV+radiotherapy. 2) The committee were aware of the lack of evidence addressing upfront treatment compared to surveillance. For this reason, they recommended active monitoring for those patients less likely to benefit from an immediate treatment, and should be actively monitored, with regular imaging and clinical assessment to identify tumour progression. Cognitive morbidity of early radiotherapy was addressed in the systematic review, with findings covering a significant follow-up time and suggesting no differences in cognitive function in patients after having received radiotherapy (Laack 2005, Prabhu 2014), which is consistent with the experience of the committee. Consequently the recommendations have not been amended. For further information, please see the summary clinical evidence profile in Table 33 and Table 35, Evidence report A. 3) The trial this recommendation is based on is significantly powered to detect differences across treatment arms and has enough follow-up to detect any major morbidity (median follow-up was 11.9 years). For this reason, the

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				low grade oligodendroglioma followed by RT would not be unreasonable for example. This option is proven as equivalent in G3 oligos, there will never likely be similar study now in G2 oligos, but there is nothing about the clinical behaviour of the G2 oligo tumours to suggest that the outcomes will be different from G3. It can be pointed out that this is extrapolation from the G3 population, but given the morbidity risks of XRT in long-term survivors, the ability of chemo to improve the radiology prior to XRT should not be downplayed.	committee considered that people have oligodendrogliomas would benefit of this intervention on this specific order. Consequently,the committee believe their recommendations are justifiable in relation to the evidence, and therefore have not amended the guideline.
Scottish Adult Neuro-Oncology Network	GL	7	17	Should have the option of Temozolomide as well as PCV for all grade 3 tumours. Given Astrocytic tumours showed no benefit to PCV in the RTOG/EORTC studies which resulted in the evidence supporting chemo for oligos, but when similar study done in Astros using TMZ (CATNON) this showed strong survival advantage - this is only one example which could be quoted to support equivalence (at least) of TMZ to PCV. Both are alkylating agents, BR12 showed equivalence, cross-resistance (and sensitivity if have to change for toxicity) is high. Other studies are quoted in these guidelines supporting equivalence – eg Table 41 in the Rationale section (Pragmatically many centres internationally use TMZ despite older trials using PCV. Much freedom is taken in extrapolating from other clinical situations in the Rationale section (see the LGG comments above) but there is a rigidity when it comes to chemo choice which doesn't make sense to many of us. - West of Scotland Cancer Centre (WoSCC)	Thank you for your comment. There is existing NICE guidance on temozolomide for high-grade gliomas which means the committee were unable to make new recommendations on this agent in the guideline. Consequently the recommendations have not been amended.
Scottish Adult Neuro-Oncology Network	GL	7	19	KPS 70 too prescriptive. Patients of KPS 60 (even 50 if this is resultant from eg right leg paresis) can be offered radical intervention if it is deemed in their best interests by the clinician and likely tolerated. Especially giving chemo first in codeleted patients can improve PS significantly allowing consideration of adjuvant XRT.- WoSCC	Thank you for your comment. The evidence on which this recommendation was based used KPS 70 as the inclusion criteria for the trial and therefore the committee believed that this was as far as they could reasonably extend the evidence base. Consequently no change to the recommendation has been made.
Scottish Adult Neuro-Oncology Network	GL	8	6	KPS 70 too prescriptive. CATNON eligibility criteria were ECOG PS 0-2, which is less prescriptive than KPS 70, and we have seen no breakdown of CATNON data based on PS. – WoSCC	Thank you for your comment. The committee believes that most trials use KPS for their entry criteria and that therefore it is appropriate to express recommendations in terms of KPS rather than ECOG PS in order that information from several trials can be synthesised. While the translation between the two performance scales is not direct, the committee believe that KPS 70 or more is the closest KPS score to ECOG PS 0-2. Consequently no change to the recommendations has been made.
Scottish Adult Neuro-Oncology Network	GL	8	11	Wording at present suggests clinicians should be pro-active in introducing to patients these options then explaining they do not work which seems counter-intuitive and potentially distressing for patients. Wording should reflect that if raised, it should be explained there is no evidence to support these. Also the list is not exhaustive - Clomipramine could also be added given frequency it is enquired about. I understand it is to stop some clinicians prescribing treatment with poor evidence base, but seems better to state that there is no evidence for these treatments in glioma at present and they should not be prescribed. Same applies to section 1.2.27 about GBM. What would seem a less biased approach is to state that "there is no evidence to support any additional therapy, including such examples as….." and list some. - WoSCC	Thank you for your comment. The recommendation has been changed to begin, "If asked...". The reason for the list containing the treatments it does is that evidence was searched for in these indications but not uncovered. Consequently the committee cannot say whether evidence exists or not for - for example - clomipramine.
Scottish Adult Neuro-Oncology Network	GL	9	8	Seems to exclude patients with biopsy only from getting chemoRT. We think this is probably an error, and the line about maximal safe debulking as a requirement should be removed. Appreciate the fact that chemoXRT remains an option in the section for "those not fitting these criteria" but it should be clear that it is standard of care for most GBM if fit enough (again we consider KPS 70 too prescriptive). Also, given such little morbidity / QoL impact of adding TMZ to radical radiotherapy, we feel it should be more strongly stated that if a patient is deemed suitable for radical XRT, then adding TMZ is recommended unless there are specific contra-indications. –WoSCC	Thank you for your comment. The recommendation has been amended to explicitly include biopsy only. The recommendation has not been amended to make KPS cut-offs less prescriptive as this was based on trial entry criteria. The committee did not see evidence that radiotherapy+TMZ was superior to radiotherapy alone, and thus were unable to make the recommendation stronger (although they believed that placing radiotherapy+TMZ above radiotherapy alone in the list of options at least indicated a 'hierarchy' of treatment options).

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Scottish Adult Neuro-Oncology Network	GL	10	1.2.23	The advice on this guideline may be better understood through a flow diagram.	Thank you for your comment. A flow diagram is being produced for these recommendations and will be published alongside the guideline.
Scottish Adult Neuro-Oncology Network	GL	10	17	We are far from a supporter of “novocure” TTF but not sure if the wording here is too prescriptive. Like it or not there is a large trial of randomised evidence presented at international oncology meetings showing modest survival benefit in newly diagnosed GBM, so simply stating it should not be offered without comment on why, is probably not acceptable (Health Economics is best of course). The level of criticism of the trial in the GL summary table reflects the community’s concerns over this therapy whose mode of action is difficult to comprehend, and we too do not believe it is beneficial. However if this Guidance is to be evidence based, it is hard to simply ignore a randomised trial. It may not yet be published and peer reviewed (expected late 2017 apparently, before these guidelines are finally published very probably) but then neither is CATNON, yet its interim, non-peer-reviewed results are accepted as a recommendation. We think there needs to be more nuance to this statement (even if its actual recommendation is supported by most clinicians). - WoSCC	Thank you for your comment. The explanation as to why tumour treating fields are not recommended is captured in the 'benefits and harms' section, where it explains that the recommendation is based on cost-effectiveness considerations. Furthermore, its cost has also been discussed in the 'cost effectiveness and resource use' section. However we have added a sentence making the decision making process explicit in the 'rationale and impact' section to ensure the discussion is well signposted.
Scottish Adult Neuro-Oncology Network	GL	11	10	Should have PC as an option as well as PCV and single agent lomustine. The use of vincristine, a drug with no demonstrated single agent activity in gliomas in the PCV regimen can be criticised, and we think that C, PC or PCV should all be stated as reasonable palliative options.	Thank you for your comment. The committee have only made recommendations on PCV as this was the only combination for which there was evidence.
Scottish Adult Neuro-Oncology Network	GL	11	22	We would strongly suggest a statement suggesting caution over the option of considering repeat radiation. Regimens, volumes, potential benefit and risks are all poorly understood and we are uncomfortable with simply stating as a therapy option without comment	Thank you for your comment. The committee understands there are ongoing trials in this area and therefore were unwilling to make recommendations which could be contradicted by trials which are reporting shortly. Consequently they have not amended the recommendations.
Scottish Adult Neuro-Oncology Network	GL	12	1.2.26	The use of 5 ALA should be encouraged to improve extent of resection. However, 5 ALA should only be used in cases where the “surgical intent” is to achieve greater than >90% resection. The surgical intent should be discussed, agreed and documented at the multidisciplinary meeting. In some cases >90% or complete resection is not feasible due to high risk of morbidity and the surgical intention is partial debulking. 5ALA should be avoided in these circumstances.	Thank you for your comment. The recommendation has been amended to read that 5-ALA should be offered if 'the multidisciplinary team believes that surgical resection of all enhancing tumour is possible'.
Scottish Adult Neuro-Oncology Network	GL	16	General	On meningioma management, we think the comment attached to inoperable disease in Table 4 on page 17 is pertinent to include as a guideline to general management of any meningioma (biopsied / debulked / resected / residual disease or otherwise) - “Clinically assess location, growth and likelihood to cause significant symptoms during life expectancy. Consider active monitoring or radiotherapy [insert – or surgery] accordingly.” –WoSCC	Thank you for your comment. In response to your comment, the committee agreed that this wording merely duplicated the general considerations applicable to any meningioma (discussed in the following recommendations) and so have cut this line from the guideline.
Scottish Adult Neuro-Oncology Network	GL	22	General	We think it is important to stress that systemic options for CNS metastases should be explored in sensitive diseases. Beyond a comment on using site of disease as a guide to treatment options, this is not made explicitly clear. The guidance is radiotherapy heavy – for disease like Small Cell Lung Cancer, it is likely that SACT will be the optimal option. We do not think this is explicit enough in these guidelines (SACT is not referenced once that we can see, except to ensure not delivered as concomitant therapy).- WoSCC	Thank you for your comment. A recommendation has been added recommending SACT if the tumour is likely to be responsive.
Scottish Adult Neuro-Oncology Network	GL	26	12-18	No mention of SACT, as noted above. Radiotherapy is not the only option for CNS metastases, especially in the face of active systemic disease. SACT needs mentioned; this is not a guideline on radiotherapy management, but on tumour management.	Thank you for your comment. A recommendation has been added recommending SACT if the tumour is likely to be responsive.
Scottish Adult Neuro-Oncology Network	GL	26	3	Too prescriptive again – should be radiotherapy, either fractionated or SRS. Large randomised studies have demonstrated local control benefit using fractioned RT not SRS in relation to reduced local recurrence post surgery. It is feasible to rationalise that local fractionated XRT round resection site gives	Thank you for your comment. The guideline has been amended to read "stereotactic radiosurgery or stereotactic radiotherapy" everywhere where one technique was not explicitly meant, with the committee taking the description ‘stereotactic radiotherapy, to mean more than one fraction of stereotactic

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				same level of local control benefit without toxicity of whole brain treatment. SRS has not been shown to be superior to fractionated therapy in randomised studies, so cannot be prescriptively recommended. SRS is not available in all sites. Should be clear that there is no survival benefit with this treatment and the pros and cons of any subsequent treatment should be discussed with the patient. - WoSCC	radiosurgery. The committee are aware of the difference between SRS, stereotactic radiotherapy and conventional fractionated radiotherapy, but sought to encourage the best availability and discussion of conformal techniques with patients prior to treatment, with consideration of fractionated radiotherapy where therapeutically superior and/or safer.
Scottish Adult Neuro-Oncology Network	GL	26	5	Too prescriptive again – even if progressing systemic disease, if good PS, low volume, slowly progressing, systemic options exist, it may be perfectly sensible to offer SRS for multiple (small volume / number) metastases to optimise local control with minimal morbidity. It is also becoming an increasingly frequent referral to establish CNS control before having option of SACT either on or off a clinical trial (i.e. in face of active systemic disease).	Thank you for your comment. The guideline has been amended to read "stereotactic radiosurgery or stereotactic radiotherapy" everywhere where one technique was not explicitly meant.
Scottish Adult Neuro-Oncology Network	GL	29	1	Patients with Brain tumours often present with Epilepsy. 80% of LGG and 30% of HGG, as well as 25% of Meningiomas present with seizures. It is important that Brain Tumour patients with seizures or Epilepsy are seen by a Neurologist, preferably with an interest in Tumour Associated Epilepsy, as well as having access to the local Epilepsy Nurse Specialist. In addition there maybe cost implications for supporting Low Grade Glioma patients through a dedicated LGG Clinical Nurse Specialist. The support of LGG is an unmet need in a number of centres.	Thank you for your comment. The committee believed that the existing NICE guidance on epilepsies: diagnosis and management was sufficient to ensure good management of the condition. Consequently they included a link to the guideline, but no other reference to the management of epilepsy in brain tumours. The committee did not uncover any information on dedicated clinical nurse specialist support (for low or high grade glioma) during their systematic reviews of the literature. However as there was evidence that people with brain tumours valued key workers, the committee amended this recommendation to explain that based on their experience the key worker was often a clinical nurse specialist.
Scottish Adult Neuro-Oncology Network	GL	29	9	Table 11 – is this necessary or informative? Follow-up of CNS metastases is a situation so dependent on multiple factors that suggesting even a possible schedule seems entirely meaningless. It will be driven by individual patient and disease-specific factors.	Thank you for your comment. The committee were unable to uncover any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example table might be helpful to clinicians and Trusts in planning the timing and extent of follow-up scans. Since the table is not intended to be prescriptive, the committee believe it is both necessary and informative.
Society of British Neurological Surgeons (SBNS)	GL	General	General	We consider the document overall to be helpful for specialists involved in these MDTs	Thank you for your kind comments.
Society of British Neurological Surgeons (SBNS)	GL	General	General	The entire section on meningioma was confusing and it would have been beneficial to comment or appraise on the debate between surgery and SRS/T	Thank you for your comment. The committee recognised that the guideline could only look at a limited number of clinical questions and that each question could only look at a limited number of factors. They agreed that the biggest clinical variation exists in situations where surgery is not possible, has been attempted once already or is clinically contraindicated (for example, because SRS/T is the preferred treatment option). Therefore the debate between surgery and SRS/T as a first-line treatment was not prioritised for inclusion in the guideline, and the systematic review of the literature on SRS/T and further surgery as a second-line treatment had weak evidence that did not allow the committee to comment substantially on those aspects of the debate.
Society of British Neurological Surgeons (SBNS)	GL	5	19 - 21	We are concerned that the statement “maximal surgical resection” may be misleading and encourages practice that exposes patients to risk and is not based on high quality clinical evidence. It also risks increasing costs across the healthcare system. As defined, you could apply this concept to virtually every patient (it is always possible to safely remove some of a glioma, even if it might only be a very small proportion). The SBNS are aware of situations in which this practice, when liberally applied, has produced poor outcomes for some patients. Whilst the evidence is of low quality throughout, there is more evidence to suggest that complete or close-to-complete resection may improve prognosis. In contrast, there is very little (or no) good evidence to suggest that incomplete/partial resection (of small-moderate tumour	Thank you for your comment. As you note, the evidence is of poor quality throughout and therefore the committee have altered the wording of this recommendation to read "remove as much of the tumour as safely possible after discussion of the possible extent of resection at MDT meeting and with the person with the brain tumour, and their families and carers".

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				proportion) positively improves prognosis but it does increase risk. Therefore, the statement needs to be qualified, either relating to % of tumour resected or to residual tumour volume or using more generic terms to avoid risk, such as “optimal”.	
Society of British Neurological Surgeons (SBNS)	GL	5	22 - 23	As above, stating that a biopsy should only be advised if “maximal safe resection” is not possible is a risky statement and concept and lacking in high quality evidence (it is almost always possible to safely remove some of a glioma, even if it might only be a very small proportion but it might not be advisable if the % resection is limited or the residual volume still high). For biopsy it could be clarified that samples should be taken from different locations within a tumour as they may be heterogenous.	Thank you for your comment. The committee agreed that this recommendation could be misunderstood, and consequently now advise a biopsy only if "surgical resection is not appropriate". The evidence was not strong enough to justify a recommendation explicitly recommending how a biopsy should be conducted, and consequently the committee were unable to make recommendations on this issue.
Society of British Neurological Surgeons (SBNS)	GL	6	15 - 20	Interestingly, for astrocytoma II, a more pragmatic approach is presented “consider” rather than offer treatment which seems sensible, although some clinicians may be more concerned about early progression with these tumours that the oligodendroglial sub-types. Many teams would still advocate 1.2.8 active surveillance but many of these patients after surgery but it would be optimal to state that the treatments can be considered with your patients using shared decision making. Again many patients and oncologists might favour temozolomide over PCV when considering the risks, benefits and side-effects of either option.	Thank you for your comment. On the basis of the trial this recommendation is based on, the committee concluded that the greatest benefit from this active approach was probably observed when 1p/19q codeletion was present, but that there also appeared to be benefit for non-codeleted tumours, provided there was IDH mutation and hence made two recommendations of different strength. The committee did not believe that patients would benefit from active surveillance in the presence of residual tumour on postoperative MRI, due to concerns about progression. Furthermore, they were aware of clinical opinion that temozolomide could be effective, however this could not be recommended as there is no available evidence supporting the use of it.
Society of British Neurological Surgeons (SBNS)	GL	6	9-14	“Offer radiotherapy” then chemotherapy to patients with oligodendroglioma immediately after surgery exposes them to a lifetime risk of morbidity bearing in mind likely survival times in excess of 10 years, in particular the delayed consequence of radiotherapy. Many clinical teams, bearing this in mind, and the evidence base, would discuss the option of active surveillance with their patients, trying to defer radiotherapy (and its risks and side-effects) for as long as possible. Optimally this statement might read that the clinical teams should discuss the pros and cons of early versus late treatment with their patients using shared decision-making techniques. Many oncologists (and patients) currently prefer temozolomide over PCV in this situation, again the pros and cons of either options would best be discussed with the patient. An option not mentioned is to use chemotherapy as the first line treatment, again to avoid the long-term consequences of RT. The term “consider” may have been more appropriate and emphasis on shared decision making	Thank you for your comment. On the basis of the evidence this recommendation is based on, the committee considered that low-grade gliomas with prognosis closer to a typical grade III glioma will benefit from radiotherapy followed by PCV as earlier intervention is associated with extended time to disease progression. Furthermore, the committee were aware of clinical opinion that temozolomide could be effective, however they decided not to recommend temozolomide in low grade tumours as the only evidence they uncovered on temozolomide alone in this population demonstrated no effect versus radiotherapy alone and therefore the committee could not recommend TMZ+radiotherapy on the basis of the existing evidence, especially as there was direct evidence of improved overall survival for PCV+radiotherapy. With regard to the long-term consequences of radiotherapy, cognitive morbidity of early radiotherapy was addressed in the systematic review, with findings suggesting no differences in cognitive function in patients after having received radiotherapy (Laack 2005, Prabhu 2014), which is consistent with the experience of the committee. For further information, please see the summary clinical evidence profile in Table 33 and Table 35, Evidence report A.
Society of British Neurological Surgeons (SBNS)	GL	6	43287	As above consider re-wording or developing more clarity over concept and application of “maximal safe resection”	Thank you for your comment. 'Maximal safe resection' has been reworded throughout to read 'surgical resection' to make explicit that resection should not be undertaken simply to remove as much tumour as possible, but instead only if that tumour removal would be clinically advisable.
Society of British Neurological Surgeons (SBNS)	GL	7	17 - 24	Some patients and clinicians might prefer temozolomide against PCV.	Thank you for your comment. The committee were aware of clinical opinion that temozolomide could be effective, however they decided not to recommend temozolomide in low grade tumours as the only evidence they uncovered on temozolomide alone in this population demonstrated no effect versus radiotherapy alone and therefore the committee could not recommend TMZ+radiotherapy on the basis of the existing evidence, especially as there was direct evidence of improved overall survival for PCV+radiotherapy. Consequently the recommendations have not been amended.

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Society of British Neurological Surgeons (SBNS)	GL	7	1-5	An option for progressive oligodendroglial tumours is primary chemotherapy alone in first instance (not mentioned but should be considered as an option and discussed with your patient). Same comment throughout about PCV vs temozolomide.	Thank you for your comment. The committee only uncovered very weak evidence for the use of primary chemotherapy alone in this indication, and consequently did not recommend it. Therefore the recommendations have not been amended.
Society of British Neurological Surgeons (SBNS)	GL	8	11	These treatments are currently being prescribed to patients mainly by private clinicians. The wording needs to be stronger if it is intended for this to be prevented.	Thank you for your comment. The intent is not to prevent people receiving these treatments, but to highlight that evidence for their efficacy is currently lacking in order to allow patients to make an informed choice about whether they wish to receive these treatments. Consequently no change has been made to recommendations.
Society of British Neurological Surgeons (SBNS)	GL	9	14 - 23	1.2.20 and 1.2.21 are actually identical i.e. you are saying the methylation status does not change treatment, so 1.2.21 should be removed and the second bullet point in 1.2.20 should read “have a newly diagnosed grade IV glioma (GBM) irrespective of MGMT methylation status”	Thank you for your comment. The distinction is that 1.2.20 begins with 'offer' which gives the recommendation more strength than 1.2.21 which begins with 'consider' . This reflects the evidence demonstrating a very clear response to treatment in those with MGMT methylation and a suggestive but not statistically significant response in those without.
Society of British Neurological Surgeons (SBNS)	GL	9	8-13	Why have the guidelines excluded patients with a biopsy only proven GBM from chemoradiotherapy? They were not excluded in the Stupp publication. The second bullet point should simply be removed in 1.12.19	Thank you for your comment. The recommendation has been amended to explicitly include biopsy only.
Society of British Neurological Surgeons (SBNS)	GL	12	13 - 16	The same observations about the use of the term “maximal safe resection” apply here. The evidence is contradictory but best supports this option only when complete or close-to-complete resection can safely be achieved – this needs to be explicitly stated to avoid teams being encouraged to apply this concept to essentially all patients, exposing them to risk without proven benefit. Evidence has shown this to be effective for extents of resection from 78%-98% and above, but there is very little evidence that it is effective for lower % resections. The wording needs to be changed to reflect this. Partial resections can, of course, be advocated for the control of raised intracranial pressure, etc but this does not apply to all patients.	Thank you for your comment. This recommendation has been edited to say that 5-ALA should be offered if the surgical resection of all enhancing tumours is possible. As you describe, controlling raised intracranial pressure would be an exceptional case not covered by these recommendations.
Society of British Neurological Surgeons (SBNS)	GL	12	17 - 18	We agree that awake craniotomy may be considered for maximising the extent of resection and maintaining safety – this might be a better statement that the one enclosed. Again same issues with no qualifications around “maximal safe resection”.	Thank you for your comment. The recommendation has been amended to 'help preserve neurological function' without the reference to maximal safe resection, to avoid the issues you point out in this comment.
Society of British Neurological Surgeons (SBNS)	GL	13	6-8	DTI may be a useful adjunct to aid planning of surgery to help identify functionally important tracts, but over- reliance on this technique may expose users and patients to a risk. The evidence base to suggest it will “minimise damage” is poor. It would be better to state that “DTI techniques aid planning by identifying functionally important fibre tracts”	Thank you for your comment. The recommendation has been changed to 'minimise damage to functionally important fibre tracts' to incorporate your comment, but the committee believed it was important to acknowledge that neurosurgery to the brain in areas is difficult and fraught with risk: mapping and recognising these tracts is about not damaging them.
Society of British Neurological Surgeons (SBNS)	GL	13	1	Generally intra-operative imaging has been used to maximise the extent of surgical resection, especially for lower grade tumours, although there is little high-quality evidence of benefit in this context. The statement that iMRI helps to preserve neurological function is not really supported by good quality evidence, nor is that it’s primary aim and it should be removed.	Thank you for your comment. This has now been amended to read: ‘Consider intraoperative MRI to help achieve surgical resection of both low-grade and high-grade glioma while preserving neurological function, unless MRI is contraindicated'. The committee supported the use of iMRI because the evidence showed that this technique achieves a higher rate of tumour resection without compromising areas of the brain implicated in language. The committee acknowledged the lack of high quality evidence in this field, and were aware of the limitations of the trial this recommendation is based on (Senft 2011), however they agreed that it would not have been possible to conduct a trial comparing surgical techniques masking surgeons and patients.
Society of British Neurological Surgeons (SBNS)	GL	13	4	Again, intra-operative ultrasound may be of some potential use to maximise surgical resection for some tumours (although lacking a clear-cut evidence base), however, we are not aware of good evidence that this would improve safety of resection (indeed there is a potential risk of encouraging resection thereby potentially increased risk and harm). The word “Safe” then should be removed.	Thank you for your comment. This has now been amended, removing the word ‘safe’ as you have suggested. The revised recommendation now reads: ‘Consider intraoperative ultrasound to help achieve surgical resection of both low-grade and high-grade glioma’.

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Society of British Neurological Surgeons (SBNS)	GL	15	1	For some patients undergoing chemoradiotherapy for GBM, an earlier post-RT scan might be advised, prior to commencement of next phase of temozolomide	Thank you for your comment. The committee were unable to uncover any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example table might be helpful to clinicians and Trusts in planning the timing and extent of follow-up scans. Since the table is not intended to be prescriptive, clinicians with patients who might be require an earlier post-RT scan are not excluded from offering this as an option.
Society of British Neurological Surgeons (SBNS)	GL	15	8	We strongly disagree that patients with grade 1 tumours be discharged at 12 months if they have a clear MRI. These tumours do recur late, often several years later due to their slow rate of growth. Earlier detection of recurrence may allow better choices of on-going treatment strategies (for example including SRS) that would not be possible if recurrence was detected late with a larger tumour. An option of scanning at years 1,2,3,5,10 & 15 could be considered.	Thank you for your comment. The recommendations contained in this table are just suggestions based on the clinical consensus of the committee and intended to be modified in respect to individual clinical characteristics of a tumour and the person's preferences. Stakeholder feedback is mixed over whether the recommendations are recommending scans too frequently or too infrequently, and therefore the committee does not believe there is clinical consensus on amending the table. Consequently the table has not been amended.
Society of British Neurological Surgeons (SBNS)	GL	15	8	Scanning a patient with a low grade oligo every 6 months after treatment for 2 years is too frequent given the excellent anticipated prognosis (10-15 years survival). Annually would be sufficient, as the chance of progression within a six month timeframe is miniscule	Thank you for your comment. The recommendations contained in this table are just suggestions based on the clinical consensus of the committee and intended to be modified in respect to individual clinical characteristics of a tumour and the person's preferences. Stakeholder feedback is mixed over whether the recommendations are recommending scans too frequently or too infrequently, and therefore the committee does not believe there is clinical consensus on amending the table. Consequently the table has not been amended.
Society of British Neurological Surgeons (SBNS)	GL	15	8	Where is the recommendation for follow up for grade II Astrocytoma? Seems to be missing. Suggest again baseline at 3 months after treatment, then 1 year, annually for life	Thank you for your comment. The table has been lengthened to include recommendations on grade II 1p/19q non-codeleted, IDH mutated glioma.
Society of British Neurological Surgeons (SBNS)	GL	16	10	Perhaps it should say “or if surgery not performed” rather than “not possible”, as sometimes a patient may not want it or it may not be advisable, although technically possible	Thank you for your comment. The committee argued that a patient not wanting surgery was an absolute contraindication to performing that surgery, and therefore surgery would not be possible in this case, but to clarify this point the phrase ‘including if the person declines surgery’ has been added to the guideline. Moreover, if surgery has not been performed it might imply that the person is early in their treatment pathway and surgery is still an option to be considered which could lead to confusion and ambiguity.
Society of British Neurological Surgeons (SBNS)	GL	16	11	“inoperable” is a subjective term and might best be avoided. This is a decision between surgeons and patients and options other than surgery now need to be considered, for example many patients are now treated with suspected meningiomas with stereotactic radiosurgery/radiotherapy (SRS/T), not because they are “inoperable” but because of patient preference as part of shared decision making. This is commissioned by NHSE according to specific criteria and a current document on meningioma treatment cannot really be published without reference to this.	Thank you for your comment. In response to your comment, the word 'inoperable' has been removed and replaced with 'No surgery (radiological only diagnosis)'. To clarify your point about patient preference, the phrase ‘including if the person declines surgery’ has been added to the guideline.
Society of British Neurological Surgeons (SBNS)	GL	17	3-8	Really this section goes without saying and is meaningless without clarification. All of these features would be taken into account with any treatment for any patient with any tumour! More useful, but not mentioned, would be guidance around best types of radiotherapy e.g. SRS/T versus conformal/IMRT, etc or even guidance on the choice between SRS/T and surgery for meningiomas.	Thank you for your comment. The committee believed that not all centres varied their treatment option based on these factors (that is, some centres used only one modality on all patients) and therefore the recommendations are important in driving standards.
Society of British Neurological Surgeons (SBNS)	GL	17	1	There is no mention of the evidence-based and nationally commissioned treatment of meningiomas with SRS/T, as above. Making a clear distinction between different modalities of radiotherapy i.e. SRS/T versus conformal, etc would aid in better understanding of treatment recommendations, otherwise there is a risk of patients receiving the incorrect treatment. It is not clear throughout table 4 if the word “radiotherapy” was intended to include all modalities including SRS/T or not.	Thank you for your comment. The committee systematically reviewed the literature on factors which could affect response to radiotherapy treatment and were unable to make recommendations on the choice between SRS/T versus conformal.

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Society of British Neurological Surgeons (SBNS)	GL	17	1	The concerns about the term inoperable remain as above and it would best be avoided. The biopsy only category must be vanishingly rare, as no one would biopsy a likely meningioma and they are routinely treated without a tissue diagnosis (for example with SRS/T). Perhaps this column would better be removed. (it is probably best described as Simpson V and therefore included anyway). It is difficult to understand what is meant by performing more surgery for incompletely excised tumours in column 2 – they would presumably have been more completely excised if possible upfront. This might be different at recurrence but that features in another column. As it stands table 4 is extremely confusing and illogical and without specific reference to SRS/T potentially, harmful to patients.	Thank you for your comment. In response to your comment, the 'inoperable' category has been moved into a 'Simpson V' category as suggested, and a new category added for meningioma where no surgery was undertaken to incorporate the comments you make about SRS/T.
Society of British Neurological Surgeons (SBNS)	GL	19	2	What type of radiotherapy is being referred to here? Again, there are different risks and benefits with different modalities but it almost seems that this includes all in one group? Better to have made it clear and perhaps had different risks for say SRS/T or for conformal/IMRT which have a very different risk profile. If it is just supposed to be about conformal/IMRT fractionated treatment then this should be explicitly stated.	Thank you for your comment. The committee determined that Table 5 would not be a substitute for informed clinical decision making taken in collaboration with the person with the tumour and consequently did not believe it was appropriate to specify the exact type of radiotherapy to which the table referred - the broad classes of risks and benefits which should be discussed are thought to be similar for most modalities, but the specific risk varies radically with modality and individual patient characteristics. Whereas the committee have amended the guideline in response to your earlier comments on stereotactic radiosurgery/radiotherapy, they have not amended this table as the risks of radiotherapy vary so radically with the modality.
Society of British Neurological Surgeons (SBNS)	GL	20	8	What are the “suitable radiotherapy techniques” we are referring to? Presumably a radiation oncologist would always generally aim to minimise the dose to normal brain? More clarity or explanation required here	Thank you for your comment. Suitable radiotherapy techniques are those which are still suitable following consideration of the bulleted list above (that is, the preferences of the person, tumour grade tumour location and tumour size). However in order to clarify the second part of the recommendation this has been amended to read 'From the suitable radiotherapy techniques, choose the one which maximises the chances of local tumour control while minimising the dose to normal brain tissue.'
Society of British Neurological Surgeons (SBNS)	GL	22	2	Table 7 could benefit from simplification, especially given it is not really based on any good quality evidence. For example, all of the grade 1 sections could be combined as the differences between them are subtle. For grade 1 tumours a simple option might then be scan at year 1, 2, 3, 5, 10 (+/-15, as surgeons have commented there is evidence of recurrence beyond 10 years), unless growth was observed during this observation time. It would be simplest to state that all patients in all categories have a baseline scan at 3 months after treatment to avoid confusion. For patients with asymptomatic incidental meningiomas you might advocate a similar plan to grade 1 (above), especially for younger patients with a real prospect of progression (there is little reason to think they would behave differently from say grade 1 tumours residual after surgery, indeed consideration might be given to an earlier then 12/12 first scan eg 3/12 if any doubt over diagnosis or concerning features). For very small tumours in elderly patients this may not be appropriate as the chance of symptomatic progression during normal life time is so low (indeed for many of these cases it might be reasonable as an option to suggest no imaging at all).	Thank you for your comment. The committee were unable to find any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example table might be helpful to clinicians and Trusts in planning the timing and extent of follow-up scans. Since the table is not intended to be prescriptive, no change has been made to the recommendations regarding simplification as clinicians are not expected to follow the table if it is not appropriate for their practice.
Society of British Neurological Surgeons (SBNS)	GL	23	10-11	There is an important omission – get a tissue diagnosis from the primary site where possible if not already established from past history (this directly impacts on treatment options). The neuro-oncology MDT cannot make reasonable recommendations without a tissue diagnosis. Where this isn’t possible neurosurgery may be required to establish the diagnosis.	Thank you for your comment. The recommendation has been updated to include taking a biopsy from the primary site if possible.
Society of British Neurological Surgeons (SBNS)	GL	23	20	Might it better say the primary tumour site, type and molecular profile. There is no mention of prognosis, whereas NHSE commissioning guidelines mention this as an important factor in determining if focal treatment is to be advocated	Thank you for your comment. This has now been amended to say: 'the primary tumour site, type, and molecular profile'.

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				i.e. is the life expectancy with treatment (of local and systemic disease) thought to be in excess of 6 months.	
Society of British Neurological Surgeons (SBNS)	GL	23	23	Suggest clarify to “stereotactic radiosurgery/radiotherapy…….”	Thank you for your comment. Your suggestion has been incorporated into the final guideline.
Society of British Neurological Surgeons (SBNS)	GL	24	43221	Suggest add “requirement for tissue diagnosis” (such that if diagnosis is not established or in doubt then surgery may be a better option than SRS/T)	Thank you for your comment. The section of the guideline this relates to is the management of confirmed tumour, and therefore a tissue diagnosis should already have been undertaken if it is possible to do so. However a later recommendation suggests that obtaining a more up-to-date tissue sample could be a good reason for selecting one treatment over another. Consequently no change to the guideline has been made.
Society of British Neurological Surgeons (SBNS)	GL	25	1-2	Again better term is SRS/T, see above.	Thank you for your comment. Your suggestion has been incorporated into the final guideline.
Society of British Neurological Surgeons (SBNS)	GL	26	3	Is there evidence that SRS/T to the resection cavity improves overall survival? If not and it exposes patients to additional morbidity and risk and the healthcare system to additional cost, should it really be considered upfront? If it were to be considered should there be guidance on in whom? For example, there is evidence that local recurrence is higher with piecemeal resection rather than en bloc. If post-op MRI raises concerns about residual it could be advised, perhaps if completely clear and en bloc resection it should not? The practice option is 3 monthly MRIs and treatment only if recurrence)and on-going good prognosis, etc). The document suddenly jumps from single cerebral metastases to 1-3 – this is somewhat confusing.	Thank you for your comment. The committee found weak evidence that surgical cavity irradiation reduced both local recurrence rates and time to local recurrence, but no evidence that it improved overall survival. Although the evidence on recurrence was not statistically significant, the committee argued that it was plausible that irradiation of the cavity could delay recurrence, and so were persuaded by it on the basis that reduced or delayed recurrence should improve quality of life. The quality of the evidence was not good enough to make more detailed recommendations, for example in whom cavity irradiation should be offered. However to make this more explicit, the committee added that volume of surgical cavity should be considered before decisions on radiotherapy are made. The committee attempted to present the recommendations in a logical order, but also to present the evidence as accurately as possible. Consequently they believed that it was logical to move from one metastasis exactly to one-to-three metastases to more than one metastases even though this might allow a small amount of ambiguity in certain cases. The reason for this is that the evidence in these cases is ambiguous so the committee was unable to make a strong recommendation. Consequently the committee did not change the recommendations.
Society of British Neurological Surgeons (SBNS)	GL	26	8	Add the phrase “and prognosis” to end of sentence.	Thank you for your comment. Number and volume of metastases is highly predictive of prognosis, and the committee believed that their phrasing accurately reflected the evidence. Consequently the recommendation has not been updated, but the committee's discussion of the evidence has been updated to explain that prognosis is an important purpose of estimating number and volume of metastases.
Society of British Neurological Surgeons (SBNS)	GL	27	10	It does not say who should do the follow up i.e. the local oncologists or a neurosciences team? In this section it would help to state that no follow up is appropriate for many patients with cerebral metastases where prognosis is poor and treatment not being offered – good palliative care should be advised.	Thank you for your comment. The committee did not uncover any evidence on who should do the follow-up, and therefore did not make any recommendations on this topic (provided the individual was qualified). However the committee have given some examples of what sort of individuals might be qualified to perform the follow-up.
Society of British Neurological Surgeons (SBNS)	GL	30	29	This statement is unnecessarily patronising and should be removed. It goes without saying as part of being a clinician and following good medical practice that communications with patients would be professional (as opposed to unprofessional!). If it were to be used it would be more sensible to change the term to compassionate rather than empathetic.	Thank you for your comment. The precise wording of this recommendation was carefully debated, as the committee pointed out that many people would also hope the information was provided in a ‘kind and caring’ or compassionate manner, but this was not universal (for example, some people would want the facts delivered as straightforwardly as possible). The committee concluded that the varying preferences of people for the provision of information was adequately covered by the professional rapport implied by requiring that the information be provided in an ‘empathetic’ manner, which the

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					committee took to mean that the clinician would listen to the patient about their preferred manner of receiving information and vary their delivery accordingly. The statement was not included with the intention of being patronising. Consequently the recommendation has now been changed to call for 'realistic and empathetic' communication.
Society of British Neurological Surgeons (SBNS)	GL	33	6-9	Could it be stated that patients at risk of visual or hearing loss be advised to self-report these symptoms and follow up then be patient-triggered?	Thank you for your comment. Patients are unlikely to self-report until visual impairment or hearing loss has occurred, and therefore the committee thought it was most appropriate to concentrate on identifying those that are at risk of visual impairment or hearing loss in the first instance. Any other change in symptoms will be investigated outside the normal schedule of follow-up, and therefore this might include self-reports. Consequently no change has been made to the guideline.
Society of British Neurological Surgeons (SBNS)	GL	36	12	The confusion over radiotherapy and meningiomas continues. It is quite unusual to give standard say conformal /IMRT fractionated radiotherapy for a meningioma grade 1. The real question currently is much more commonly whether or not to give immediate SRS/T to residual – this review does not reflect standard practice and current dilemmas without addressing this or clarifying what is meant by radiotherapy.	Thank you for your comment. The intervention has been clarified to be 'Immediate radiotherapy, understood to usually mean stereotactic radiotherapy/radiosurgery to the residual depending on clinical characteristics' and a similar change has been made to the comparison.
Society of British Neurological Surgeons (SBNS)	GL	40	12-19	As described this policy over irradiation of low grade gliomas might result in earlier treatment with RT than is current practice in many MDTs. This isn't reflected here, indeed the opposite seems to be suggested as an impact. The guidelines as written could involve a further shift to earlier treatment and more patients living many more years with the consequences of radiotherapy.	Thank you for your comment. The guideline has been updated with a discussion of the potential resource and patient impact of earlier radiotherapy.
Society of British Neurological Surgeons (SBNS)	GL	45	9-11	What does this mean? Extrapolating MRI features of gliomas to classification of meningiomas? In the absence of any evidence really this statement should be removed, especially as we know from evidence (and experience) that there is poor correlation of MRI features with meningioma grade	Thank you for your comment. This section has been clarified to explain that this means distinguishing healthy brain tissue from meningioma.
The Brain Tumour Charity	GL	General	General	The suppliers' factsheet for TMZ states that: Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing Pneumocystis jirovecii pneumonia (PCP). Thus, prophylaxis against PCP is required for all patients receiving concomitant TMZ and RT for the 42-day regimen (with a maximum of 49 days) regardless of lymphocyte count. If lymphopenia occurs, they are to continue the prophylaxis until recovery of lymphopenia to grade ≤ 1. However, there is no mention of this within the guideline. We know from our community through our support services of people affected who at end of life have developed pneumonia, which could have been avoided had the individual been given the prophylaxis.	Thank you for your comment. The recommendations in this guideline about temozolomide have been incorporated from TA23 in line with NICE processes. We are not able to amend the wording of this guidance and therefore cannot make the change you suggest. However, clinicians should read NICE guidelines and Technology Appraisals in conjunction with the relevant Summary of Product Characteristics (SPCs).
The Brain Tumour Charity	GL	General	General	There is no mention within the guideline of banking tissue for the purpose of research. A Government report Your Data: Better Security, Better Choice, Better Care recognised that sharing information and data offers immense potential to unlock new treatments but that the benefits rely on patients having the confidence for their data and information to support the NHS and the knowledge that the use of their data is appropriate and legal, with data held securely. People affected by a brain tumour should be empowered and told that their tissue sample may be used for purposes beyond direct care if appropriate. Where tissue banking is available patients should be made aware of how their tissue is banked and what it means. For example, snap frozen tissue samples allow researchers to carry out the in-depth molecular analysis required to accelerate understanding of tumour biology. This information is also relevant to patients interested in genomic brain tumour sequencing. Furthermore, we know that banking of tissue is not routine. If patients are made aware of how their tissue is banked and what opportunities	Thank you for your comment. An investigation into whether tissue banking for the purpose of research is necessary to the direct care of the person with the tumour was not prioritised for review. Making recommendations on this topic is therefore not possible.

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				may arise as a result they may be more empowered to ask questions and raise issues around best practice in this area.	
The Brain Tumour Charity	GL	General	General	There is no reference in the guidance to opportunities for patients to be involved in research. Around just 3% of brain tumour patients take part in a clinical trial compared to an average of 7% for all cancers. The Brain Tumour Charity believe that every patient is a research patient. There is evidence that patients involved in clinical trials have better reported experience of treatment and care. Furthermore, a conversation about research could provide greater awareness of molecular testing and tissue banking. As the draft guidance states, increasing awareness among patients can lead to faster adoption of best practice outlined in NICE guidance. People affected by a brain tumour are also willing to share their data for research. A survey by The Brain Tumour Charity of people affected showed that 97% of respondents wanted their data shared and 94% were happy to share information even if they could potentially be identified from it. Better awareness of data use within the NHS and its benefits for research can help push innovation in treatment and care. We think that a point about the value of data should be included.	Thank you for your comment. The guideline contains a number of recommendations for further research where evidence was found to be limited or lacking. The guideline also makes a number of recommendations where a treatment is recommended only in research. We believe that these recommendations should provide opportunities for people with brain tumours to be involved in research.
The Brain Tumour Charity	GL	5	5-8	We would suggest that fusion gene is changed to “mutations” in line 5 to be more encompassing. We would recommend removing “consider” from lines 6 and 8, given the pivotal role that methylation status and TERT promoter play. Removing the word consider would go towards more accurate diagnosis and empower patients.	Thank you for your comment. 'Mutations' has been added and 'consider' removed from the recommendation on MGMT status, but the committee believed that the clinical consensus on TERT was not as strong as that for MGMT and consequently did not remove the 'consider' from this recommendation.
The Brain Tumour Charity	GL	5	15	The document states that surgical expertise should include access to awake craniotomy with language and other appropriate functional monitoring. The guidance should acknowledge the potential psychological impact that awake craniotomy may have on the patient and that additional support may be needed to address this. It is crucial that a speech and language therapist is present during this treatment.	Thank you for your comment. Detail on the potential support requirements for awake craniotomy are given in recommendations 1.2.40 - 1.2.42 and includes considering speech and language therapists.
The Brain Tumour Charity	GL	8	2	Fertility preservation is rightly recognised in the document. We recommend that people affected by a brain tumour ask their medical team if treatment could affect their fertility and if they should speak to a fertility specialist. The document raises fertility preservation as a factor to consider when deciding between chemotherapy and radiotherapy first. The speed of fertility preservation can vary considerably across trusts and clinical commissioning groups. If the facilities aren’t in place it may not be discussed at all. If appropriate, it is critical that those affected have a conversation with their medical team about fertility.	Thank you for your comment. We have added a recommendation that fertility be discussed with the person with the tumour, and that recommendation in existing NICE guidance on fertility problems: assessment and treatment (CG156) be followed if appropriate.
The Brain Tumour Charity	GL	8	11	The document states that the available evidence does not support the use of a number of therapies including the ketogenic diet and cannabis oil. We agree that there is not currently enough evidence supporting the effectiveness of those interventions listed here in treating brain tumours. However, we know anecdotally through the support services we provide that people affected by a brain tumour do seek these interventions to self-medicate and may take multiple complementary medicines concurrently. The prognosis for brain tumours is often poor, changes to quality of life can be radical and long lasting and there are few treatment options. People diagnosed with a brain tumour and their loved ones have varying propensity to risk and some are willing to try complementary treatments that are not readily available or are not recommended by their clinician. It means a lot to families to be able to know that they have done everything in their power to help a loved one. Some patients and their families want to lift the ceiling so to speak and seek complementary treatments. Clinicians should be open to conversations about complementary treatments, such as those listed here, if prompted to do so by the patients. Patients should be given a clear understanding of what the	Thank you for your comment. We believe that the statement as it appears in the guideline ('the available evidence does not support the use of') is accurate without being distressing, since it does not prevent those who wish to try a treatment with a limited evidence base from doing so. However the committee were concerned that those who wish to try a treatment with limited evidence were able to do so from a position of complete understanding of the reason why their clinician might not have initially suggested it. The committee agrees that clinicians who are asked by a patient about a complementary therapy in which they do not have experience should typically refer to a service with experience of that therapy, but do not consider this specific to brain tumours and so should form part of a clinician's background knowledge. Therefore no change has been made to the recommendation.

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				available evidence states. On this subject, we know from our community who we talk to regularly through our support services that people affected that their clinician was too readily dismissive of treatments not recommended by the NHS. If clinicians do not feel comfortable doing this then at the very least there needs to be an outlet for these conversations. We also know that very often patients will not talk to their clinician about complementary therapies they are taking. Patients often only feel they can talk about this in a non-judgemental space which promotes openness and honesty. It is essential that patients report to their clinician any complementary treatments that they are taking, so that the clinician can make the patient aware of any potential harmful effects. We understand that clinicians will not necessarily have knowledge of a wide variety of complementary treatments that are not recommended by the NHS. We think that the guidance should include a statement that tells clinicians refer the patient to charities that provide support and information services in the patient does seek further advice on complementary treatments, such as those listed. *The term complementary treatments as used here refers to those used alongside conventional NHS recommended treatments.	
The Brain Tumour Charity	GL	30	2	The guideline recognises there may be significant challenges to cognition for people affected by a brain tumour. Quality communication is essential to meet the care needs of the patient. The Brain Tumour Charity Patient Guide recommends that information should be given face to face and in a private space, out of respect to the gravity of the situation and emotion vulnerability of the patient and family. Family and friends should be encouraged to be in attendance in meetings with doctors. Additional care must be taken to ensure information has been successfully communicated to the patient, if necessary via a family member or carer. Clinicians should also be aware that some patients and their carers will not be health literate and information should be delivered in a way which is accessible and easily interpreted. This is particularly important for those patients with cognitive difficulties or memory difficulties as a result of their tumour and/or treatment. Additional care should be taken to minimise interruptions when information is being presented. We think the guidance should reiterate these points so that the person affected can be best supported. The document states that clinicians should discuss health and social care support needs with the person with a brain tumour and their relatives and carers and to set aside enough time to discuss the impact of the brain tumour on the person and their relatives and carers. We think the guideline should recommend clinicians should consider talking to the carer alone in addition to the carer and patient together. There should be more opportunity for the carer to speak privately with the clinical team in charge of the patient's care to give the carer a private space to speak openly without risk of upsetting or offending the patient. Identifying support for the carer is vital for their own health and that of the patient.	Thank you for your comment. The committee did not review evidence on the best way to communicate with a person with a brain tumour, since this has already been investigated in NICE guidance on patient experience in adult NHS services: improving the experience of care for people using adult NHS services (CG138). Consequently they cross-referred to this guideline and would expect clinicians involved in the care of a person with a brain tumour to be familiar with it. In addition, the recommendation has been updated to include reference to the NHS England Accessible Information Standards which also addresses the points you have raised.
The Brain Tumour Charity	GL	30	14	It is suggested that health and social care professionals involved in the care of people with brain tumours should address complex needs including maintaining a sense of hope. We have heard from some individuals that a reinforcement of hope is not helpful, particularly when individuals are at end of life. The document does not provide any evidence to suggest that maintaining a sense of hope is beneficial for the patient or their family and carers. As we mentioned earlier in this submission, individuals hold differing propensities to risk. Everyone will react differently to the diagnosis of a brain tumour. We think the guidance should emphasise the importance of healthcare professionals responding to the individual in a way which is reflective of those individual's perception of the situation. This involves an open discussion, so that those affected are well informed about their options. We also know that 1 in 2	Thank you for your comment. The evidence included in the systematic review did show that maintaining a sense of hope was important, and consequently the committee recommended that this is an area which should be addressed. NICE cannot comment on the financial situation of those affected by its guidance, as this is outside its remit.

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				people affected by a brain tumour face financial difficulty. We think that there should be a reference to financial difficulty included in this list. Whilst health and social care professionals are not trained to give financial advice they should be mindful of potential impact.	
The Brain Tumour Charity	GL	30	22	The guidance rightly refers to the role of the key worker. Access to a key worker is variable, particularly for people with low grade tumours. Our research has shown that those with a high grade tumour were statistically significantly more likely to agree that they had a single point of contact than those with a low grade tumour. Just over half (53%) of low grade tumour patients said they had a single point of contact, compared to three-quarters (76%) of those with a high grade tumour. We recommend a reference to signposting to third sector organisations which might provide a range of information and support to people with a brain tumour, including advice around access to benefits and access to online communities of people affected by the condition.	Thank you for your comment. The committee believes that in making its recommendations it will improve access to key workers directly, and therefore a reference to third sector organisations providing support in this area would be unneeded. Consequently the guideline has not been altered in response to this comment.
The Brain Tumour Charity	GL	32	17	We think that this paragraph should include a reference to sharing the treatment summary with an individual's GP in a timely manner so as to ensure a better experience of care.	Thank you for your comment. The written treatment summary is a document intended to be shared with GPs. Recommendation 1.9.5 highlights the necessity of a named healthcare professional to coordinate the health and social care of the person with a brain tumour and therefore the committee did not amend the guideline as you have suggested as that recommendation has been made to ensure a better experience of care.
The Brain Tumour Charity	GL	38	15 - 17	We are pleased to see the inclusion of molecular markers in this document as a whole and the lists provided for different tumour types are comprehensive. In our research into the provision of biomarker tests we found that the length of time between the biopsy and delivery of results, which enables the neuropathologist to advise the MDT, varies considerably across centres. Typically, this is in part determined by whether the centres are able to perform a test in-house or outsource to another centres. The delay in some centres can have a big knock on effect for an individual's treatment. For example, one centre reported that in 2017, just 18% of patients with a glioblastoma had their tumour tested for MGMT within 21 days. Clinicians may outline the purpose of biomarker testing and the timeline for results. Clinicians should make it clear that while biomarkers help in classifying types and sub-types of brain tumours it may not influence treatment. We think there should be a reference to a suggested quality performance indicator to give an indication of what best practice is. We are also concerned about how more routine biomarker testing will be implemented in practice with the introduction of NHS England's new commissioning pathway for molecular biomarker tests. The new pathway may compromise the delivery of molecular testing for brain tumours with its focus on genomics, the removal of some brain-tumour specific markers from the NHS England consultation and the establishment of regional hubs, some of which do not currently test for brain tumours. We understand that the new pathway is the remit of NHS England and the draft guidance recognises that the time it takes to implement the new molecular tests will vary significantly between departments. To help overcome this challenge NHSE should be supportive of this aim and willing to explore how to support the implementation of the guidance.	Thank you for your comment. The committee was unable to find any evidence on the optimal timescale regarding the length of time between the biopsy and delivery of results. Consequently it was not possible to make a recommendation on this topic. We will pass your comments about pathway design on to the appropriate body at NHSE.
The National Hospital for Neurology and Neurosurgery	GL	15	8 Table 3	The increasing interval between follow up scans for patients with grade 2 and 3 disease is illogical, all be it common practice. Patients are most likely to transform/progress around 5-years post diagnosis. Scans should if anything be more frequent at this stage not once every two years	Thank you for your comment. The recommendations contained in this table are just suggestions based on the clinical consensus of the committee and intended to be modified in respect to individual clinical characteristics of a tumour and the person's preferences. Stakeholder feedback is mixed over whether the recommendations are recommending scans too frequently or too infrequently, and therefore the committee does not believe there is clinical

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					consensus on amending the table. Consequently the table has not been amended.
The Society and College of Radiographers	GL	26	3.2.5	The Society and College of Radiographers believe that there is not currently commissioning for adjuvant SRS to surgical cavities so a review of the commission of SRS is required to facilitate this change	Thank you for your comment. NICE recommends treatments based on an assessment of the available clinical evidence and cost-effectiveness of those treatments, but not on the basis of existing commissioning structures. It will be a matter for local implementation to commission services to enable the recommendations in this guideline to be delivered.
The Walton Centre	General	General	General	The guidance provides a good update on the previous guidelines and is to be commended for their support of the use of 5ALA, iMRI, iUS, and the routine use of molecular markers. This will make it easier for hospitals to drive forward the changes needed to make these standard across the country.	Thank you for your kind comments.
The Walton Centre	GL	9	17	We are concerned about the stance on Tumour Treating Fields and feel the committee has not taken into account the strength of the evidence supporting this novel (and slightly off the wall) treatment. The long term results are good, and the improvement in outcome in the published randomised controlled trial for this group of patients is better than that seen with the Stupp (TMZ) trial. We believe this cannot be ignored. We do accept that the treatment is not affordable on the NHS as it currently stands, but that is different than it not being effective. It is a novel and unusual cancer treatment, but should not be ignored. We would urge the committee to consider altering the line to read 'Tumour treating fields have been shown to be of benefit, but they are not currently cost effective (or are awaiting a health care model, but are unlikely at present to be cost effective), and so cannot be recommended at this time' or something to that effect.	Thank you for your comment. The committee outline their decision-making process to not recommend Tumour Treating Fields in the full guideline "Based on RCT evidence and published cost effectiveness evidence, the committee concluded that tumour treating fields did not offer sufficient improvement in overall survival and progression free survival to justify the additional cost". Consequently it would not be appropriate to alter the recommendation, since it is correct that at the current time this treatment should not be offered.
University Hospital Southampton NHS FT	GL	General	General	We consider the document overall to be helpful for specialists involved in these MDTs	Thank you for your kind comments.
University Hospital Southampton NHS FT	GL	General	General	The entire section on meningioma was confusing and it would have been beneficial to comment or appraise on the debate between surgery and SRS/T	Thank you for your comment. The committee recognised that the guideline could only look at a limited number of clinical questions and that each question could only look at a limited number of factors. They agreed that the biggest clinical variation exists in situations where surgery is not possible, has been attempted once already or is clinically contraindicated (for example, because SRS/T is the preferred treatment option). Therefore the debate between surgery and SRS/T as a first-line treatment was not prioritised for inclusion in the guideline, and the systematic review of the literature on SRS/T and further surgery as a second-line treatment had weak evidence that did not allow the committee to comment substantially on those aspects of the debate.
University Hospital Southampton NHS FT	GL	5	19 - 21	We are concerned that the statement "maximal surgical resection" may be misleading and encourages practice that exposes patients to risk and is not based on high quality clinical evidence. It also risks increasing costs across the healthcare system. As defined, you could apply this concept to virtually every patient (it is always possible to safely remove some of a glioma, even if it might only be a very small proportion). The SBNS are aware of situations in which this practice, when liberally applied, has produced poor outcomes for some patients. Whilst the evidence is of low quality throughout, there is more evidence to suggest that complete or close-to-complete resection may improve prognosis. In contrast, there is very little (or no) good evidence to suggest that incomplete/partial resection (of small-moderate tumour proportion) positively improves prognosis but it does increase risk. Therefore, the statement needs to be qualified, either relating to % of tumour resected or to residual tumour volume or using more generic terms to avoid risk, such as "optimal".	Thank you for your comment. As you note, the evidence is of poor quality throughout and therefore the committee have altered the wording of this recommendation to read "remove as much of the tumour as safely possible after discussion of the possible extent of resection at MDT meeting and with the person with the brain tumour, and their families and carers".

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University Hospital Southampton NHS FT	GL	5	22 - 23	As above, stating that a biopsy should only be advised if “maximal safe resection” is not possible is a risky statement and concept and lacking in high quality evidence (it is almost always possible to safely remove some of a glioma, even if it might only be a very small proportion but it might not be advisable if the % resection is limited or the residual volume still high). For biopsy it could be clarified that samples should be taken from different locations within a tumour as they may be heterogenous.	Thank you for your comment. The committee agreed that this recommendation could be misunderstood, and consequently now advise a biopsy only if "surgical resection is not appropriate". The evidence was not strong enough to justify a recommendation explicitly recommending how a biopsy should be conducted, and consequently the committee were unable to make recommendations on this issue.
University Hospital Southampton NHS FT	GL	6	15 - 20	Interestingly, for astrocytoma II, a more pragmatic approach is presented “consider” rather than offer treatment which seems sensible, although some clinicians may be more concerned about early progression with these tumours that the oligodendroglial sub-types. Many teams would still advocate 1.2.8 active surveillance but many of these patients after surgery but it would be optimal to state that the treatments can be considered with your patients using shared decision making. Again many patients and oncologists might favour temozolomide over PCV when considering the risks, benefits and side-effects of either option. Nothing mentioned regarding other high risk features in low grade gliomas: In High risk low grade tumour Multivariate analysis of two phase III trials conducted by the EORTC revealed that age ≥40 years, astrocytoma histology (half of patient transform in 5 years), dimension of tumour ≥6 cm, tumour crossing midline, and presence of neurologic deficit before resection were unfavourable prognostic factors and treatment should be considered. Patients with 2 or more of these factors should be considered for treatment? Although IDH status is known to be of prognostic significance its impact on treatment selection is not prospectively tested.	Thank you for your comment. On the basis of the trial this recommendation is based on, the committee concluded that the greatest benefit from this active approach was probably observed when 1p/19q codeletion was present, but that there also appeared to be benefit for non-codeleted tumours, provided there was IDH mutation and hence made two recommendations of different strength. The committee did not believe that patients would benefit from active surveillance in the presence of residual tumour on postoperative MRI, due to concerns about progression. Furthermore, they were aware of clinical opinion that temozolomide could be effective, however this could not be recommended as there is no available evidence supporting the use of it.
University Hospital Southampton NHS FT	GL	6	9-14	“Offer radiotherapy” then chemotherapy to patients with oligodendroglioma immediately after surgery exposes them to a lifetime risk of morbidity bearing in mind likely survival times in excess of 10 years, in particular the delayed consequence of radiotherapy. Many clinical teams, bearing this in mind, and the evidence base, would discuss the option of active surveillance with their patients, trying to defer radiotherapy (and its risks and side-effects) for as long as possible. Optimally this statement might read that the clinical teams should discuss the pros and cons of early versus late treatment with their patients using shared decision-making techniques. Many oncologists (and patients) currently prefer temozolomide over PCV in this situation, again the pros and cons of either options would best be discussed with the patient. An option not mentioned is to use chemotherapy as the first line treatment, again to avoid the long-term consequences of RT. The term “consider” may have been more appropriate and emphasis on shared decision making	Thank you for your comment. On the basis of the evidence, the committee considered that low-grade gliomas with prognosis closer to a typical grade III glioma will benefit from radiotherapy followed by PCV as earlier intervention is associated with extended time to disease progression. Furthermore, the committee were aware of clinical opinion that temozolomide could be effective, however they decided not to recommend temozolomide in low grade tumours as the only evidence they uncovered on temozolomide alone in this population demonstrated no effect versus radiotherapy alone and therefore the committee could not recommend TMZ+radiotherapy on the basis of the existing evidence, especially as there was direct evidence of improved overall survival for PCV+radiotherapy.. With regard to the long-term consequences of radiotherapy, cognitive morbidity of early radiotherapy was addressed in the systematic review, with findings suggesting no differences in cognitive function in patients after having received radiotherapy (Laack 2005, Prabhu 2014), which is consistent with the experience of the committee. For further information, please see the summary clinical evidence profile in Table 33 and Table 35, Evidence report A.
University Hospital Southampton NHS FT	GL	6	43287	As above consider re-wording or developing more clarity over concept and application of “maximal safe resection”	Thank you for your comment. 'Maximal safe resection' has been reworded throughout to read 'surgical resection' to make explicit that resection should not be undertaken simply to remove as much tumour as possible, but instead only if that tumour removal would be clinically advisable.
University Hospital Southampton NHS FT	GL	7	17 - 24	Some patients and clinicians might prefer temozolomide against PCV. For GIII Glioma: PCV/ or Temozolomide without radiotherapy can be an option for patients with any contraindication for radiotherapy (based on Findings from the German Neuro-Oncology Group (NOA)-04 trial showed that alkylating chemotherapy alone (eg, PCV or temozolomide) was as effective as was radiotherapy alone in terms of progression-free survival, and overall survival. Specially in MGMT methylated. Till full outcome of CATNON is available.	Thank you for your comment. The committee were aware of clinical opinion that temozolomide could be effective, however they decided not to recommend temozolomide in low grade tumours as the only evidence they uncovered on temozolomide alone in this population demonstrated no effect versus radiotherapy alone and therefore the committee could not recommend TMZ+radiotherapy on the basis of the existing evidence, especially as there was direct evidence of improved overall survival for PCV+radiotherapy. Consequently the recommendations have not been amended.

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University Hospital Southampton NHS FT	GL	7	1-5	An option for progressive oligodendroglial tumours is primary chemotherapy alone in first instance (not mentioned but should be considered as an option and discussed with your patient). Same comment throughout about PCV vs temozolomide.	Thank you for your comment. The committee only uncovered very weak evidence for the use of primary chemotherapy alone in this indication, and consequently did not recommend it. Therefore the recommendations have not been amended.
University Hospital Southampton NHS FT	GL	8	11	These treatments are currently being prescribed to patients mainly by private clinicians. The wording needs to be stronger if it is intended for this to be prevented.	Thank you for your comment. The intent is not to prevent people receiving these treatments, but to highlight that evidence for their efficacy is currently lacking in order to allow patients to make an informed choice about whether they wish to receive these treatments. Consequently no change has been made to recommendations.
University Hospital Southampton NHS FT	GL	9	14 - 23	1.2.20 and 1.2.21 are actually identical i.e. you are saying the methylation status does not change treatment, so 1.2.21 should be removed and the second bullet point in 1.2.20 should read “have a newly diagnosed grade IV glioma (GBM) irrespective of MGMT methylation status”	Thank you for your comment. The distinction is that 1.2.20 begins with 'offer' which gives the recommendation more strength than 1.2.21 which begins with 'consider'. This reflects the evidence demonstrating a very clear response to treatment in those with MGMT methylation and a suggestive but not statistically significant response in those without.
University Hospital Southampton NHS FT	GL	9	8-13	Why have the guidelines excluded patients with a biopsy only proven GBM from chemoradiotherapy? They were not excluded in the Stupp publication. The second bullet point should simply be removed in 1.12.19	Thank you for your comment. The recommendation has been amended to explicitly include biopsy only.
University Hospital Southampton NHS FT	GL	10	19	Error: The wording needs to change to grade IV gliomas	Thank you for your comment. This has been corrected.
University Hospital Southampton NHS FT	GL	12	13 - 16	The same observations about the use of the term “maximal safe resection” apply here. The evidence is contradictory but best supports this option only when complete or close-to-complete resection can safely be achieved – this needs to be explicitly stated to avoid teams being encouraged to apply this concept to essentially all patients, exposing them to risk without proven benefit. Evidence has shown this to be effective for extents of resection from 78%-98% and above, but there is very little evidence that it is effective for lower % resections. The wording needs to be changed to reflect this. Partial resections can, of course, be advocated for the control of raised intracranial pressure, etc but this does not apply to all patients.	Thank you for your comment. This recommendation has been edited to say that 5-ALA should be offered if the surgical resection of all enhancing tumours is possible. As you describe, controlling raised intracranial pressure would be an exceptional case not covered by these recommendations.
University Hospital Southampton NHS FT	GL	12	17 - 18	We agree that awake craniotomy may be considered for maximising the extent of resection and maintaining safety – this might be a better statement that the one enclosed. Again same issues with no qualifications around “maximal safe resection”.	Thank you for your comment. The recommendation has been amended to 'help preserve neurological function' without the reference to maximal safe resection, to avoid the issues you point out in this comment.
University Hospital Southampton NHS FT	GL	13	6-8	DTI may be a useful adjunct to aid planning of surgery to help identify functionally important tracts, but over- reliance on this technique may expose users and patients to a risk. The evidence base to suggest it will “minimise damage” is poor. It would be better to state that “DTI techniques aid planning by identifying functionally important fibre tracts”	Thank you for your comment. The recommendation has been changed to 'minimise damage to functionally important fibre tracts' to incorporate your comment.
University Hospital Southampton NHS FT	GL	13	1	Generally intra-operative imaging has been used to maximise the extent of surgical resection, especially for lower grade tumours, although there is little high-quality evidence of benefit in this context. The statement that iMRI helps to preserve neurological function is not really supported by good quality evidence, nor is that it’s primary aim and it should be removed.	Thank you for your comment. This has now been amended to read: 'nsider intraoperative MRI to help achieve greater surgical resection of both low-grade and high-grade glioma while preserving neurological function, unless MRI is contraindicated'. The committee supported the use of iMRI to because the evidence showed that this technique achieves a higher rate of tumour resection without compromising areas of the brain implicated in language. The committee acknowledged the lack of high quality evidence in this field, and were aware of the limitations of the trial this recommendation is based on (Senft 2011), however they agreed that it would not have been possible to conduct a trial comparing surgical techniques masking surgeons and patients.
University Hospital Southampton NHS FT	GL	13	4	Again, intra-operative ultrasound may be of some potential use to maximise surgical resection for some tumours (although lacking a clear-cut evidence base), however, we are not aware of good evidence that this would improve safety of resection (indeed there is a potential risk of encouraging resection	Thank you for your comment. This has now been amended, removing the word ‘safe’ as you have suggested. The revised recommendation now reads: ‘Consider intraoperative ultrasound to help achieve surgical resection of both low-grade and high-grade glioma’.

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				thereby potentially increased risk and harm). The word “Safe” then should be removed.	
University Hospital Southampton NHS FT	GL	15	1	For some patients undergoing chemoradiotherapy for GBM, an earlier post-RT scan might be advised, prior to commencement of next phase of temozolomide	Thank you for your comment. The committee were unable to uncover any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example table might be helpful to clinicians and Trusts in planning the timing and extent of follow-up scans. Since the table is not intended to be prescriptive, clinicians with patients who might be require an earlier post-RT scan are not excluded from offering this as an option.
University Hospital Southampton NHS FT	GL	15	8	We strongly disagree that patients with grade 1 tumours be discharged at 12 months if they have a clear MRI. These tumours do recur late, often several years later due to their slow rate of growth. Earlier detection of recurrence may allow better choices of on-going treatment strategies (for example including SRS) that would not be possible if recurrence was detected late with a larger tumour. An option of scanning at years 1,2,3,5,10 & 15 could be considered.	Thank you for your comment. The recommendations contained in this table are just suggestions based on the clinical consensus of the committee and intended to be modified in respect to individual clinical characteristics of a tumour and the person's preferences. Stakeholder feedback is mixed over whether the recommendations are recommending scans too frequently or too infrequently, and therefore the committee does not believe there is clinical consensus on amending the table. Consequently the table has not been amended.
University Hospital Southampton NHS FT	GL	15	8	Scanning a patient with a low grade oligo every 6 months after treatment for 2 years is too frequent given the excellent anticipated prognosis (10-15 years survival). Annually would be sufficient, as the chance of progression within a six month timeframe is miniscule	Thank you for your comment. The recommendations contained in this table are just suggestions based on the clinical consensus of the committee and intended to be modified in respect to individual clinical characteristics of a tumour and the person's preferences. Stakeholder feedback is mixed over whether the recommendations are recommending scans too frequently or too infrequently, and therefore the committee does not believe there is clinical consensus on amending the table. Consequently the table has not been amended.
University Hospital Southampton NHS FT	GL	15	8	Where is the recommendation for follow up for grade II Astrocytoma? Seems to be missing. Suggest again baseline at 3 months after treatment, then 1 year, annually for life	Thank you for your comment. The table has been lengthened to include recommendations on grade II 1p/19q non-codeleted, IDH mutated glioma.
University Hospital Southampton NHS FT	GL	16	10	Perhaps it should say “or if surgery not performed” rather than “not possible”, as sometimes a patient may not want it or it may not be advisable, although technically possible	Thank you for your comment. The committee argued that a patient not wanting surgery was an absolute contraindication to performing that surgery, and therefore surgery would not be possible in this case, but to clarify this point the phrase ‘including if the person declines surgery’ has been added to the guideline. Moreover, if surgery has not been performed it might imply that the person is early in their treatment pathway and surgery is still an option to be considered which could lead to confusion and ambiguity.
University Hospital Southampton NHS FT	GL	16	11	“inoperable” is a subjective term and might best be avoided. This is a decision between surgeons and patients and options other than surgery now need to be considered, for example many patients are now treated with suspected meningiomas with stereotactic radiosurgery/radiotherapy (SRS/T), not because they are “inoperable” but because of patient preference as part of shared decision making. This is commissioned by NHSE according to specific criteria and a current document on meningioma treatment cannot really be published without reference to this.	Thank you for your comment. In response to your comment, the word 'inoperable' has been removed and replaced with 'No surgery (radiological only diagnosis)'. To clarify your point about patient preference, the phrase ‘including if the person declines surgery’ has been added to the guideline.
University Hospital Southampton NHS FT	GL	17	3-8	Really this section goes without saying and is meaningless without clarification. All of these features would be taken into account with any treatment for any patient with any tumour! More useful, but not mentioned, would be guidance around best types of radiotherapy e.g. SRS/T versus conformal/IMRT, etc or even guidance on the choice between SRS/T and surgery for meningiomas.	Thank you for your comment. The committee believed that not all centres varied their treatment option based on these factors (that is, some centres used only one modality on all patients) and therefore the recommendations are important in driving standards.
University Hospital Southampton NHS FT	GL	17	1	There is no mention of the evidence-based and nationally commissioned treatment of meningiomas with SRS/T, as above. Making a clear distinction between different modalities of radiotherapy i.e. SRS/T versus conformal, etc would aid in better understanding of treatment recommendations, otherwise there is a risk of patients receiving the incorrect treatment. It is not clear	Thank you for your comment. The committee systematically reviewed the literature on factors which could affect response to radiotherapy treatment and were unable to make recommendations on the choice between SRS/T versus conformal.

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				throughout table 4 if the word “radiotherapy” was intended to include all modalities including SRS/T or not.	
University Hospital Southampton NHS FT	GL	17	1	The concerns about the term inoperable remain as above and it would best be avoided. The biopsy only category must be vanishingly rare, as no one would biopsy a likely meningioma and they are routinely treated without a tissue diagnosis (for example with SRS/T). Perhaps this column would better be removed. (it is probably best described as Simpson V and therefore included anyway). It is difficult to understand what is meant by performing more surgery for incompletely excised tumours in column 2 – they would presumably have been more completely excised if possible upfront. This might be different at recurrence but that features in another column. As it stands table 4 is extremely confusing and illogical and without specific reference to SRS/T potentially, harmful to patients.	Thank you for your comment. In response to your comment, the 'inoperable' category has been moved into a 'Simpson V' category as suggested, and a new category added for meningioma where no surgery was undertaken to incorporate the comments you make about SRS/T.
University Hospital Southampton NHS FT	GL	19	2	What type of radiotherapy is being referred to here? Again, there are different risks and benefits with different modalities but it almost seems that this includes all in one group? Better to have made it clear and perhaps had different risks for say SRS/T or for conformal/IMRT which have a very different risk profile. If it is just supposed to be about conformal/IMRT fractionated treatment then this should be explicitly stated.	Thank you for your comment. The committee determined that Table 5 would not be a substitute for informed clinical decision making taken in collaboration with the person with the tumour and consequently did not believe it was appropriate to specify the exact type of radiotherapy to which the table referred - the broad classes of risks and benefits which should be discussed are thought to be similar for most modalities, but the specific risk varies radically with modality and individual patient characteristics. Whereas the committee have amended the guideline in response to your earlier comments on stereotactic radiosurgery/radiotherapy, they have not amended this table as the risks of radiotherapy vary so radically with the modality.
University Hospital Southampton NHS FT	GL	20	8	What are the “suitable radiotherapy techniques” we are referring to? Presumably a radiation oncologist would always generally aim to minimise the dose to normal brain? More clarity or explanation required here	Thank you for your comment. Suitable radiotherapy techniques are those which are still suitable following consideration of the bulleted list above (that is, the preferences of the person, tumour grade tumour location and tumour size). However in order to clarify the second part of the recommendation this has been amended to read 'From the suitable radiotherapy techniques, choose the one which maximises the chances of local tumour control while minimising the dose to normal brain tissue.'
University Hospital Southampton NHS FT	GL	22	2	Table 7 could benefit from simplification, especially given it is not really based on any good quality evidence. For example, all of the grade 1 sections could be combined as the differences between them are subtle. For grade 1 tumours a simple option might then be scan at year 1, 2, 3, 5, 10 (+/-15, as surgeons have commented there is evidence of recurrence beyond 10 years), unless growth was observed during this observation time. It would be simplest to state that all patients in all categories have a baseline scan at 3 months after treatment to avoid confusion. For patients with asymptomatic incidental meningiomas you might advocate a similar plan to grade 1 (above), especially for younger patients with a real prospect of progression (there is little reason to think they would behave differently from say grade 1 tumours residual after surgery, indeed consideration might be given to an earlier then 12/12 first scan eg 3/12 if any doubt over diagnosis or concerning features). For very small tumours in elderly patients this may not be appropriate as the chance of symptomatic progression during normal life time is so low (indeed for many of these cases it might be reasonable as an option to suggest no imaging at all).	Thank you for your comment. The committee were unable to find any evidence on the optimal regular clinical review schedule for any of the brain tumour types they investigated. However, they were aware that an example table might be helpful to clinicians and Trusts in planning the timing and extent of follow-up scans. Since the table is not intended to be prescriptive, no change has been made to the recommendations regarding simplification as clinicians are not expected to follow the table if it is not appropriate for their practice.
University Hospital Southampton NHS FT	GL	23	10-11	There is an important omission – get a tissue diagnosis from the primary site where possible if not already established from past history (this directly impacts on treatment options). The neuro-oncology MDT cannot make reasonable recommendations without a tissue diagnosis. Where this isn’t possible neurosurgery may be required to establish the diagnosis.	Thank you for your comment. The recommendation has been updated to include taking a biopsy from the primary site if possible.

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University Hospital Southampton NHS FT	GL	23	20	Might it better say the primary tumour site, type and molecular profile. There is no mention of prognosis, whereas NHSE commissioning guidelines mention this as an important factor in determining if focal treatment is to be advocated i.e. is the life expectancy with treatment (of local and systemic disease) thought to be in excess of 6 months.	Thank you for your comment. This has now been amended to say: 'the primary tumour site, type, and molecular profile'.
University Hospital Southampton NHS FT	GL	23	23	Suggest clarify to “stereotactic radiosurgery/radiotherapy…….”	Thank you for your comment. Your suggestion has been incorporated into the final guideline.
University Hospital Southampton NHS FT	GL	24	43221	Suggest add “requirement for tissue diagnosis” (such that if diagnosis is not established or in doubt then surgery may be a better option than SRS/T)	Thank you for your comment. The section of the guideline this relates to is the management of confirmed tumour, and therefore a tissue diagnosis should already have been undertaken if it is possible to do so. However a later recommendation suggests that obtaining a more up-to-date tissue sample could be a good reason for selecting one treatment over another. Consequently no change to the guideline has been made.
University Hospital Southampton NHS FT	GL	25	1-2	Again better term is SRS/T, see above.	Thank you for your comment. Your suggestion has been incorporated into the final guideline.
University Hospital Southampton NHS FT	GL	26	3	Is there evidence that SRS/T to the resection cavity improves overall survival? If not and it exposes patients to additional morbidity and risk and the healthcare system to additional cost, should it really be considered upfront? If it were to be considered should there be guidance on in whom? For example, there is evidence that local recurrence is higher with piecemeal resection rather than en bloc. If post-op MRI raises concerns about residual it could be advised, perhaps if completely clear and en bloc resection it should not? The practice option is 3 monthly MRIs and treatment only if recurrence)and on-going good prognosis, etc). The document suddenly jumps from single cerebral metastases to 1-3 – this is somewhat confusing.	Thank you for your comment. The committee found weak evidence that surgical cavity irradiation reduced both local recurrence rates and time to local recurrence, but no evidence that it improved overall survival. Although the evidence on recurrence was not statistically significant, the committee argued that it was plausible that irradiation of the cavity could delay recurrence, and so were persuaded by it on the basis that reduced or delayed recurrence should improve quality of life. The quality of the evidence was not good enough to make more detailed recommendations, for example in whom cavity irradiation should be offered. However to make this more explicit, the committee added that volume of surgical cavity should be considered before decisions on radiotherapy are made.
University Hospital Southampton NHS FT	GL	26	8	Add the phrase “and prognosis” to end of sentence.	Thank you for your comment. Number and volume of metastases is highly predictive of prognosis, and the committee believed that their phrasing accurately reflected the evidence. Consequently the recommendation has not been updated, but the committee's discussion of the evidence has been updated to explain that prognosis is an important purpose of estimating number and volume of metastases.
University Hospital Southampton NHS FT	GL	27	10	It does not say who should do the follow up i.e. the local oncologists or a neurosciences team? In this section it would help to state that no follow up is appropriate for many patients with cerebral metastases where prognosis is poor and treatment not being offered – good palliative care should be advised.	Thank you for your comment. The committee did not uncover any evidence on who should do the follow-up, and therefore did not make any recommendations on this topic (provided the individual was qualified). However the committee have given some examples of what sort of individuals might be qualified to perform the follow-up.
University Hospital Southampton NHS FT	GL	30	29	This statement is unnecessarily patronising and should be removed. It goes without saying as part of being a clinician and following good medical practice that communications with patients would be professional (as opposed to unprofessional!). If it were to be used it would be more sensible to change the term to compassionate rather than empathetic.	Thank you for your comment. A decision was taken at scoping that the content of neurological rehabilitation was sufficiently complex that separate guidance was required rather than including it as a question in this guideline. Therefore the content of information delivered about neuro-rehabilitation is outside the scope of this guideline, and may be included in the scope of future NICE guidance.
University Hospital Southampton NHS FT	GL	33	6-9	Could it be stated that patients at risk of visual or hearing loss be advised to self-report these symptoms and follow up then be patient-triggered?	Thank you for your comment. Patients are unlikely to self-report until visual impairment or hearing loss has occurred, and therefore the committee thought it was most appropriate to concentrate on identifying those that are at risk of visual impairment or hearing loss in the first instance. Any other change in symptoms will be investigated outside the normal schedule of follow-up, and therefore this might include self-reports. Consequently no change has been made to the guideline.

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University Hospital Southampton NHS FT	GL	36	12	The confusion over radiotherapy and meningiomas continues. It is quite unusual to give standard say conformal /IMRT fractionated radiotherapy for a meningioma grade 1. The real question currently is much more commonly whether or not to give immediate SRS/T to residual – this review does not reflect standard practice and current dilemmas without addressing this or clarifying what is meant by radiotherapy.	Thank you for your comment. The intervention has been clarified to be 'Immediate radiotherapy, understood to usually mean stereotactic radiotherapy/radiosurgery to the residual depending on clinical characteristics' and a similar change has been made to the comparison.
University Hospital Southampton NHS FT	GL	40	12-19	As described this policy over irradiation of low grade gliomas might result in earlier treatment with RT than is current practice in many MDTs. This isn't reflected here, indeed the opposite seems to be suggested as an impact. The guidelines as written could involve a further shift to earlier treatment and more patients living many more years with the consequences of radiotherapy.	Thank you for your comment. The guideline has been updated with a discussion of the potential resource and patient impact of earlier radiotherapy.
University Hospital Southampton NHS FT	GL	45	9-11	What does this mean? Extrapolating MRI features of gliomas to classification of meningiomas? In the absence of any evidence really this statement should be removed, especially as we know from evidence (and experience) that there is poor correlation of MRI features with meningioma grade	Thank you for your comment. This section has been clarified to explain that this means distinguishing healthy brain tissue from meningioma.
University Hospitals Birmingham	GL	26	1-2	We are concerned that this recommendation advises against whole brain radiotherapy post surgical resection of solitary brain metastasis. Surgical excision usually for larger lesions (ie unsuitable for radiosurgery) which will have higher risk of relapse within cavity. Local control for the surgical cavity is better after fractionated radiotherapy than with observation alone or cavity radiosurgery (Brown et al, Lancet Aug 2017; Cochrane review 2014). Whole brain / fractionated radiotherapy has a clear role in our opinion in providing optimum local control in surgical cavity in selected patients. Statements to avoid whole brain radiotherapy should be restricted to current evidence ie patients with lung cancer and inoperable brain metastases with a poor performance status.	Thank you for your comment. The committee considered several trials showing no evidence that whole brain radiotherapy improved overall survival in making their recommendations, while still exposing patients to risk. In addition the Brown et al (2017) trial which was included in the evidence review demonstrated weak evidence in favour of postoperative stereotactic radiosurgery. The committee believe that three-fraction stereotactic radiotherapy can be delivered to moderately large volumes and therefore the evidence is stronger that stereotactic radiosurgery/radiotherapy should be considered before whole-brain radiotherapy in this group of people, and therefore the committee does not believe it is appropriate to alter the recommendation except to clarify that both stereotactic radiotherapy and radiosurgery should be considered in this role.

Registered stakeholders