NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Carmustine implants and temozolomide for the treatment of newly diagnosed glioma

Responses to consultee and commentator comments on the Appraisal Consultation Document

Patient representatives and clinical experts

Consultee	Comment	Action/response
Patient expert 1	Having approached this appraisal with an open mind and with no particular axe to grind on behalf of these treatments, I find that the experience has helped form my opinions. I am disappointed with the committee's recommendations as I felt there was clear evidence from clinical trials that these treatments prolonged life with few side effects. They clearly represent the best treatment currently available for patients suffering from high grade glioma, and as such, I believe they should be made available as first line treatment.	Comments noted.
	If these treatments were approved, the number of patients for whom they would be suitable would be very small and the cost to the NHS overall would therefore be relatively small. By comparison, for example, with Herceptin, which is applicable to far more people and which leapfrogged the system owing to public pressure and political intervention, the cost would be tiny. The committee's recommendation not to approve these treatments takes no account of the fact that they only apply to a small minority of extremely disadvantaged patients.	Commonness or rarity of the condition is not considered by the Committee.
	Unfortunately for those with glioma, the disease itself is so devastating that neither patients nor families are likely to be in a position to engineer the kind of public outcry that accompanied Herceptin and has recently accompanied treatments for Alzheimers. If sheer force of numbers is allowed to determine what treatments are approved then minority groups will inevitably be discriminated against.	The Committee is required to resist pressure to make decisions that are not in the broad public interest (Social value judgements [SVJ] Principle 12).

Consultee	Comment	Action/response
Patient expert 1 (continued)	The committee's criticisms of some of the data in the clinical trials seemed at odds with its apparent willingness to be overwhelmingly influenced by an economic model that is itself deeply flawed. Patient groups' and clinicians' criticisms of the economic model appear to have been largely ignored, and the rigour rightly demanded of the clinical trials does not seem to have been demanded of the bizarre and rigid system used to assess the cost effectiveness of the treatments in question.	The Committee considered the criticisms, but concluded that the assessment group model provided the best available estimates of cost effectiveness. Where appropriate, the assessment group performed additional analyses to address consultees' criticisms.
	I am fully appreciative of the hard decisions that have to be made and of the need to balance cost with benefits, and of the role of the QALY. I believe that quality of life is paramount in establishing the value of a treatment. However, I do not believe the following factors were taken into account when establishing cost effectiveness:	
	There was only a token acknowledgement of the discrepancy between patients' own view of their quality of life and the view of clinicians/relatives.	The Committee considered the testimonies of the patient representatives. The Committee took the limited life expectancy of people with high grade glioma into account – see Final Appraisal Determination (FAD) section 4.3.26.
	There was a blanket assumption that the value of life went down correspondingly the closer the patient got to death. In fact, anyone will tell you that life increases dramatically in value when it is about to end. To a condemned person, (particularly a relatively young person as many glioma sufferers are) an extra two months with loved ones may be worth far more than the two months of 'normal' life.	The Committee also noted that the quality of life of patients may deteriorate rapidly following the onset of disease progression – see FAD section 4.3.20.
	Although the increase in survival was small, this represents a considerable improvement in outcome for patients suffering from this type of brain tumour. There was no acknowledgement of the fact that, for glioma sufferers, the benefits of these treatments represent a huge step forward.	The Committee took the limited life expectancy into account in their decision – see FAD section 4.3.26.

Consultee	Comment	Action/response
Patient expert 1 (continued)	No differentiation was made regarding the age of the patient, even though younger people were shown to respond better to the treatment and, as a percentage of overall lifespan, the improvement in survival means much more to a younger patient.	NICE clinical guidance should only recommend the use of an intervention for a particular age group when there is clear evidence of differences in clinical effectiveness in different age groups that cannot be identified by any other means (SVJ Principle 6). The Committee considered that it was most clinically appropriate to consider subgroups defined by performance status – see FAD section 4.3.23.
	The committee is calling for more and better clinical trials to prove the effectiveness of these drugs, even though it heard expert evidence about the difficulties of conducting clinical trials in this area. This demand for further proof effectively condemns patients suffering from high grade glioma to many more years in the wilderness. Again, this is a form of discrimination against minority groups with intractable diseases. Wonder drugs don't spring out of nowhere overnight, and if these small steps forward cannot be acted upon, and built upon, no progress will be made.	The Committee does not discriminate on the basis of rarity of diseases.
	Lastly, this decision will put Britain out of step with the rest of Europe, where Temozolomide, in particular, is widely used in first line treatment.	Noted
Patient expert 2	1. Whether I consider that all the relevant evidence has been taken into account As a formal patient/carer expert, present at the Health Technology Appraisal meeting on 23rd November 2005, I strongly disagree with the preliminary recommendations that carmustine implants and temozolomide are technologies which are not recommended for people newly diagnosed with high-grade gliomas. I do not believe that all the relevant evidence has been taken into account for the following reasons:-	

Consultee	Comment	Action/response
Patient expert 2 (continued)	• The patient perspective is not fully taken into account. In spite of personal testimonies of those who have lived with someone with a high-grade glioma, there is no reference made to the value of extending the patients life and the impact that this can have on the whole family. • The evidence does not reflect the patient's experience – time is not on the side of a patient with a high-grade glioma. Brain tumours account for one of the highest contributions of all cancers to "person-years of life lost" – years of life lost due to early death. Losing someone to this sort of cancer which affects the person physically and mentally, is agonising and this is not mentioned. • These two technologies are ground-breaking for the brain tumour community and yet no reference has been made to this fact. They have been accepted in the US and many European countries as standard treatments so not only will we be left behind these countries, but we will be in danger of putting a halt to future research and treatments for brain tumour patients. No reference was made to the fact that during the meeting one of the clinical experts stated that if leukaemia therapies had been analysed in this way, the success of treatments for this disease would never have developed in the way they have. 2. Whether I consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	The Committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness The Committee took the limited life expectancy into account in their decision – see FAD section 4.3.26. The Committee acknowledged that previously used chemotherapy regimens have not demonstrated a benefit in survival for patients with newly diagnosed high-grade glioma – see FAD section 4.3.26.

Consultee	Comment	Action/response
Patient expert 2 (continued)	• How can you compare cost effectiveness of one of these treatments with the life of a loved one – If it is your loved one who is given a short time to live following the diagnosis of a high-grade glioma and you know there is a treatment available but you can't have access to it, how would you respond to them – "I'm sorry love, but as we can't afford to go privately to receive the treatment, you won't be able to have it which means that sadly you are going to die sooner than you should." I'd like to see one of the NICE committee saying that to their husband, wife or child. Or would they be able to afford to go private? I seriously question the statement "the committee are aware of the quality of life of a patient at all stages of the disease" because for the first time in decades, brain tumour patients have been given the opportunity to prolong their lives. I strongly believe that it is not sufficient to be aware of this, but to act upon it and make these technologies available.	Decisions are made on the basis of clinical and cost effectiveness. The Committee took the limited life expectancy of these people into account in their decision – see FAD section 4.3.26.
	• I would question why we are focusing on median survival rather than the long term benefits over a period of two years?	The Committee were aware of the survival data at two years for temozolomide. Temozolomide is recommended for patients with performance status of 0.
	• The cost-effective reality is that conditions which are relatively low in incidence are going to be more expensive per individual. However, brain tumour patients should not be disadvantaged because they have a low incidence condition – it isn't their fault that they have a brain tumour. At least the costs are quantifiable as the numbers being considered are smaller.	The Committee does not discriminate on the basis of rarity of diseases.
	• The technologies do not interfere with everyday life and the side effects are minimal. Temozolomide can be administered at home and is uncomplicated, it doesn't need a nurse, nor does it need expensive equipment in order for it to be administered.	Comments noted.

Consultee	Comment	Action/response
Patient expert 2 (continued)	• It is premature to use the MGMT methylation test to deny access to temozolomide as the trial is still on-going and is yet to be validated.	The Committee rejected the notion of patient selection on the basis of this marker – see Section 4.3.25. Temozolomide is recommended for patients with performance status of 0.
	• Having been in the room at the time all the evidence from charities and clinical experts was being given, it does not appear that this evidence has been incorporated into the final decision. It seems that recommendations were made based purely on the economic model and without reference or referral to the evidence given. I would question the relevance of this model to brain tumours?	The Committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness.
	3. Whether I consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS	
	• Categorically no, I would like the committee to reconsider their recommendation. As these two technologies represent the first effective treatments for high grade gliomas in twenty years, I would like to see guidance which recommends their use for the treatment of newly diagnosed high-grade glioma patients.	Temozolomide is recommended for patients with performance status of 0.
	• I do not feel it is appropriate to wait for clinical studies to include research into the impact on quality of life, long-term effectiveness, subgroups for which the treatments may be particularly cost effective or comparison with other chemotherapy regimens. As stated earlier, we DO NOT have time to wait for these clinical trials. The life of a brain tumour patient is too short and too valuable to put these technologies on hold.	Temozolomide is recommended for patients with performance status of 0. The Committee concluded that there was insufficient evidence to recommend the use of carmustine implants for patients with newly diagnosed high grade glioma.

Consultee	Comment	Action/response
Patient expert 2 (continued)	• Furthermore, if we wait until 2009 to review these technologies, not only is it unlikely we will have further clinical data (because research opportunities and funding will have been taken away) but also about 6,000 patients will have been denied treatment and the UK will fall behind Europe and the US standards. What will this say to the general public?	If significant new evidence becomes available in the interim, consultees can request an early review.
Clinical expert 1	**1 Introduction** The Appraisal Committee preliminary recommendations on Carmustine implants and Temozolomide for the treatment of newly diagnosed high grade glioma were arrived at without discussion and advice from invited experts and without taking into account all the relevant evidence. The analysis as presented is largely guided by health economic considerations with flawed interpretation of the clinical research data and using models with limited factual base. The provisional recommendations are not considered sound. **2 Corrections to ACD** 2.1 Section 2.4 There is insufficient data to show that grade 3 mixed oligoastrocytomas have better prognosis than grade 3 astrocytomas. 2.2 Section 2.6 The description of management of malignant glioma is incorrect. 2.3 Section 3.1 Carmustine is not known to interact with RNA; as an alkylating agent it alkylates DNA. 2.4 Section 3.2 Marketing authorization does not equate with indication.	The usual procedure was followed – see Guide to the Methods of Technology Appraisal section 6.2.2.1 (Available from URL http://www.nice.org.uk/page.aspx?o=201974) This section has been amended. This section has been amended. This section has been amended. This section has been amended.

Consultee	Comment	Action/response
Clinical expert 1 (continued)	2.5 Section 3.5 Alkylation by MTIC results principally in DNA strand breaks and not cross links. 2.6 Section 4.1.5 Reanalysis of data is not available in peer reviewed publication and the timing and rationale are not known. 2.7 Section 4.1.12 The EORTC generated the data independent of the manufacturer. 2.8 Section 4.2.1 Independent health economic analysis has been performed by EORTC and their partners (also applies to section 4.2.5). 2.9 Section 4.2.7 The applicability of general population health-utility scoring to patients with uncommon brain tumours is questionable and not validated.	This section has been amended. These data are publicly available – albeit not in a journal This information was submitted to the Institute as part of the manufacturer's submission. The model was submitted to the Institute as part of the manufacturer's submission. The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.3.4 (Available from URL http://www.nice.org.uk/page.aspx?o=201974). The Committee carefully considered the utility estimates included in the analyses and the results of sensitivity analyses.

Consultee	Comment	Action/response
Clinical expert 1 (continued)	2.10 Sections 4.2.8 & 4.2.9 The analyses make unverified assumptions on the use (and cost) of treatment at recurrence, which are at variance with factual resource use data from the RCTs and this is likely to be a major determinant of the differences in cost effectiveness. 2.11 Section 4.3.1 It is not clear what the objective impact of such qualitative evidence is and the statement is largely misleading.	Disagreement with the Assessment Group approach is noted. The Committee considered the results of additional analyses – see FAD sections 4.2.12, 4.2.13 and 4.3.22. This is a standard paragraph referring to the evidence considered by the NICE Appraisal Committee.

Consultee	Comment	Action/response
Clinical expert 1 (continued)	2.12 Section 4.3.3 This section requires considerable correction, as a balanced personal statement may have been misunderstood. The facts are as follows: i) No single randomized trial has shown convincing survival benefit for nitrosourea containing adjuvant chemotherapy in newly diagnosed malignant glioma patients. ii) A meta-analysis of all randomized trials of adjuvant nitrosourea containing chemotherapy showed a 5% improvement in survival. iii) The consensus in UK oncology community is that the benefit seen in the metaanalysis is not of sufficient magnitude to recommend routine use of adjuvant nitrosourea containing chemotherapy for newly diagnosed patients with malignant glioma. iv) The results reported for Carmustine implants and Temozolomide, which are both principally alkylating agents, are in the same direction as the results reported for nitrosoureas (also alkylating agents). v) An unpublished comparison of the magnitude of benefit seen in the metaanalysis and in the EORTC trial shows that the confidence intervals of the two survival outcomes do not overlap (i.e. the magnitude of benefit is significantly larger in the recent RCT). 2.13 Section 4.3.3 While it is acknowledged that there are no trials comparing Carmustine implants or Temozolomide with adjuvant nitrosourea containing chemotherapy the recent RCTs used the correct controls and the implied criticism in the selection of the control group is not justified. 2.14 Section 4.3.5 line 4 (typo) Temozolomide is substituted for Carmustine implant	The FAD has been amended to reflect this - see FAD section 4.3.6. No criticism was intended by these factual statements. This section has been amended.

Consultee	Comment	Action/response
Clinical expert 1 (continued)	2.15 Section 4.3.7 It is assumed (but not clearly specified) that the comments on RCT refer specifically to Carmustine implants.	Section 4.3 of the FAD has been amended to differentiate between the considerations for carmustine implants and temozolomide.
	2.16 Section 4.3.9 The confident statements about validity of the model used do not acknowledge the uncertainties and the theoretical nature of some of the estimates. The assertion of the committee on the superiority of the AG model is open to considerable discussion.	Noted – the Committee are familiar with the uncertainties involved in economic analysis.
	2.17 Section 4.3.11 While the committee acknowledges the impact of therapy at progression on the cost-effectiveness analysis, the absence of a serious data based analysis largely invalidates the calculations. The committee's opinion on the "use of NHS resources", taken without consultation with the experts, is contrary to the factual approach taken and at variance with the real clinical situation. Without a real calculation of resource use of second line treatment at the time of recurrence, which takes into account real data (to be obtained either from the RCT or from UK data collection) the present cost-effectiveness analysis is largely worthless.	Such data were not available to the Assessment Group and Committee. Additional analyses were performed using different assumptions about second-line treatment – see FAD sections 4.2.12, 4.2.13 and 4.3.22.
	2.18 Section 4.3.13 The committee failed to consider the potential impact of the therapies on subgroups of patients defined by known prognostic factors. The EORTC RCT prospectively stratified patients by performance status and the extent of surgery. Patients with WHO performance status 0 and patients aged < 50 years of age had a survival benefit of 4 months. Conversely, patients with WHO performance status 2 and patients following biopsy alone had little survival benefit.	Additional analyses were performed to consider these subgroups – see FAD sections 4.1.13, 4.2.13, 4.3.23, 4.3.24, 4.3.26. Temozolomide is recommended for patients with performance status of 0.
	The committee chose to select information on the potential future value of MGMT analysis which indeed requires validation.	The Committee rejected the notion of patient selection on the basis of this marker – see FAD section 4.3.25.

Consultee	Comment	Action/response
Clinical expert 1 (continued)	2.19 Section 5.1 The comments need clarification. A randomized UK NCRI trial is currently testing PCV chemotherapy vs Temozolomide at the time of first recurrence with second randomization comparing conventional vs high dose Temozolomide. The trial design preceded information on MGMT status and patients are not prospectively stratified. RTOG/NCI (USA) and EORTC are planning a study of low dose vs high dose adjuvant Temozolomide in the initial therapy of patients with glioblastoma which has not yet been activated. The information on MGMT status may be of value in the future which is likely to be additional to the information on the recognized prognostic factors.	This section has been amended.
	2.20 Section 5.2 This section attests to the lack of consultation with the experts and with the research bodies involved in brain tumour trials. The suggestions presented lack understanding of the current evidence and the important issues in this field and seriously invalidate the APC.	This section has been amended.
	2.21 Section 6 The serious flaws in the analysis (above) make the conclusion untenable and at variance with the views of the experts.	See responses to specific comments.
	3 General comments From a clinical and academic perspective the assessment of the technology should take into account: a) quality and reliability of the research data used in the assessment of efficacy of the technology, b) prospectively collected data on resource use with model based considerations used as supporting evidence and c) standard therapies in malignant glioma as practiced in UK.	The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group. The reliability of the available evidence is considered by the Committee when formulating its recommendations.

Consultee	Comment	Action/response
Clinical expert 1 (continued)	Only one reasonably powered randomized study provides data on which the efficacy of Carmustine implants could be assessed. The results summarised in 4.1.2 – 4.1.6 of the ACD describe some of the difficulty in the assessment of the technology. In addition the study was conducted and analysed by the manufacturer with possible consequences to the independence of the study analysis as already highlighted in the FDA and NICE assessment. The principal peer reviewed publication lacks robust statistical conclusions on survival benefit and a subsequent analysis (not generally permitted in trials run by independent trial organisations without clear rationale set by an independent committee) is not available as a peer reviewed publication. Hence the data, while intriguing is not fully validated. The outcome data is applicable only to the population of patients studied which is restricted to patients who undergo radical tumour resection. The primary decision to be taken by the committee is on the validity of the data, based on the peer reviewed publications with inclusion of factual information on the use of second line treatment and stratification by prognostic factors.	Comments noted.
	The RCT assessing the value of Temozolomide was a robust, appropriately powered study (2nd largest study of primary therapy in malignant glioma and the largest in glioblastoma) conducted and analysed by an independent research organization albeit with industry sponsorship. Resource use and quality of life information were prospectively collected.	Comments noted.
	Notwithstanding the incorrect appraisal (summarised in Section 2) it seems inappropriate to assess the two technologies without taking into account the considerations outlined above.	See responses to specific comments above.
	4 Conclusions Based on the above considerations the Appraisal Consultation Document is flawed and its conclusions unsound.	See responses to specific comments above.

Consultee	Comment	Action/response
Clinical expert 2	The high clinical impact of the decision on individuals and families diagnosed with this rapidly fatal disease is incompatible with the very high level of uncertainty acknowledged by Pentag in their health economic model. This drug is in extensive use in UK and Europe as first line therapy. I suggest that Appraisal Committee consider identifying TMZ as an ""orphan drug"" for selected patients based upon MGMT status as it is the only drug with any demonstrable effect in this disease. I strongly support the proposal for an active programme of research.	Temozolomide is recommended for patients with performance status of 0. Commonness or rarity of the condition is not considered by the Committee. The Committee rejected the notion of patient selection on the basis of this MGMT status – see FAD section 4.2.25.
	This disease affects people of all ages. The impact on children, young people, adults in early, mid and late life when confronted by this diagnosis is acknowledged to be profound because of the lack of hope, the prospect of disability and death, which are most disturbing to those who are young. Public and professional awareness of this drug places it in a category where withdrawal of access to it outside commercially funded clinical trials will promote a further lowering of public and professional confidence in current NHS cancer services and be in open conflict with National Cancer Plan targets to ""save more lives"" and maintain ""comparable survival rates with Europe"". The anomaly between this assessment from NICE compared to that from LCNDG who on the basis of the same science did recommend concomitant TMZ/RT and then maintenance TMZ (Ref LCNDG July 2005) is stark. There is widespread support for TMZs use in those most likely to respond.	Noted. Temozolomide is recommended for patients with performance status of 0.
	Within the TMZ cost benefit model the costs of the drug are assessed with great certainty. There is no effort to assess the costs of measuring MGMT status.	The Committee rejected the notion of patient selection on the basis of this MGMT status – see FAD section 4.2.25

Consultee	Comment	Action/response
Clinical expert 2 (continued)	The 12 & 24 month improvement in survival of 61% for RT+TMZ vs 50% for RT alone and 27% vs 10% respectively are ignored by this report. This is not compatible with oncology practice, takes no account of the impact of MGMT status for selecting those most likely to benefit. The health economic model is compromised methodologically by exclusion of patients or experienced clinicians in its generation, the high uncertainty of derived health indices & reliance upon median survival. It disregards the economic impact on family linked to disability, is not informed by sub-analyses of known prognostic factors ie marital status, resection, age, MGMT status and genetic mutations indicative of chemosensitivity. The health index is derived from very small patient and normative samples and cannot exclude potential bias of these, despite sensitivity analyses. The psychological literature regarding the impact of denied access to treatment, confrontation of anticipated acquired disability and other personal and family factors is entirely disregarded and is incompatible with the experience of optimal clinical practice in this patient group.	The Committee carefully considered the issue of subgroups by prognostic factors – see FAD sections 4.1.13, 4.2.13, 4.3.23, 4.3.24, 4.3.26.
	The denial of TMZ funding and recommendations for additional trials are mutually incompatible as one undermines the other and will inevitably compromise the UKs capacity to participate in trials of this drug in CNS tumours for the foreseeable future. This will place NICE in the position that it will be reliant upon non UK data for future assessments unless extensive drug industry or grant funding is forthcoming. The concern is that this will similarly undermine efforts to investigate this drug in children and young people where research information is currently unavailable and for whom one trial is open and a second is in development. Neither have agreed commercial funding in UK. I strongly support the need for additional research concerning the use of this drug in all ages of patients.	Temozolomide is recommended for patients with performance status of 0.
	The resource impact of the current proposal will be in the form of savings as this drug is in extensive use in many regions as part of first line therapy. Reclassification to ""orphan status"" for patients with MGMT status would arguably have a zero impact as only a small proportion fall into this category. However funding sources for MGMT testing would need to be determined.	Commonness or rarity of the condition is not considered by the Committee. The Committee rejected the notion of patient selection on the basis of this MGMT status – see FAD section 4.2.25

Consultee	Comment	Action/response
Clinical expert 2 (continued)	Consideration should be given to providing NHS funding for this drug for selected patients based on ""orphan status"" and in clinical trials as part of attempts to promote the currently inactive CNS tumour trial programme in adult practice. In childhood practice there is one trial in high grade astrocytoma using TMZ open and a second involving brain stem glioma in development. The option for NHS funding for drug use in trials in children and young people should be given special consideration as part of the proposal to promote research.	The research recommendations have been amended.
	Adult neuro-oncology in the UK is an underdeveloped sub-specialty. The current cancer service guidance for improving outcomes is proposing substantial investments. The plight of the current inadequate clinical services nationally, has been recognised by political debate in Parliament. The proposed negative recommendation for TMZ, based upon highly uncertain health economic justification is coinciding with proposals for substantial investment in CNS tumour services. This coincidence seems philosophically, mutually incompatible. The appraisal committee is encouraged to reflect upon whether it will find itself uncomfortable by, on the one hand, recommending substantial investment for CNS tumour services knowing that it has, on the other hand, blocked the use, on highly uncertain economic grounds, of the first drug in 30 years to offer effective treatment for a recognisable sub group of the commonest CNS tumour type, with the worst prognosis of all human cancer. This will occur whilst this drug is actively in use in Europe and being further investigated as the standard arm of future international phase 3 trials in which UK patients may not be able to participate.	Noted

Consultee	Comment	Action/response
Clinical expert 2 (continued)	The high levels of uncertainty, intrinsic to the economic appraisal, combined with re-analyses of current trials data means that new information regarding this drug could dramatically alter interpretation of its applicability in the eyes of NICE. A deferral of a further review for 3 years would be acceptable if it was granted orphan status for patients with MGMT status and further experience was gained with selection of patients by collecting and refining data for more extensive sub analyses aimed at refining groups most likely to benefit and reducing the uncertainty of the health economic model	Commonness or rarity of the condition is not considered by the Committee. The Committee rejected the notion of patient selection on the basis of this MGMT status – see FAD section 4.2.25

Professional, patient/carer, and research groups

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group (Joint response on behalf of Royal College of Radiologists, Joint Collegiate Council on Clinical Oncology and Royal College of Physicians)	***Introduction*** The NCRI Brain Tumour Clinical Studies Group (BTCSG) is disappointed by the appraisal consultation document from NICE on the use of carmustine implants and temozolomide in patients with newly diagnosed high grade glioma (HGG). The recommendations do not support important clinical developments for patients with one of the most lethal cancers, and will undermine research efforts in the future. It is particularly disappointing that the appraisal consultation document was written without direct input from any neuro-oncologist, nor any brain tumour patient representative. Although an appraisal of cost effectiveness is an essential component of any appraisal, the BTCSG has concerns over the methodology used, and the lack of inclusion of a parameter representing the social value of the life of a patient with HGG. The recommendations within the consultation document are not supported by any opinion leaders, at home or abroad, nor even by any of the Committee's own experts. The Group believes that NICE has a duty to look beyond simple assessment of cost or cost effectiveness, in order to support the rational introduction of clinical developments of value to patients and to promote current research efforts.	Comments on research impact noted. The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formulating its recommendations. In developing clinical guidance for the NHS, no priority should be given based on individuals' income, social class or position in life and individuals' social roles, at different ages, when considering cost effectiveness (SVJ principle 8).

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	***The clinical context for patients with high grade glioma*** A typical patient with a grade IV glioma (glioblastoma), treated with radical intent using current protocols, has a dismal prognosis, with a median survival of only 9 – 10 months. Although CNS tumours account for only 2% of crude mortality for cancer, the individual patient burden is much higher, with an average of 20 years of life lost (AYLL) per patient affected. This low figure results from the combination of a low cure rate in patients who may be affected at a young age. This loss of life per patient is greater than for any other adult cancer, and this has not been taken into account in the NICE appraisal. The advances in disease-free and overall survival which have been achieved with carmustine implants and temozolomide represent the biggest step forward in the radical treatment of HGG for half a century or more. Patients with these tumours do not have a significant media presence, in large part because of the poor outlook, and this reduces the influence they have on debates over public health matters.	The Committee took the limited life expectancy of these people into account in their decision – see FAD section 4.3.26.
	CNS tumours also attract an extremely small proportion of research spending, only 1.5% of the NCRI spending in 2002. Patients with CNS tumours have not only a poor outlook clinically, but can also expect only a minimum of financial support for research for their condition. The annual NCRI research spending divided by the average years of life lost is lower for CNS tumours than any other adult cancer except cancer of the corpus uteri, and is almost 20 times lower than the figure for breast cancer.	Noted
	Research implications The BTCSG has grave reservations regarding the impact on future research if these recommendations are implemented.	Noted.

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	Firstly, it is difficult to see how the pharmaceutical industry would in future wish to support or develop any research in the area of CNS tumours, or indeed for any uncommon cancer with a low public profile. It would normally be accepted that the availability of 2 randomised controlled trials (RCTs) with the same result constitutes a very high level of evidence of effect, and would lead to incorporation into clinical practice. This is the case for temozolomide (TMZ). If introduction of a new treatment with this level of evidence is not permitted, particularly given the size of the advantage and the clinical context, there can be no expectation of further support in the UK for drug-related research. This would apply across the complete spectrum of drug development, from the development of new agents at one end to the conduct of Phase III RCTs at the other.	Noted
	Secondly, this result might affect even the more common cancer sites if this appraisal is considered to set a precedent. If this did occur, then very significant levels of support might be lost from the UK.	Noted
	Thirdly, there is no motivation internationally to address the same question again, so it is unlikely that repeat studies could ever be run. Within the UK, such a further study would be very difficult. It is unlikely that scientific funding could be obtained for a further study within the UK, given that excellent, consistent evidence already exists. Moreover, assuming that the trial were restricted to those most likely to benefit, numbers would be relatively limited, and accrual would take several years. For these reasons it is hard to see how the UK will ever be able to introduce new treatments from the foundation of solid research.	Noted

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	Fourthly, the use of TMZ in particular is now viewed as a standard of care across the western world. All future clinical studies, including Phase III trials, are expected to include TMZ as part of a standard treatment arm. If this is not permitted within conventional care in the UK, it is unlikely that we would be able to join other multi-national studies, such as those run by the European Organisation for Research and Treatment of Cancer (EORTC). This will also impact on trials for paediatric patients. There is no expectation that the additional costs for this treatment in the UK would be met by a pharmaceutical company.	Noted
	Fifthly, any future UK study of developments in other treatment modalities (such as surgery, radiotherapy (RT) or gene therapy) or of tumour imaging if linked to patient outcome, is unlikely to be recognised or accepted internationally. This is liable to present important problems for academic clinical science in this area in the UK, making publication and funding harder to obtain, and to lead to further disillusionment. It will also make it impossible to influence international practice.	Noted
	Sixthly, efforts to develop markers which describe tumour behaviour or response to treatment will be rendered useless. This applies to fundamental molecular science of HGG but also to novel imaging technologies, such as MR spectroscopy and diffusion tensor imaging. These techniques need to be fully appraised now, but cannot be developed to be tested in Phase III trials unless optimal current treatment, as accepted world-wide, is available.	Noted
	Seventhly, failure to include new, proven agents into experimental treatment programmes may reduce their efficacy to the extent of rendering them non-curative. This may lead to inappropriate abandonment of clinical studies which could be of value to patients in the UK, and more widely. For example, studies of neurosurgery, radiotherapy, and gene therapy, as well as new pharmaceutical products, are in development. Part of the assessment of a new strategy is to assess its efficacy. Unless this can be within the context of the best available treatment programme, it may be less likely to show an effect, and its value will be questioned even if the trial is positive.	Noted

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	Finally, it is unhelpful for the Committee to recommend research in areas which have already been conducted, are already underway, such as the NCRI BR12 study, or are not feasible, such as a study of TMZ in children alone. **Temozolomide** TMZ combined with radiotherapy has been assessed in two separate randomised clinical trials, the larger of which has been run by the European Organisation for Research and Treatment of Cancer (EORTC). This study was carried out robustly and shows a substantial, clinically important difference, with improved disease-free and overall survival in the combined modality arm. Following the publication of the results from these two trials, particularly the EORTC trial, combined temozolomide plus radiotherapy has become a standard of care, at least for patients with glioblastoma (Grade IV glioma) within Western Europe and North America. Against this background, it will be exceptionally difficult for the UK alone to carry out a further research study addressing the same question. Moreover, it is relatively unlikely that Cancer Research UK would consider it appropriate to fund such a study, given that two well conducted randomised controlled trials are already available, showing a statistically and clinically significant difference in outcome with the new treatment. Whilst research questions do remain, such as the importance of MGMT within tumours, the underlying clinical question is unlikely to be addressed again. This leads to an invidious problem in the UK if the existing evidence cannot be accepted, where we would be unable to deliver the highest quality of clinical care available abroad, whilst also being unable to conduct a further study to substantiate the benefits.	The research recommendations have been updated for the FAD. The Committee has considered this evidence. See FAD sections 4.1.9 – 4.1.16.

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	The EORTC study enrolled patients with Performance Status (PS) in the range 0-2. UK practice more typically treats radically only those patients with PS of 0, or 1 in exceptional cases. That study contained in the 2 arms 49% and 47% of patients with PS of 1, and 12% and 13% of patients with PS 2. The study also treated patients up to the age of 70. Both PS and age are very strong determinants of survival. We recommend that the Committee review the potential value and cost effectiveness if combined TMZ + RT is restricted to the better prognosis group of patients, which more realistically reflects actual UK practice.	Temozolomide is recommended for patients with performance status of 0.
	This would restrict use to perhaps half of the patients treated in the EORTC trial, representing approximately 20-30% of patients with HGG, but would achieve the greatest advantage in disease-free and overall survival, and a substantially reduced cost per QALY. The EORTC has also published recently evidence to show that administration of TMZ concurrently with RT does not adversely affect quality of life in patients with glioblastoma.	Noted. The FAD has been amended to note the data on quality of life – see FAD section 4.1.15.
	The NCRI Brain Tumour Group is keen to develop further studies with existing technologies and new drugs. Within the international context, for patients with glioblastoma, a control arm including temozolomide plus radiotherapy will be essential. Any such study would be difficult to resource unless this treatment was part of routine clinical practice. In effect, if NICE disallows the use of concurrent temozolomide with radiotherapy, further randomised trials of new treatments for patients with glioblastoma may become impossible in the UK. Even studies to evaluate different (possibly cheaper) TMZ schedules are likely to be impossible.	Noted.
	The EORTC study had better results in both arms of the trial than standard treatment in the UK. This might in part be due to the high proportions of patients in both arms who underwent resection. This has led to pressure to increase the proportion of patients undergoing resection, at least in some centres in the UK, which demonstrates that the clinical community is able and willing to respond to developments to improve patient outcome. This impetus may be lost if the underlying evidence base is deemed to be irrelevant, and would further disadvantage patients with glioblastoma in the UK.	Noted

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	TMZ with RT has become a standard of care in Western Europe and North America. In an informal study of 11 member countries of the EORTC Brain Tumour Group other than the UK, only in Latvia is this not considered standard treatment now. In Australia and Canada the regime has also become the standard. This demonstrates the isolated position into which NICE will force the UK neuro-oncology community, with great disservice to patient care and research effort.	Noted
	Currently, typical patients have very high expectations of treatment with temozolomide, which has been extensively publicised over the last few years. There will be major psychological distress caused for patients coming to terms with the lack of availability of this treatment. It is likely, given the clinical improvement demonstrated in the RCTs, that patients will be able to obtain concurrent RT+TMZ treatment in the private sector, undermining equity of access to health care. It is also possible that patients will seek treatment abroad and challenge the legal position of the NHS in Europe.	Comments noted. Temozolomide is recommended for patients with performance status of 0.
	Carmustine (Gliadel) implants Since carmustine implants have been accepted for use within the NHS in Scotland for the treatment of newly diagnosed HGG, difficulties from post-code prescribing are likely to emerge.	
	Although the difference in median survival after carmustine implants was modest, at only 2.2 months, this represents a 19% absolute improvement. Particularly important are the differences at longer survival times. To raise the 3 year survival from 1.7% (which is a typical figure) to 9.2% is extremely important in this disease. Although patient numbers are small, this difference suggests a powerful effect, at least in a subset of patients. It also suggests an opportunity for future work to identify this group and to build further on this foundation.	The Committee carefully considered the evidence relating to the survival benefits of carmustine. See sections 4.3.7 to 4.3.11 of the FAD.

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	Given the improvement in 2 year and 3 year survival, it is inconceivable that there is no effect on disease free survival times in those patients who survive to these periods. This demonstrates a flaw in the appraisal, which needs to be carefully reviewed by NICE.	The Committee carefully considered the evidence relating to progression free survival see FAD sections 4.3.4 and 4.3.9.
	At present it is not possible to identify accurately a subgroup of patients who will benefit most from treatment including carmustine implants, but this represents an important area for development. Such studies might actually reduce the amount of Gliadel actually used, delivering better clinical and financial value. If no first line use is allowed by NICE, then such studies are unlikely to be possible, in the UK.	The Committee recognised that it is not currently possible to identify a subgroup of patients for who carmustine implants would be more effective or cost effective – see FAD sections 4.3.16 and 4.3.17.
	Failure to allow consideration of the use of carmustine implants will reduce the potential to develop additional chemotherapy, or viral agents, for incorporation into implantable polymers. This will reduce potential clinical developments and inhibit UK developments which might be commercially exploitable.	The recommendations, based on the clinical and cost effectiveness of carmustine implants, have no obvious relationship to the effectiveness of other chemical entities in similar formulations used for other indications.
	Although there are concerns that the rate of intra-cranial hypertension was higher in the carmustine implant group in the largest RCT, this provides a basis for development of surgical techniques to improve this complication rate.	Noted.
	Specific comments on the consultation document	
	Paragraph 2.6 is factually incorrect in implying that if resection is not possible then palliative treatment is usual. Deep-seated tumours may not be suitable for resection, but in young patients with good performance status radical treatment is appropriate.	This section has been amended.
	Paragraph 3.5. TMZ may also act synergistically with RT, producing better tumour cell kill than either modality alone, in effect sensitising tumour to the effects of RT. It is not clear that other agents, such as PCV necessarily act in the same way.	This does not appear to have been established – no change to FAD

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	**Paragraph 4.1.5**. It is unlikely that there is no effect on disease free survival, at least in the subgroup of patients who survive to 3 years or beyond. A 5 times increase in 3 year survival of cannot occur without some difference in disease free survival.	These results are as reported in the clinical trial. The Committee carefully considered the evidence relating to progression free survival see FAD Sections 4.3.4 and 4.3.9.
	Section 4.2. The main conclusions from the appraisal appear to be based predominantly on the cost-effectiveness estimates. The health economic analysis method is novel and has not been validated. In addition, there has been no effort to examine the cost effectiveness in subgroups of patients with higher survival. These groups have been well defined by the RCT of Temozolomide and RT and it is these patients who are likely to gain most from adjuvant treatment. There has been no focus on the clinical context of a rare tumour with very high loss of life per affected patient, ie AYLL. This is likely to relate to the loss of future earnings, which should at least be considered in an assessment.	The Committee carefully considered the issue of subgroups – see FAD sections 4.1.13, 4.2.13, 4.3.23, 4.3.24, 4.3.26. Temozolomide is recommended for patients with performance status of 0. In developing clinical guidance for the NHS, no priority should be given based on individuals' income, social class or position in life and individuals' social roles, at different ages, when considering cost effectiveness (SVJ principle 8).
	There are concerns over the use of the QALY model, which is based on members of the general public who are well assessing chronic, hypothetical health states. It is also generally accepted that the use of QALY's in extreme health states is questionable. Particularly in the case of glioblastoma, patients are more likely to value an extension of survival, at almost any cost to themselves, and value their 'symptomatic' health state only secondarily. This model also takes no account of the value of extension of life to relatives. Finally, there is no attempt to estimate the value of the life to society, such as with the use of the "Value of a Statistical Life" (VOSL).	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.3.4 (Available from URL http://www.nice.org.uk/page.aspx?o=201974)

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	It was admitted by the Peninsula Group that they did not find a validated source of utility values for patients with high grade glioma from which to calculate their QALYs. They therefore developed their own, using quality of life data from a small subset of patients. The method of selection and the composition of this group are not given, and the resulting QALY analysis cannot be considered to have been validated. The conclusions are therefore not necessarily as robust as is suggested.	The Committee noted that published utility data for patients with high grade glioma were not available. The methods used to derive estimates of health-related utility are described in more detail in section 5.5.2 of the Assessment Report. Sensitivity analyses around these estimates were also conducted.
	The model they used is particularly sensitive to the median survival. It is possible that use of survival at 2 years, rather than the median survival, may alter the results of the modelling. The costs of treatment appear not to include the costs of TMZ as second line chemotherapy at relapse, in patients who have been treated with RT alone. In fact, in the context of primary treatment with RT alone, many relapsed patients will receive TMZ after PCV. This will increase the costs of the radiotherapy only treatment, and decrease the cost differential.	The survival estimates in the economic analyses were based on the survival curves for the entire study periods. Additional analysis was performed for temozolomide with differential post-progression treatment. See FAD sections 4.2.12, 4.2.13 and 4.3.22.
	Paragraph 4.2.3. It is curious that the AG were concerned at the use of median (rather than mean) time to symptoms since median time is considered more robust by oncology statisticians. The use of median times avoids skewing resulting from occasional patients with unusually long times.	Mean results are more appropriate for use in economic analyses. However, both summary measures were considered by the Committee. This section has been revised in the FAD for clarity.
	Paragraph 4.2.4. The committee should justify their reasons for assuming that the incremental cost-effectiveness ratio (ICER) was under estimated and should discuss the treatment costs the AG felt were omitted. Since the decision to operate is made independently of the availability of the carmustine wafers, additional treatment costs to those for the wafers are fixed.	See assessment report section 5.3.4.4.

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	**Paragraph 4.3.3**. A comparison of TMZ with PCV is currently under trial, including quality of life measures, in the BR12 RCT, run by the NCRI BTCSG. Although this is addressing efficacy and toxicity at relapse, it will suggest which is would be more effective as a treatment at first presentation. It is also important that absolute numbers of long term survivors cannot be a useful measure when extremely few patients reach even 3 – 4 years with standard treatment. A simple count of numbers of patients surviving does not represent a statistical test of a difference between treatment arms.	Noted
	The suggestion that other chemotherapies may be as effective when given concurrently with RT is supposition. TMZ is given daily, continuously throughout RT. The mechanisms of interaction of TMZ with RT are likely to be different from PCV, and the bone marrow toxicity from PCV would prevent its concurrent use.	Noted – but it remains true that temozolomide has not been compared with strategies other than radiotherapy alone in randomised controlled trials (RCTs)
	Paragraph 4.3.4. The longer survival in the control arm of the EORTC study compared to conventional UK outcome is likely to be due to the increased proportion of patients undergoing more radical surgery and earlier radiotherapy. This is a separate issue from that of the addition of TMZ or carmustine implants. It can be used as an argument to improve surgical management and timing of RT, but not as an argument against concurrent or adjuvant chemotherapy. The use of the concomitant regime to start within a specified time after surgery could be an effective driver to improve RT waiting times in this patient group.	Noted
	Paragraph 4.3.5. This is factually incorrect, in suggesting that there was a 'placebo arm' in the EORTC trial of TMZ + RT. The statement suggests that the Committee may have misunderstood the study, and therefore its analysis.	This section has been amended. The Committee understood the design of the trial.

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	**Paragraph 4.3.7**. Quality of life is improved for patients who are without neurological deficit. Prolongation of survival without deficit is a very important endpoint. It is important to note that patients may function independently until relapse, without the need for expensive community care. It is possible that delay to progression may lead to a reduced time to death, and a consequent reduction in burden and cost to community services. Though this is not proven, and remains an important research question, it is suggested by the EORTC trial of timing of RT in low grade glioma. We recommend that the Committee review this aspect of treatment, balancing increased costs of care in the community against treatment costs, and appraise the effect on quality of life.	The Committee acknowledged the importance of extending progression free survival – see FAD section 4.3.3. The Committee also acknowledged the difficulties of measuring progression free survival and carefully considered the evidence from the RCTs of the impact of the treatments upon progression free survival – see FAD 4.3.4, 4.3.9 and 4.3.18.
	Paragraph 4.3.9. Since the Committee dismisses the economic analyses for both carmustine and TMZ on grounds relating to "assumptions" and "omissions" which are not specified, it would be helpful for the Committee to open its own methods to scrutiny. Their model is based on estimates of survival of only 2 of the four RCTs, and considers estimates of the effect of the disease on health-related quality of life which is recognised as difficult to quantify.	The Assessment report is available for scrutiny (available from URL http://www.nice.org.uk/page.aspx?o=285589)
	Paragraph 4.3.13. The assumption that MGMT status will be a strong predictive indicator of response is based on a single study in which only 50% of tumours could be assessed. Moreover, a formal test for interaction with treatment effect was non-significant, therefore giving no good evidence on which to select which patients should get temozolomide. This cannot be used as an argument against treating the whole GBM population until these data are validated in additional studies.	The Committee rejected the notion of patient selection on the basis of this marker – see FAD section 4.2.25.
	Paragraph 5.2. As noted above, failure to permit an appropriate standard of care will prevent the very research recommended here. It is unhelpful for the Committee to recommend repeating research which has already been accepted by the international community, to suggest work which is already underway, or which is impractical.	The research recommendations have been amended. The use of the technologies in the context of clinical trials is not excluded by the recommendations.

Consultee	Comment	Action/response
NCRI Brain Tumour Clinical Studies Group Joint response (continued)	**Paragraph 7.2**. The suggestion that the 2 agents should be evaluated in further clinical trials is well intentioned, but unlikely to be supported or supportable by the scientific community, given the Class 1 evidence now available. Thus the recommendations of the committee are likely to result in a Catch 22 situation that will impede clinical research and prevent implementation of treatment which can significantly improve the outcome of brain tumour patients in the UK. **Conclusions** The recommendations from the Committee have important negative implications for clinical care, and research. The NCRI Brain Tumour Clinical Studies Group believes that NICE has a duty to reconsider cost issues for a good prognosis group of patients, and to support important clinical developments which will also underpin future research.	Comments noted. Noted. Temozolomide is recommended for patients with performance status of 0.
Cancer Research UK	**Section 1: Appraisal Committee's preliminary recommendations** This NICE appraisal consultation has not recommended temozolomide in combination with radiotherapy for the treatment of newly diagnosed high grade glioma patients. Cancer Research UK does not support NICE's decision. Temozolomide is a good example of the achievements of the enormous investment in cancer research in the UK. The use of temozolomide in combination with radiotherapy has received worldwide acclaim as the gold standard for the treatment of glioblastoma multiforme (GBM). The development of temozolomide is an example of the UK leading the global fight against cancer. This recommendation would deny patients in England and Wales access to the benefits of this treatment which patients throughout Europe and the US are able to receive.	Noted Temozolomide is recommended for patients with performance status of 0. Temozolomide is recommended for patients with performance status of 0.

Consultee	Comment	Action/response
Cancer Research UK (continued)	**Section 4: Evidence and interpretation** The decision not to recommend this treatment relies heavily on the cost implications to the NHS, based on economic modelling. There is an implicit assumption in the Appraisal Committee's evaluation that all patients with newly diagnosed and high grade glioma would be prescribed temozolomide. However clinical practice is unlikely to reflect this.	
	Clinicians are more likely only to prescribe the drug to patients who are having full or partial resections or who have a performance status of one or better. This would be a much smaller subset of patients than included in the Institute's economic estimations. Thus the resulting cost implications to the NHS would likely be lower.	Temozolomide is recommended for patients with performance status of 0.
	There is evidence to demonstrate that temozolomide and radiotherapy combination therapy is particularly useful in subsets of patients with good performance status or who have a full or partial resection of their tumour. This research has reported clinical benefits in this subset of patients in median survival estimates superior to the overall study population. Looking at the median value across the whole patient population attenuates this benefit. We recommend that the Appraisal Committee reconsider re-running this model, looking at the cost per life year gained by this subset alone.	Further analysis has been performed by the Assessment Group. See FAD sections 4.2.13, 4.3.23, 4.3.24 and 4.3.26. Temozolomide is recommended for patients with performance status of 0.
	We therefore ask that, before making a final recommendation, the Appraisal Committee carry out a re-assessment of the cost-effectiveness of temozolomide in combination with radiotherapy in these sub-groups alone.	
	The economic model used in the appraisal relies on median survival values across the entire population. Long-term survival is more important than median survival in rare cancers, especially where side-effects are minimised. Temozolomide has shown an improvement in survival at two years from 10% to 26%. This is significant.	The survival estimates in the economic model were based on the entire Kaplan-Meier survival curves and not just median survival – see Assessment Report section 5.5.1. The Committee noted this improvement. See FAD section 4.1.10.

Consultee	Comment	Action/response
Cancer Research UK (continued)	The special nature of brain cancer treatment makes patient access to temozolomide particularly important. Individually, none of the interventions that we use to treat brain cancer patients provide much difference in terms of prolonging life, but incrementally they provide big gains. A patient receiving no treatment would have a life expectancy of two to three months. Treating this patient with surgery might give them a prognosis of four to five months, and adding radiotherapy could take survival to a year. Giving temozolomide, in a small subset of patients as a first line therapy could extend this survival further still. We also question whether QALYs are the most sensitive estimate in brain cancer patients, as these patients often have only a very few months, rather than years, to live. We suggest that the Appraisal Committee reconsider the appropriateness of QALYs in brain cancer patients. We refer the Committee to the validated economic evaluation instrument used in the EORTC trial of temozolomide as a more appropriate alternative to QALYs. **Section 5: Proposed recommendations for further research** The recommendations for further research in this Document require revision following consultation with the brain cancer research community. The Committee has noted that large trial comparing conventional to high dose temozolomide is planned. However, we understand that this trial does not include prospective stratification of patients by MGMT status. Furthermore, this UK NCRI trial does compare temozolomide with the PCV regimen. It could be argued that research over and above this would be a duplication of effort, and unlikely to gain support from research funders. It is also worth bearing in mind that as temozolomide in combination with radiotherapy is widely accepted as the preferred treatment for GBM, it may be difficult to get ethical approval for a trial that uses less effective treatment options in its control arm.	Temozolomide is recommended for patients with performance status of 0. The Committee noted that people with high grade glioma have a relatively short life expectancy – see FAD section 4.3.26. The reference case stipulates that the cost effectiveness of treatments should include an assessment of quality of life and be expressed in terms of incremental cost per quality-adjusted life year. In addition the Committee considered the results of the study of the quality of life of patients in the EORTC trial – see FAD section 4.1.15. Section 5 has been amended.

Consultee	Comment	Action/response
Cancer Research UK (continued)	**Conclusion** This Document states that quality of life for patient's is paramount. However, the importance to many patients of the prolongation of life should not be underestimated. Temozolomide has been shown to be well tolerated and to have no detrimental effect on quality of life. We therefore ask the Appraisal Committee to reconsider its decision not to recommend temozolomide in combination with radiotherapy for the treatment of newly diagnosed high-grade glioma, except in well-designed clinical trials.	Both quality and quantity of life are encapsulated in the QALY. The Committee considered the results of the study into the quality of life of patients in the EORTC trial – see FAD section 4.1.15. Temozolomide is recommended for patients with performance status of 0.
Brain Tumour UK	Gliomas are the most common type of brain tumour. Whereas brain tumours represent a small percentage of all primary cancers, their impact on the patients and family is profound. Gliomas have a poor prognosis, with high-grade gliomas being rapidly fatal. Conventional treatment for high-grade gliomas consists of surgical resection to the extent possible, followed by adjuvant radiotherapy. The outlook for these patients remains, however, very bleak, with few patients surviving more than one year. There is therefore a huge need for treatments that can improve and prolong their life, even when it is not possible to cure their underlying disease. Adjuvant chemotherapy has been evaluated since the 1970's, but only the recent introduction of particularly temozolomide and carmustine implants has given any real hope to these patients. Recent studies have shown that particularly the addition of temozolomide to radiotherapy for newly-diagnosed glioblastoma, the most malignant type, resulted in a clinically meaningful and statistically significant survival benefit with minimal toxicity. Other studies have shown that these agents can also prolong the disease-free interval and quality of life in patients with a relapse following earlier conventional treatment. The clinical specialists that were consulted were unanimously in favour of allowing these drugs. However, NICE did not acknowledge this, but seems to have based its recommendations upon an economic, financial model, which we believe is flawed. Brain Tumour UK therefore does not agree with the NICE preliminary advice not to recommend these agents for the management of newly-diagnosed high-grade gliomas, except in well-designed clinical studies.	The Committee noted that people with high grade glioma have a relatively short life expectancy – see FAD section 4.3.26. The Committee noted that previously used active chemotherapy regimens have not demonstrated a benefit in survival for patients with newly diagnosed high-grade glioma – see FAD section 4.3.26. Recommendations are based on evidence of both clinical and cost effectiveness.

Consultee	Comment	Action/response
Brain Tumour UK (continued)	**Preliminary recommendations** These preliminary recommendations are not acceptable to us for the following reasons: • The quality of life has already been assessed (see Taphood et al) • The MGMT trial is up and running, which was not acknowledged • The subgroups that are incorporated into current studies have been partially done in the temozolamide study, which was not acknowledged • Recommending that future research should be conducted to compare temozolomide or carmustine implants with other chemotherapy regimens suggests these treatments have already been accepted as the standard or care. This is counterintuitive since NICE have not recommended the use of these agents for the treatment of newly diagnosed high-grade glioma.	The Committee has considered this study – see FAD section 4.1.15. This information was included in the ACD, but has been amended following comments from other consultees. This information has been added to the FAD – see FAD section 4.1.13. The research recommendations have been amended.

Consultee	Comment	Action/response
Brain Tumour UK (continued)	**Clinical need and practice** There is a great clinical need to help patients with high-grade glioma, because under the present circumstances their life expectancy and quality of life are so dire, and the impact on their families is massive. Time is not on their side. The NICE recommendations make no comment about these factors, and especially the number of person-years lost. There is furthermore a number of studies showing that the addition of temozolomide to radiotherapy for newly-diagnosed glioblastoma (the most malignant form of high-grade glioma) significantly improved survival with minimal toxicity and without a negative effect on the health-related quality of life (Stupp et al, Taphoorn et al). In a large multi-centre study, the two-year survival rate of patients that had was 26.5 percent with radiotherapy plus temozolomide and 10.4 percent with radiotherapy alone. The two-year survival rate of patients who had treatment was 26.5 per cent with radiotherapy plus temozolomide, and 10.4 per cent with radiotherapy alone. Concomitant treatment with radiotherapy plus temozolomide resulted in grade 3 or 4 haematological toxic effects in 7 percent of patients. **Evidence and interpretation** 4.1.4 The median survival time that was used to evaluate the results is not necessarily the most accurate way to assess these data. The actual data show that there is a marked improvement in the long-term (2-year survival) when compared with radiotherapy alone, which was most marked for the temozolomide group, but also evident for those with carmustine implants. Patients that had surgery followed by radiotherapy and temozolomide treatment had a 16.5% higher survival rate at 2 years, whereas this was 8.3% for the carmustine group. This longer-term survival is of immense benefit to patients and families.	The Committee took the limited life expectancy of these people into account in their decision – see FAD section 4.3.26. This evidence was considered by the Committee – see FAD sections 4.1.9 to 4.1.15. The two-year survival data was considered by the Committee – see FAD section 4.1.10.

Consultee	Comment	Action/response
Brain Tumour UK (continued)	4.1.11 A MGMT trial to assess response to therapy and prognosis of patients with high-grade glioma is currently ongoing. However, even though it is possible that MGMT may be a predictor of benefit from treatment with temozolomide, this trial has not yet been validated. Such data are still preliminary.	The Committee noted the preliminary nature of these data and rejected the notion of patient selection on the basis of this marker – see FAD section 4.2.25.
	4.1.12 The ACD reports that subgroup analysis showed increased benefit and survival following temozolomide treatment in patients that had a complete rather than a partial resection. But, these subgroup data were not included in the evaluation of the potential benefits of this drug. The Assessment Group should have conducted an analysis to assess the cost-effectiveness of temozolomide in this patient group. Temozolomide might have major benefits for such subgroups.	The Committee considered additional analyses based on subgroups based on data from the largest RCT of temozolomide – see FAD sections 4.1.13, 4.2.13, 4.3.23, 4.3.24, 4.3.26. Temozolomide is recommended for patients with performance status of 0.
	4.3.1 Committee have commented that they considered the clinical evidence and comments from the patient groups, but seem to have based their decision purely on the AG economic model. However, the AG model acknowledges their model is sensitive to certain data and the assumptions they have used. As the economic model appears pivotal to the success/failure of this assessment, we need to establish whether the model has been properly validated, and if so how and by whom.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment Report.
	4.3.2 Available evidence suggests that temozolomide/carmustine implants do not have a detrimental effect on quality of life. Rather, they improve it by increasing progression-free and overall survival without causing appreciable toxicity, thus providing a major benefit to both patients and their families.	The Committee considered the results of the quality of life of patients in the EORTC trial – see FAD sections 4.1.15 and 4.3.20.

Consultee	Comment	Action/response
Brain Tumour UK (continued)	4.3.3 We do not understand why the number of patients treated with radiotherapy plus temozolomide is considered too small to draw conclusions about the effectiveness of temozolomide in increasing survival. To date, three large, international, multi-centre, placebo-controlled, randomised and controlled trials have been conducted to evaluate the effects of post-operative radiotherapy alone versus radiotherapy with concomitant and adjuvant temozolomide chemotherapy (Stupp et al, Taphoorn et al, van den Bent et al). These studies totalled over 1700 patients, half of whom were treated with radiotherapy plus temozolomide, the other half with radiotherapy alone. This is a very large number of patients. Surely, these must be relevant and significant data. Furthermore, all these studies showed that addition of temozolomide during and after radiotherapy significantly improved survival, especially at 2-years, whereas it was also shown not to have negative effects on health-related quality of life.	The Committee noted the difference in two year survival and took this into account in their decision to recommend temozolomide for patients with performance status of 0.
	4.3.4 Post-operative radiotherapy, with or without adjuvant chemotherapy, is considered to be more effective when started before or around 6 weeks post surgery. Concerns about access to radiotherapy in some units should, however, not be used as an argument not to recommend temozolomide/carmustine. It is evident that clinicians would not treat with either temozolomide and/or carmustine if radiotherapy was not available – this would be a waste of resource.	The Committee considered it important to optimise the timing and extent of radiotherapy – see FAD section 4.3.5. Concern about access to radiotherapy was not a reason for the Committee's recommendations.

Consultee	Comment	Action/response
Brain Tumour UK (continued)	4.3.9 QALY analysis may not be appropriate in this case, since it can only give poor results in a disease that has such a bleak prognosis. A 50% increase in life expectancy but fewer overall years does not carry much weight in this model, even though it would have huge positive implications for both patients and their families. Furthermore, quality of life data was assessed in the temozolomide trial using a disease specific instrument. There is no validated methodology for estimating utilities based on this instrument. The NICE model is also sensitive to median survival and does not take into consideration that survival might be disproportionately greater in certain subgroups. Median survival time is not necessarily the most accurate way to assess these data. The actual data show that there is a marked improvement in the long-term (2-year survival) when compared with radiotherapy alone, which was most marked for the temozolomide group, but also evident for those with carmustine implants. In the light of these factors, cost utility analysis was not feasible.	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The survival estimates in the economic model were based on the entire Kaplan-Meier survival curves and not just median survival – see Assessment Report section 5.5.1.
	4.3.11 'The Committee concluded on the balance of the economic evidence that the use of carmustine implants and temozolomide for the treatment of newly diagnosed gliomas would not be a cost-effective use of NHS resources.' However, we have been given to understand that temozolomide may have a major indication in the second line treatment of relapsing glioma, and this would obviously be affected by this decision.	The Institute has already issued guidance on temozolomide for recurrent malignant glioma.
	4.3.13 No specific mention is made of subgroup analysis for temozolomide, although this has been examined in a number of the submissions. When done, subgroup analysis highlighted increased benefits in specific groups. E.g. Stupp's study showed that adjuvant temozolomide had the greatest benefits in patients that were fittest at the beginning and had the greatest degree of tumour resection, and similar data were also presented in the manufacturer's submission.	Additional analyses considering subgroups, including by performance status, have been performed by the Assessment group – see FAD sections 4.1.13, 4.2.13, 4.3.23, 4.3.24, 4.3.26. Temozolomide is recommended for patients with performance status of 0.

Consultee	Comment	Action/response
Brain Tumour UK (continued)	**Proposed recommendations for further research** Europe, the USA and Australia currently use these treatments as the standard care based on the trials conducted to date. Trials are ongoing for these treatments for e.g. temozolomide and MGMT. If temozolomide and carmustine are not recommended in the UK, research here would be pulled. This would include the study that Edinburgh are currently participating in. The UK will then fall behind the rest of the world in treating patients with gliomas. ACD preliminary recommendation is restricted use to well designed RCTs. Since about 1800 patients a year are diagnosed with high-grade-glioma in the UK, the vast majority of these patients will be denied treatment. **Proposed date for review on guidance** Research based charities would be discouraged from funding research if the next technology review is not until 2009. The overall outcome would be a tremendous setback for glioma patients in the UK.	Noted. If significant new evidence becomes available in the interim, consultees can request an early review
Brain and Spine Foundation	The Brain and Spine Foundation strongly challenges the recommendations proposed by the committee, namely that temozolomide and carmustine implants should not be recommended for people newly diagnosed with high grade glioma.	Recommendations for temozolomide have been revised. Temozolomide is recommended for patients with performance status of 0.

Consultee	Comment	Action/response
Brain and Spine Foundation (continued)	Only passing reference is made to the patient perspective in the ACD and the issues specific to patients with high grade glioma's are not considered. NICE currently adopts utility values based on those of a panel of people who are asked to envisage what a condition is like to have. We argue that it is impossible for someone to imagine what it is like for a person, often with young children, to be given the diagnosis of a high grade glioma. There is no other cancer which can potentially affect some many aspects of a person's life (cognitive, physical and psychological), or indeed the very essence of their self. It is impossible to imagine what value these people and their families place on increasing the lives by a few months. The chance of a treatment (without any detriment in quality of life) is priceless, but society at large may find it hard to comprehend this.	The Committee are aware of the difficulties associated with estimating health-related utility. It was aware of the relative short life expectancy of people with high grade glioma and the importance of extending survival without disease progression – see FAD section 4.3.26.
	A recent audit revealed that every call to our helpline on high grade glioma involved a request for further information about clinical trials or treatment options. Our experience on the helpline and from consulting with people, including children, affected by brain tumours has clearly indicated that they want the treatments under consideration here to be made available on the NHS. It is unacceptable that they will only be available on an ability-to-pay basis or only in those parts of the country where clinicians are able to fund clinical trials thus maintaining the postcode lottery that NICE was originally established to redress.	Noted
	In general, NICE considers a treatment costing less than £20,000 per QALY as cost effective. We argue that this discriminates against conditions such as high grade gliomas because they have a low incidence and a poor prognosis. It will be many years before a treatment will be developed that will add years to a person's life and not just months. NICE will reject all of these treatments, not because they are ineffective but because their model is inappropriate.	The Committee took the limited life expectancy of these people into account in their decision – see FAD section 4.3.26.

Consultee	Comment	Action/response
Brain and Spine Foundation (continued)	**Specific Comments** Section 1 1.3 We challenge the recommendations made for further clinical studies on these treatments: • Quality of life has already been assessed in a study by Taphoorn et al (2005). Quality of life was assessed using reliable and valid measures, namely the European Organisation for Research and Treatment for Cancer (EOTRC) quality of life questionnaire (QLQ-C30) and the EORTC brain cancer module (EOTRC BN-20). It is highly improbable that any additional funding will be secured to investigate this is more detail, especially in the UK, if these treatments are not recommended. • The MGMT trial is already in progress. The committee highlight the apparent importance of MGMT status, however this alone is unlikely to predict response to temozolomide. We already know that the extent of resection and performance status do predict response survival time. Section 2 We would like to emphasis the number of life years lost rather than the incidence of this particular cancer. Burnet et al (2005) calculated years of life lost, a population-based mortality indicator, across different cancer sites. Brain and CNS tumours are calculated to have the highest number of average life year lost, namely 20.1 yrs, out of all the cancer sites. Despite this, it only attracts 1.5% of the National Cancer Research Institute spending. Section 3 No comment	The research recommendations have been amended. Details of this study were considered by the Committee and have been added to the FAD – see FAD section 4.1.15. Recommendations for temozolomide have been revised. Temozolomide is recommended for patients with performance status of 0. Noted

Consultee	Comment	Action/response
Brain and Spine Foundation (continued)	Section 4 4.1.4 and 4.1.10 Throughout the report emphasises the median survival data detracting attention away from the long term survival advantage gained from these treatments. For example, in the Stupp et al (2005) trial the 18 month survival rates for radiotherapy plus temozolomide are 39.4% compared to 20.9% for radiotherapy only. Furthermore, an increase survival of 3 months for someone who may only live for 12 months is a 25% increase. The economic model should reflect the proportionate, and not the absolute, increase in survival time	The Committee noted the improvement in long term survival. See FAD section 4.1.10.
	4.1.11 MGMT status may be a predictor of response to temozolomide but this is yet to be established. It is not a basis on which to defer i.e. wait until a review, before deciding whether to fund this treatment on the NHS. The existing data already indicate which clinical factors predict response to treatment.	The Committee noted that it was premature to use MGMT promoter status to identify suitable subgroups and rejected the notion of patient selection on the basis of this marker – see FAD section 4.2.25. Temozolomide is recommended for patients with performance status of 0.
	4.1.12 The existing data already indicates which sub groups of patients will benefit from the treatment. The numbers are small but this is likely to be a problem for any treatment involving such a patient population.	Further analysis has been performed by the Assessment Group and considered by the Committee – see FAD sections 4.1.13, 4.2.7, 4.2.13, 4.3.17, 4.3.24 and 4.3.26. Temozolomide is recommended for patients with performance status of 0.

Consultee	Comment	Action/response
Brain and Spine Foundation (continued)	4.3.1 The economic model seems to be particularly sensitive to relatively small changes in certain parameters. The values that have been used are very much open to question. Given the challenges made by several well respected clinicians about the use of this model, we seek further clarification on its validity and robustness. The committee note that the characteristics of the trial populations do not match those of the general patient population which limits the findings. However, in clinical practice these treatments would not be offered to patients with a low performance score or where surgery is not possible or indicated. Thus we argue that the trials population is representative of the patients who would be offered these treatments. The total cost to the NHS would therefore be significantly less than quoted. Section 9 Why was 2009 chosen as the review date? Was this decision based on when further clinical trial data is expected to be available? **Summary** • It appears that NICE has adopted one model and one process, irrespective of the condition or the type of treatment under consideration. One size does not fit all. • Temozolomide and carmustine implants represent the first effect treatments for high grade gliomas in many years. • These treatments are highly valued by clinicians. Clinicians want to prescribe these treatments for a sub-group of patients and their submissions support their efficacy. • Both patients and clinicians are extremely concerned about the possibility that these treatments will not be made available. This decision will have far reaching ramifications for the brain tumour community and will severely impede research in this country.	The Committee considered detailed sensitivity analyses around the individual parameter estimates – see Assessment Report 5.6.2 and 5.7.2. Temozolomide is recommended for patients with performance status of 0. The review date has been set according to the standard processes (see Section 5 of the Guide to Technology Appraisal Process available from URL http://www.nice.org.uk/page.aspx?o=201972). Consultees can request an early review if significant new data become available.

Consultee	Comment	Action/response
Association of British Neurologists	Thank you for you sending me the results of the Appraisal Committee's deliberations regarding the above which I am replying to on behalf of the **Association of British Neurologists**	Comments noted.
	I am surprised and disappointed by the view that the Committee has taken that both carmustine implants and temozolomide should not be recommended for the treatment of newly diagnosed high-grade glioma, except in well-designed clinical studies. This will effectively deny these treatments to the vast majority of patients with high-grade glioma who are not being treated within the context of clinical trials and undermines the substantial body of evidence that has accumulated already from well-designed randomized controlled trials. It will also act as a deterrent for any future clinical trials to be carried out in this country. Furthermore, as carmustine implants have just been accepted for use within NHS Scotland for the treatment of newly-diagnosed high-grade glioma this will inevitably create a true situation of post-code prescribing that NICE was set up to abolish. Of the two technologies, I consider the evidence for the effectiveness of carmustine improving progression-free survival to be weaker than that for temozolomide and would therefore anticipate that The Scottish Medicines Consortium (SMC) will accept the use of temozolomide as well in the future.	Temozolomide is recommended for patients with performance status of 0.
	This decision needs to be considered in the light of current practice in other developed countries specifically the United States and Europe. In the US, the FDA approved temozolomide almost immediately after the phase II study was published in 2002 (Stupp R *et al.* Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol. 2002 Mar 1;20(5):1375-82) and as a result the concomitant regime has been standard therapy for newly diagnosed high-grade glioma since then. The rest of Europe adopted it immediately after the NEJM article came out in April 2005.	
	If the NICE guidance is adopted the UK will be the only industrialised country in the world (except Belgium) that has not agreed to fund treatment.	

Consultee	Comment	Action/response
Association of British Neurologists (continued)	With respect to these specific points raised by the Appraisal Committee: 1) I do not consider that they have considered all the relevant evidence, specifically they failed to take into consideration the subset analysis of median overall survival by prognostic factors from the Stupp (EORTC) Study which was published on-line as an addendum. They showed that the benefit of combined treatment with temozolomide and radiotherapy for patients under the age of 50 was significantly better than those under the age of 50 years who received radiotherapy alone (median survival of 17.4 months vs 13.2 months p<0.001). In comparison, the benefit of the combined treatment compared to radiotherapy alone for patients over the age of 50 years was also statistically significant although not as impressive in absolute terms (13.6 months vs 11.9 months). As expected, patients who had had surgical resection fared better than patients who had just been biopsied in both groups (15.8 months vs 9.4 months in the combined arm) and patients with WHO performance status of 0 or 1 also had significantly longer survivals than WHO performance status 2 (17.4 and 14.0 months vs 9.9 months). I therefore believe that there is a sub-group of 'better prognosis' younger patients with high performance status and surgical resection who stand to benefit considerably more from the additional temozolomide than 'poor prognosis' patients and I feel that the appraisal committee have not given due consideration to these factors.	The Committee considered these data which have now been noted in the FAD – see Section 4.1.13. Additional analyses were performed to consider subgroup data – see FAD sections 4.2.13, 4.3.24 and 4.3.26. Temozolomide is recommended for patients with performance status of 0.

Consultee	Comment	Action/response
Association of British Neurologists (continued)	As regards cost effectiveness, I am a little perplexed by the conclusion that if the maximum acceptable amount for an additional QALY gained is £50,000 or more and the mean incremental cost per QALY was just under £37,000 for better prognosis patients treated with carmustine and £43,000 treated with temozolomide, why did the committee conclude that they were not cost effective? Clearly the resource impact and implications on the NHS are appropriate if one accepts their conclusions that neither of these technologies should be recommended for use.	This section has been amended for clarity. The NICE methods guide states that *"Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make reference to explicit factors including: the degree of uncertainty surrounding the ICERs, the innovative nature of the technology, the particular features of the condition and population receiving the technology, where appropriate, the wider societal costs and benefits, Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong."*
	For the above reasons, I do not consider that the provision recommendations of the appraisal committee are sound and at the end the day, it seems that they have been far too heavily influenced against the technologies by virtue of economic considerations alone.	Decisions are made on the basis of both clinical and cost effectiveness.

Consultee	Comment	Action/response
Association of British Neurologists (continued)	In every area of cancer treatment, there are new technologies, which offer small but significant survival advantages. Notwithstanding various concerns about the data analysis in the carmustine trial, both these technologies can be considered to offer small survival advantages and certainly in the case of temozolomide, a significant survival benefit at two years which has never yet been demonstrated for any other type of adjuvant chemotherapy. To deny patients the benefit of these technologies on the basis of relatively marginal survival benefits which have been clearly demonstrated and even more marginal cost considerations, which have not been clearly demonstrated, particularly so for good prognosis patients, seems to go against the basic principles of the NHS Cancer Plan which is to ensure that patients with cancer are not disadvantaged with respect to proven treatments in comparison to similar patients elsewhere in the world.	Temozolomide is recommended for patients with performance status of 0.
	If we are unable to give suitable patients these treatments they are not getting 'best standard' treatment, and this will have a knock-on effect in that patients will be less likely to be referred to MDTs, as they would be perceived to have nothing to offer. In addition, research would stop completely as no treatment would achieve the cost effectiveness bar and we would not be able to enroll patients in future EORTC/International Trials. If there is a possibility of giving Gliadel or Temozolomide, then non-MDT doctors are likely to refer to MDTs early to see if patients would be suitable or not rather than just resecting or biopsying without discussing at MDT. A negative response from NICE would shoot the NCCC/NICE Commissioning Guidance in the foot and fly directly in the face of the Guideline Development Group.	Comments noted. Comments in response to the Assessment Report and ACD from the Guideline Development Group were considered by the Committee. In addition representatives from the Guideline Development Group attended the second Committee meeting.

Consultee	Comment	Action/response
Society of British Neurological surgeons	1.1 NICE review of Temozolomide in 2001 related to patients with recurrent high grade tumours in which after consideration of limited evidence agreed its use after PCV treatment at a cost of around £9000 per patient for around 1.5 to 2 months median additional survival benefit from 6 months to eight months. It is unclear what the status of this recommendation is in the light of the current appraisal document. Especially where the evidence for early treatment with this agent has shown improvement in overall survival, and is currently being compared against PCV treatment at recurrence in a randomized clinical trial (NCRI/BR12).	The Institute plans to consult on a draft scope for the review of TA23 in 2006. The exact timing will depend on the progression of the MRC trial BR12.
	2.6 Incorrect information. Sentence three implies that inoperable ie non-debulkable patients will only receive palliative treatment. This shows a lack of understanding of the issues. There is as yet no clear RCT evidence to confirm that debulking is superior to biopsy where subsequent treatment involves a full course of radiotherapy. Thus patients who do not have debulking will usually have a biopsy performed and both will be considered for radiotherapy equally dependent on their performance level.	This section has been amended.
	The related issue from the two RCT studies (Stupp et al [Temozolomide] and Westphal et al [Carmustine]) is that subgroup analysis (see appraisal document 4.1.12) showed that radical resection appears to improve the response to both these treatments in this trial design.	The Committee considered the subgroup analyses from both of these trials – see FAD sections 4.1.6, 4.1.13, 4.2.7, 4.2.13, 4.3.16, 4.3.17, 4.3.24, and 4.3.26. The Committee also noted the difficulty of quantifying the extent of resection – see FAD section 4.3.16.
	3.2 Carmustine implants are not just indicated they are indeed licensed for use in newly diagnosed high grade gliomas. (cv comments made about Temozolomide 3.6 inconsistent)	This section has been amended.
	4.1.3 Despite these comments, the FDA did indeed give license for Carmustine wafers to be used in newly diagnosed high grade gliomas with extensive resection.	Noted.

Consultee	Comment	Action/response
Society of British Neurological surgeons (continued)	4.2.3 The time to onset of symptoms is discussed. It is unclear whether the concerns about estimation of period based on mean or median times relate to Temozolomide as well. It is fair to say that although the FDA felt it necessary to reanalyse the data for Carmustine wafers they still felt they had a reasonable situation to grant a licence.	These concerns only apply to carmustine implants. This has been clarified in the FAD.
	The assumption about difference in cost being primarily due and more or less entirely due to the implants themselves is justified by the data. (see section 4.2.4)	See section 5.3.4.4 of assessment report. The Committee considered that all healthcare costs related to the treatment of glioma should be included.
	A utility value of 0.8 for patients without symptoms implies that the diagnosis alone is sufficient for a drop in utility data. It was unclear where the evidence for this is within the AG document. It seems more likely that the utility value is an estimate based on the shape of the performance curve, and many patients even with a diagnosis of brain tumour will still have a high performance level and a utility value nearer to 1. The use and estimation of the utility value is clearly open to discussion where mean estimates clearly represent an average utility over a regular fall in performance. The situation is far from clear that this pattern is universally is so, and a threshold estimate may be more useful. (see later comments on 4.3.9)	The average utility of the general population is not 1. The Committee discussed this and agreed that 0.8 was not an unreasonable figure for this population.
	4.2.4 The statement that the £ per QALY for Carmustine was understated because of *(a)* "assumptions" used to estimate survivals and *(b)* omission of treatment costs. In response to *(a)* the weighting of this approach is unclear and the impact on the QALY estimate implied by this statement is implicitly damning without qualification. As regards the omission of treatment costs, other than those with implants themselves, these were excluded because <u>there are none</u> and it is incorrect to imply otherwise.	See section 5.3.4.4 of assessment report. The Committee considered that all healthcare costs related to the treatment of glioma should be included.

Consultee	Comment	Action/response
Society of British Neurological surgeons (continued)	4.2.7 It would be wrong to create a cost benefit model which stepped outside of the patient groups included in the two major trials where the additional synthesised data included could have a mutual impact on the subset of RCT data eg incorrect stratification. We have concerns about how this model has been developed and extrapolated beyond the data available from the RCT process. It is fair to say that the Markov model used by the AG is unvalidated in this patient group.	See Guide to the Methods of Technology Appraisal section 5.8.1 (Available from URL http://www.nice.org.uk/page.aspx?o=201974)
	The discussion of the local cost data model in the original technical report has not included a balanced assessment of the relative GNP and spending on cancer treatment in Europe or in this context, e.g. the relative spending on brain tumour of patients in the UK versus Europe. Hence, local analyses of cost (£ per QALY) and threshold limits should be compared with similar levels and thresholds for the European sector. The importance of this is that it would form an important prima facie basis for individual patients to mount a legitimate claim against restrictions on prescribing Carmustine and Temozolomide as a result of this draft appraisal. (See Barbara Clark case on Herceptin: Human Rights Act and European Court) This is particularly true where clinicians caring for these patients would naturally support patients to have these treatments, as the best available, comparably with the rest of Europe.	Considerations about cost effectiveness are explained in the Guide to the Methods of Technology Appraisal section 6.2.6.10 and 6.2.6.11(Available from URL http://www.nice.org.uk/page.aspx?o=201974)
	Patients do not have a constant “deteriorating quality of life” as many oncologists looking after these patients will agree. It was clear at the discussions meeting held at NICE HQ that this concept was not grasped by the committee. It is probably relevant that no oncologist or oncologist practicing in this area resides on the committee or was involved in the writing of the technical report. In our experience it is unusual for there to be such total agreement between oncologists overall and oncologists working in this area to approve these two new treatments. This discrepancy from practising clinical activity needs resolving.	The Committee considered that most patients’ health would deteriorate once progression of the disease had occurred – see FAD section 4.3.3.

Consultee	Comment	Action/response
Society of British Neurological surgeons (continued)	4.3.1 On reviewing the data we accept that the committee has a wide range of expertise and that it took advice from experts. However, we are concerned that the acceptance of these two treatments by oncologists in the UK and throughout the world but not by this committee reflects the fact that the views of patients and carers in this area has not been fairly represented in the deliberations of this committee. This is clearly true in the technical report which lacks any oncological input in the writing.	Details of the expert advisory group for the assessment report are included in appendix 2 of the assessment report.
	4.3.2 This statement is incorrect and shows lack of understanding of patients with this tumour. Patients do not universally decline once progression has occurred. Progression is hard to define as is remission in this case. Patients may develop focal signs of may notice nothing of what is grossly apparent on imaging. Most patients have fluctuation in performance with their disease and are managed accordingly. These fluctuations probably reflect ongoing disease and may be classified as progression or may not. Decline is not immediate and is not by any means “usual”. Most patients with these cancers link their quality of life with their survival and a few months increase in survival contributes significantly to quality of life. In addition, the hope that they might live for two years, i.e. from 10% to 26%, is of huge importance to both carers and to patients.	The Committee discussed the problems of assessing disease progression using radiological imaging and measures of functional status. See FAD section 4.3.4 and 4.3.9.
	4.3.3 The assessment of the committee concerning long-term survival was ill founded. There is available data that confirms that the QOL in the long-term survivors was maintained (R Rampling personal communication). Secondly, despite their bias, the differences in long-term survival from 10-26% - a considerable increase was statistically significant and, therefore, not “too small”. It was unreasonable of the committee to take this attitude if the effect of selection of patients would be to increase the likelihood that up to 25% of these patients might live two years.	The committee noted the difference in two year survival and took this into account in their decision to recommend temozolomide for patients with performance status of 0.

Consultee	Comment	Action/response
Society of British Neurological surgeons (continued)	4.3.4 We were grateful for the committee's acceptance that the whole pathway for these patients must be supported. It is important as it has relevance to the implementation of these treatments and has been underwritten by the new draft NICE IOG for patients with brain tumours. It would be illogical for the technology appraisal group to ignore the fact that the IOG group has been impressed by these RCT's and will utilise the IOG implementation to ensure that new treatments, and particularly these treatments, can be implemented effectively.	Noted
	4.3.5 It is not helpful to invoke implications about other treatments and omit unavailable data here. It implies that our lack of certainty about existing and future data would always negatively impact on the decisions to use Carmustine or Temozolomide in the future. Is there a confusion/mistake with Temozolomide and Carmustine here.	This section notes that neither treatment has been compared in RCTs to existing chemotherapy regimens, such as PCV, in patients with newly diagnosed glioma. Decisions are based on appraisal of data on both clinical and cost effectiveness.
	4.3.6 Despite the implied concerns here the FDA carefully considered the data and licensed Carmustine based on their positive assessment of the submission. It is clear that although the overall gain in survival was indeed small, but significant, and in terms of patients who live for twelve months or so, two to two and a half months improvement in survival is not small, it is considerable. It is unreasonable for the committee to downplay the impact that 2.3 months on survival can be for patients and their carers. It is particularly true when there is evidence of maintained quality of life.	The Committee took the limited life expectancy of these people into account in their decision – see FAD section 4.3.26.
	4.3.7 The experts explained that performance free survival was difficult to assess and that following disease progression, as said above, is not routinely followed by "rapid deterioration".	The Committee discussed the problems of assessing disease progression using radiological imaging and measures of functional status. See FAD section 4.3.4 and 4.3.9. The Committee considered that most patients' health would deteriorate once progression of the disease had occurred – see FAD section 4.3.3.

Consultee	Comment	Action/response
Society of British Neurological surgeons (continued)	The committee would be wrong to place much store by disease assessment based on imaging. However, this should be taken to imply that it is *the method of assessment for tumour response* that is inadequate, and that the status of performance free survival may be just as equally positive or negative and not just always negative by inference. In other words imaging 'deterioration' often has little relation to clinical deterioration.	The Committee discussed the problems of assessing disease progression using radiological imaging and measures of functional status. See FAD section 4.3.4 and 4.3.9.
	4.3.8 We are pleased that the committee recognised the difficulties in absolute pathological definition of high grade glioma. It is unclear, however, how they have taken this into account numerically in their interpretation of the information from the AG in reaching their conclusions.	After considering the difficulties in pathological definition of high grade gliomas, the Committee accepted the pragmatic evidence from the RCT as a reflection of the realities of current clinical practice and that the manufacturer's initial histological classification could be considered appropriate – see FAD section 4.3.10..
	4.3.9 We agree that both the <u>disease</u> and its <u>treatment</u> may have measurably difference effects on the quality of life and survival. However, it is clear that the understanding of quality of life (QOL) in this group of patients by both the AG and the committee was influenced by the abstract AG model which misleads on the performance after "progression". More sensitivity to the views of those experienced in defining the disease and its care would have helped correct this and would have clarified the position. For example, quality of life is very difficult to assess in the latter stages of disease and many professionals working in this area use a different paradigm to approach this.	The Committee considered sensitivity analyses around the estimates of health-related quality of life – see Assessment Report section 5.6.2.

Consultee	Comment	Action/response
Society of British Neurological surgeons (continued)	In the figure above [not reproduced in this table], the Y-axis represents performance level measured in Karnofsky units. The X-axis represents time. The three graphs A, B and C represent progression of disease in three different patients with glioblastoma multiforme. Patient A shows the pattern roughly assumed to be the normal pattern described by the AG model dying at time T1. Patient B shows early deterioration by drops in performance which is treated and measurably stable until deterioration at T2. Patient C shows an intermediate deterioration but outlives A and B to T3. However, both B and C have a prolonged but useful performance level above a Karnofsky of 60. Thus, A deteriorates later but dies earlier and B and C deteriorate earlier but have a useful existence above a recognised threshold for independence. On this basis we would question whether the AG model is valid and that the committee have been too influenced by its seeming precision without adequate regard to its weaknesses. 4.3.10 Again, there is an over-emphasis on the time of when PFS ends and deterioration begins and its rate. The comment about the Weibull statistical approach is not about whether something is an over or under estimate of survival and seems to imply that in someway the data is unreliable. We refute this but agree with the committee that its axiomatic agreement that there were improvements in survival in the two RCTs for these two compounds is substantiated.	The committee are familiar with the difficulties of dealing with this kind of uncertainly. It considered sensitivity analyses around the estimates of health-related quality of life – see Assessment Report section 5.6.2 and 5.7.2. The Assessment Group fitted Weibull curves to the data on survival from the largest RCTs. The Committee noted that this led to a slight overestimate in survival gain for temozolomide and slight underestimate in survival gain for carmustine implants in the analysis. However it also noted that sensitivity analyses suggested that this was not a concern. See Assessment Report Appendix 12 and FAD sections 4.3.12 and 4.3.21. Note that the model was not found to be sensitive to the assumption that the probability of death was based on the length of survival only.

Consultee	Comment	Action/response
Society of British Neurological surgeons (continued)	Of considerable concern, however, is the final statement in this section. If we follow the logic of this argument we would have to see an increase in survival to nearly six months between the treatment in control groups to bring the £ per QALY much lower. We doubt whether there are any recent treatments in any of the solid tumours that have been able to demonstrate a six month improvement in survival let alone a three month improvement. This is an unfair and unreasonable target for research in this area to achieve and does by implication make it impossible for these patients ever to receive a £ per QALY target that would satisfy the NICE criteria. In other words, the patients are debarred from available cancer treatment by virtue of their diagnosis – this is by NHS terms unreasonable.	The decision is made on the basis of clinical and cost effectiveness. The FAD has been amended to note that the cost of carmustine wafers also has a notable impact on the ICER – see FAD section 4.2.6.
	4.3.11 The committee has apparently misunderstood the AG analysis and are now intending to contradict themselves. Secondary treatments have apparently been shown to be ineffective whatever time they are given so that the treatment we give to patients after failing the treatments presented in these RCTs is immaterial. Furthermore, these RCT studies compared subsequent treatments in each arm and dismissed them as ineffective at influencing the outcome. Hence, there is no question about "uncertainty here". The message from the RCTs is that early treatment with these treatments produces an effect which is substantially greater than when they are used at a later date, which makes NICE's current position illogical with respect to the ruling in 2001 on Temozolomide used at recurrence. The committee should ignore discussion of subsequent or other treatments as they are by their own admission and through the acceptance of the AG report ineffective. To disbar patients from these upfront treatments by virtue of the fact that patients survive and then cost money is unreasonable.	The Committee noted that the evidence on effectiveness from the RCTs included the use of subsequent chemotherapy treatment and concluded that it was appropriate to consider this in the economic analysis – see FAD section 4.3.22.

Consultee	Comment	Action/response
Society of British Neurological surgeons (continued)	Cost effectiveness of treatment has both an economic basis as well as a societal/political basis. The latter is responsible for the setting of thresholds which assume all decisions are made on a comparably fair process to all applicants. We feel that there are significant questions about the committee's analysis of the RCT data which is at odds with international bodies, reputed journals, and the National Oncological Conference and impact on the assessment of 'willingness to pay'. There are concerns that NICE's application of cost benefit thresholds as applied fails to take account of: (i) Discrepancies between oncologists' interpretation of patient performance and the distinctions made by the committee. (ii) Misunderstandings around possible achievable improvements in survival for a particular cost. (iii) Failure to appreciate that spending on brain tumours is low and that even additional costs for these drugs remains low per capita by comparison with patients with lung and breast cancer. The impact of this is to make research in this area more expensive as the Sponsor must pick up the cost which they have to recoup in the licensing period. (iv) Even though the £ per QALY cost may be high to numbers of patients who could be selected for this treatment, the number of patients is low and will result in a reasonable and transparently determined cost to the NHS which would allow this rarer cancer to achieve equity of funding with other cancers.	Considerations about cost effectiveness are explained in the Guide to the Methods of Technology Appraisal section 6.2.6.10 and 6.2.6.11 (Available from URL http://www.nice.org.uk/page.aspx?o=201974)

Consultee	Comment	Action/response
Society of British Neurological surgeons (continued)	(v) It is reasonable to argue that factors other than health status are important in quality of life assessments since some people are unable to convert healthy life into good quality of life. However it is normal to consider quality of life in the context of what health status of a reasonably fit person of that age might hope for, and to ignore all aspects of quality of life that are not caused by illness and /or modified by treatment and care. We maintain that the knowledge that a person is in the 'best 'available treatment contributes directly to their 'health status' and that to have this denied will seriously and adversely affect there QOL to the extent that it will alter the conditions under which the AG assessment was performed. In other words the extent of the 'additional suffering' that is likely to ensue from the current NICE position must be considered.	Comments noted
National Hospital for Neurology and Neurosurgery	**General comments**. These guidelines will cause considerable disquiet in the neuro-oncology community since they suggest that the NHS in England and Wales is not able to offer effective new treatments for high grade glioma, which are widely used elsewhere and have recently been approved for NHS funding in Scotland. Temozolomide and external beam RT are considered standard approach for GBM across the world and this has already become the standard treatment arm in international studies. This will make it difficult to convince well informed patients that they should not travel elsewhere for treatment and/or seek treatment in the private sector. It is also likely to become difficult to accrue to studies with RT only as a treatment arm. The assumption that studies involving these agents will be able to produce useful additional information is likely to prove incorrect. The involved pharmaceutical companies are very unlikely to support such studies and patients will not wish to take part in them.	Comments noted.

Consultee	Comment	Action/response
National Hospital for Neurology and Neurosurgery (continued)	**Specific comments on ACD report**	
	4.2 The main conclusions are based on a novel health economic analysis which has never been validated. No separate analysis has been carried out to assess benefit in good prognosis subgroups. These have been well defined by the RCT of Temozolomide and RT and it is these patients who are likely to gain most from adjuvant treatment.	Additional analysis on subgroups has been performed subsequently. Temozolomide is recommended for patients with performance status of 0.
	4.2.10 Assumptions on the effect of Temozolomide on long term survivorship are limited by follow up in largest study. This should be re-evaluated when longer follow up data are available, this will be before the 2009 re-evaluation date suggested in the document.	Noted. If significant new evidence becomes available in the interim, consultees can request an early review.
	4.3.3 The suggestion that other chemotherapies may be as effective in this setting is supposition. Mechanisms of action/interaction with RT are likely to be different and, particularly with PCV bone marrow toxicity is more likely.	Noted – but it remains true that temozolomide has not been compared with strategies other than radiotherapy alone in RCTs
	4.3.4 Longer survival in the control arm in the EORTC study is likely to be due to increased proportion undergoing more radical surgery and early radiotherapy. This is a separate issue and may be used as an argument to improve surgical management and timing of RT rather than not give adjuvant chemotherapy. Use of concomitant regime within a specified time frame after surgery could be an effective driver to improve RT waiting times in this patient group.	Noted. The Committee considered it important to optimise the timing and extent of radiotherapy – see FAD section 4.3.5. Concern about access to radiotherapy was not a reason for the Committee's recommendations.
	4.3.13 The assumption that MGMT status will be a strong predictive indicator of response is based on a single study in which only 50% of tumours could be assessed and should not be used as an argument against treating the whole GBM population until these data are validated in additional studies.	The Committee noted that it was premature to use MGMT promoter status to identify suitable subgroups and rejected the notion of patient selection on the basis of this marker – see FAD section 4.2.25.

Consultee	Comment	Action/response
National Hospital for Neurology and Neurosurgery (continued)	**Specific comments on Evaluation Report** i. Subgroup analysis for patients with better performance status is available (supplementary material to Stupp NEJM paper). This should be used in health economic analysis, section 5.7.2.3 ii. The health economic model used makes significant assumptions about survivorship and QOL in 2 year survivors after Temozolomide. These are not supported by available data, which are too immature to address this. iii. There are now data describing the effects of adjuvant Temozolomide on QOL during treatment (Taphoorn et al Lancet Oncol Nov 17 2005). This suggests that it would be unusual for adverse effects of Temozolomide to affect cost per QALY.	 i. Temozolomide is recommended for patients with performance status of 0. ii Noted iii. Noted. This is now noted in the FAD – see section 4.1.15.
CancerBacup	Thank you for the Appraisal Consultation Document. I am writing to let you know that CancerBACUP will not be making a further submission at this stage.	No action required
Samantha Dickson Research Trust	**Section 1 : Preliminary recommendations** These preliminary recommendations are not acceptable as: • The quality of life has already been assessed (Taphoorn's study) and found that temozolomide maintains the quality of life • The MGMT trial is already in progress • Subgroup analysis is already incorporated into currently running studies • Comparison of temozolomide or carmustine implants with other chemotherapy regimens suggests that these treatments have already been accepted as the standard of care. NICE have not recommended these agents for the treatment of newly diagnosed high grade glioma.	The research recommendations have been amended.

Consultee	Comment	Action/response
Samantha Dickson Research Trust (continued)	**Section 2 : Clinical need and practice** • There is a lack of data on Person Life Years of Life Lost (YLL) with regard to brain tumours. I quote form Dr Burnett's study publishes in the British Journal of Cancer (2005) : "Specific YLL data for ..head and neck cancers are not available. …. Brain tumour patients suffer more than three times the mean loss of life with AYLL figure of just over 20 years….. Tumours of brain and CNS have the highest AYLL of all 17 tumour sites, but rather modest 1.5 % of NCRI research spending" • Time is not on the side of patients with high grade or newly diagnosed brain tumours as their prognosis is so poor **Section 4 : Evidence and interpretation** • **4.1.4 and 4.1.10** The long term survival data is significant – it shows a 40.6% improvement at 12 months survival for radiotherapy plus temozolomide over the radiotherapy only group. • **4.1.11** Subgroup analysis (MGMT) is mentioned and although MGMT is likely to be predictor of benefit form temozolomide, this trial is ongoing and not yet validated. It is amazing that this unproven data was considered and yet the completed data of subgroup analysis appears not to have been taken into consideration in the final analysis of the ACD	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.3.4 (Available from URL http://www.nice.org.uk/page.aspx?o=201974). The Committee noted that people with high grade glioma have a relatively short life expectancy – see FAD section 4.3.26. The Committee considered the long term survival data – see FAD section 4.1.10. The Committee rejected the notion of patient selection on the basis of this marker – see FAD section 4.3.25.

Consultee	Comment	Action/response
Samantha Dickson Research Trust (continued)	• **4.1.12** ACD highlights that greater benefit was observed with temozolomide in the subgroup of patients who had complete resection. Median survival was 14.2 months in the radiotherapy only group and 18.3 months in the radiotherapy plus temozolomide group. This represents a survival advantage of 4.1 months which to a terminally ill patient and their family amounts to a significant difference. Why did the Assessment Group not conduct an analysis to assess the cost-effectiveness of temozolomide in this patient group?	The Committee considered subgroup analyses from the trials of temozolomide and carmustine implants – see FAD sections 4.1.6, 4.1.13, 4.2.7, 4.2.13, 4.3.16, 4.3.17, 4.3.24, and 4.3.26. Temozolomide is recommended for patients with performance status of 0.
	• **4.3.1** Although the Committee state that they have considered the clinical evidence and comments provided by patient groups, it appears that they have based their decision purely on the AG economic model. The AG model acknowledge that their model is sensitive to certain data and the assumptions that they have used. As the economic model used appears pivotal to the success or failure of this assessment, it would be helpful to know whether the model had been properly validated and if so by whom and how? Is such a QALY dominated model appropriate for an extremely aggressive disease such as GBM?	Decisions are made on the basis of clinical and cost effectiveness. The Committee carefully considered the assumptions included in the AG model, the results of sensitivity analyses of those assumptions and comments received in response to the Assessment Report. The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.3.4 (Available from URL http://www.nice.org.uk/page.aspx?o=201974).
	• **4.3.2** The ACD states that "the quality of life of patients is paramount at all stages of the disease…" yet although available evidence suggests that temozolomide/carmustine implants do not have a detrimental effect on quality of life, this appears to have been discounted.	The Committee considered the results of the study into the quality of life of patients in the EORTC trial – see FAD sections 4.1.15 and 4.3.20.

Consultee	Comment	Action/response
Samantha Dickson Research Trust (continued)	• **4.3.4** The concerns expressed with regard to access to radiotherapy in some situations should not be used as an argument not to recommend temozolomide/carmustine. Expert clinicians would not treat with temozolomide or carmustine if radiotherapy was not available, as in their professional capacity they would realise that this would be a waste of resources.	The Committee noted that the optimisation of timing and extent of radiotherapy is important (section 4.3.5). The recommendations are not based on access to radiotherapy.
	• **4.3.5** This point is impossible to understand and needs clarification.	This point has been amended to improve clarity.
	• **4.3.9** QALY analysis may not be appropriate for this disease. The quality of life data was assessed in the temozolomide trial using a disease specific instrument. There is no validated methodology for measuring utilities based on this instrument. In the light of this, cost utility analysis was not feasible.	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.3.4 (Available from URL http://www.nice.org.uk/page.aspx?o=201974). In addition, the Committee considered the results of sensitivity analyses around the utility estimates.
	• **4.3.13** Sub group analysis for temozolomide has been ignored. Fully and partially resected patients along with fitter patients all benefit.	The Committee considered subgroup analyses from the trials of temozolomide and carmustine implants – see FAD sections 4.1.6, 4.1.13, 4.2.7, 4.2.13, 4.3.16, 4.3.17, 4.3.24, and 4.3.26. Temozolomide is recommended for patients with performance status of 0.

Consultee	Comment	Action/response
Samantha Dickson Research Trust (continued)	**Section 5 : Proposed recommendations for further research** • It should be noted that USA and Europe currently use these treatments as the standard care based on trials conducted up to now. • Trials involving the UK are already ongoing (eg temozolomide MGMT). If these treatments are not recommended, the UK would have to withdraw from the trials (this would include the current Edinburgh study). Undoubtedly the UK will drop behind the rest of the world in its treatment of glioma patients if these products are not recommended for use in the UK. (What a tragedy that a UK generated drug such as temozolomide should be used across the world but denied in the UK!) • The ACD preliminary recommendation is for restricted use to well–designed RCTs. However this means that the 1,800 (approx) patients diagnosed with high grade glioma per year in the UK would largely be denied treatment that top experts/clinicians in the UK consider to be of benefit. The emotional and psychological suffering endured by high grade glioma patients (and their families/carers) is huge. The knowledge that such patients are being denied effective treatment can only lead to an increase in stress levels for those concerned and have an adverse effect on the last months of their lives.	Comments noted. The recommendations do not prevent the use of these treatments in clinical trials. Comments noted.

Consultee	Comment	Action/response
Samantha Dickson Research Trust (continued)	**Section 9 : Proposed date for review of guidance** • The Samantha Dickson Research Trust sincerely hope that the committee's recommendations will receive further consideration and that the immediate outcome will mean access to the use of carmustine implants and temozolomide for newly diagnosed and high grade glioma patients. Any postponement for review in August 2009 will cause enormous frustration and suffering to such patients and their families/carers. It is bewildering that an NHS willing to prescribe methadone for drug addicts and patches for smokers will openly deny access to effective treatments for seriously ill patients who would give anything to have a few more months to live. • The ACD calls into question the willingness of brain charities (and members of the British public) to continue to raise funds for research if progress in the field of brain tumour research is met with such barriers.	The review date has been set according to the standard processes (see Section 5 of the Guide to Technology Appraisal Process available from URL http://www.nice.org.uk/page.aspx?o=201972). If significant new evidence becomes available in the interim, consultees can request an early review.

Manufacturers/sponsors

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd	**Executive Summary** Link Pharmaceuticals does not agree with the preliminary recommendations of the ACD with respect to carmustine implants. The evidence presented in this response document supports a cost/QALY in the Westphal ITT population of £27,900. In addition, a subgroup analysis of patients who have undergone maximal surgical resection is presented which demonstrates an even more favourable cost/QALY. The rationale supporting this is summarised in this Executive Summary and covered thoroughly in the main body of this response document, which has been structured to address the three questions posed. The comments presented are limited to carmustine implants and Link is not in a position to comment on the ACD recommendations for temozolomide. **1.** Whether you consider that all of the relevant evidence has been taken into account. The ACD has considered the two pivotal phase III clinical trials for carmustine implants, Valtonen and Westphal. However a major weakness in the ACD is that the long term follow up data which was statistically significant in an unstratified analysis has been largely disregarded. These data have been accepted for publication in Acta Neurochirurgica and demonstrates the real clinical benefit of carmustine implants for patients.	The Committee considered the additional data submitted by Link Pharmaceuticals. The Committee considered the long term data – see FAD section 4.1.4.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	**2.** Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate. 2.1 Clinical effectiveness The ACD states that the evidence for carmustine implants is questionable and small particularly with respect to: • clinical significance • quality of the clinical data • determination of the time to onset of symptoms Consequently the ACD presents an unfavourable and in part simply incorrect interpretation of the clinical evidence for carmustine implants and fails to recognise the clinical significance of the benefits of the product for patients with this devastating disease. (A condition where patient outcomes are poor, long term survival is rare and, until now, where no clinically significant advances have been made in the past 20 years.) 2.1.1 Clinical significance of the patient benefits for carmustine implants In this disease setting where the current gold standard therapy in the UK is surgery and radiotherapy, the median survival is only 12 months. The ACD does not give sufficient recognition to the clinically meaningful median survival gain of 2.2 months, (a 20% increase compared to placebo), for patients receiving carmustine implants. Similarly the ACD does not give sufficient emphasis to the five fold increase in 3 year survival giving real hope to patients treated with carmustine implants.	The Committee's considerations regarding the clinical evidence for carmustine implants are explained in sections 4.3.7 to 4.3.17 of the FAD. The Committee noted that to date, this disease has had a poor prognosis – see FAD section 4.3.2. The Committee noted that patients with high grade glioma have a relatively short life expectancy. The Committee noted the results of the long term data from this trial – see FAD section 4.1.4.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	2.1.2 Quality of the clinical data for carmustine implants The Assessment Group (AG) has placed undue emphasis on the initial deliberations of the FDA review of carmustine implants giving an impression that the data set is weak. However subsequent deliberations by the FDA, which are not in the public domain and which include consideration of the long term survival data, resulted in the licensing approval of carmustine implants for newly-diagnosed high-grade glioma in the USA in February 2003. Consequently the clinical evidence for the use of carmustine implants is considered robust and clinically meaningful for clinicians, patients and their carers. 2.1.3 Determination of the time to onset of symptoms Estimation of the symptom free survival benefit is critical in determining the true cost per QALY for carmustine implants. The AG uses progression free survival (PFS) determined by radiological imaging, (an outcome related to tumour burden rather than patient symptoms), as a measure for the onset of symptoms and consequently the AG states there is no PFS benefit from carmustine implants. PFS based on radiological imaging in the presence of carmustine implants is beset with uncertainty because it is confounded by post operative oedema, enhancement produced by the implants themselves and the subsequent effects of radiotherapy. These effects result in a diagnosis of progression/recurrence (but not necessarily the onset of symptoms) when in fact it may not have occurred and the use of this method of determining the time to onset of symptoms in these patients should be questioned. The pivotal Westphal study of 240 patients evaluated the time to decline of 11 neuroperformance measures, a prespecified and valid alternative to radiological imaging in determining the onset of symptoms. These neuroperformance results show a mean time to onset of symptoms of 7.4 weeks. Link therefore used these neuroperformance measures (which are more closely related to symptom development than radiological imaging) as the best available indicator of the onset of symptoms.	The Committee carefully considered the criticisms of the largest RCT of carmustine implants put forward by the FDA and Assessment Group – see FAD sections 4.3.7 to 4.3.10. The Committee noted the difficulties in measuring progression free survival using imaging and measures of functional status – see FAD section 4.3.3. The assessment group conducted additional analyses using different measures of progression free survival – see FAD sections 4.2.7 and 4.3.15.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	The AG rejected this approach based on the FDA reanalysis of neuroperformance data which censored patients prior to death as opposed to Westphal who included death as a timepoint. However, the FDA acknowledged that their approach lost 75% of this important data. The AG presented the FDA approach as embodying fact and the company approach as not. In practice, neither the company nor the FDA approach to censoring is intrinsically correct. Furthermore carmustine implants are administered locally at the time of surgery and release active drug over approximately 3 weeks. It is, therefore, implausible that carmustine implants do not slow progression for six months relative to placebo but then produce a survival benefit in the post progression period, several months after the drug has been eliminated from the body. The AG themselves state (p87 of Assessment Report): "*there is no good evidence that … any chemotherapy treatment delivered as first-line therapy for newly diagnosed tumours offers any benefit in slowing the rate of disease progression after recurrence"*. This is an obvious contradiction within the Assessment Report and serves to highlight and support the implausibility that the majority of any survival gain for carmustine implants will be after the onset of symptoms.	The Committee carefully considered the issues regarding the analysis of data on the time to neurological decline and the results of additional analyses using different measures of progression free survival – see FAD sections 4.2.7 and 4.3.15. The Committee noted that the largest RCT of carmustine implants demonstrated a benefit in progression free survival using measures of functional status, but demonstrated no benefit when using measures based on neurological imaging – see FAD section 4.3.15.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	*2.2 Cost effectiveness* The cost effectiveness presented in the ACD is based on flawed assumptions which result in the worst case scenario for carmustine implants. In particular this approach has underestimated the symptom free survival and the mean survival resulting in an overestimation of the ICER for carmustine implants. It is therefore an unreasonable interpretation of cost effectiveness. Different modelling structures were adopted by Link and the AG. However these are not the cause of the differences in the derived ICER estimates which are the result of markedly different assumptions about the effects of using carmustine implants (in particular the time to the onset of symptoms) and the costs of so doing (incremental costs).	The Committee noted that the Assessment Group's analysis resulted in a small underestimate of survival. It considered the results of the sensitivity analyses that showed this would not have a significant impact upon the estimates of cost effectiveness – see FAD section 4.3.12. The Committee noted the differences between the analyses put forward by Link and Assessment Group. It concluded that the Assessment Group's analysis was the most appropriate – see FAD sections 4.3.11 and 4.3.13.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	2.2.1 Quality Adjusted Life Years (QALYs) The key issue is the measure of time to onset of symptoms and the profound effect this has on the cost estimates is best demonstrated diagrammatically and is illustrated in Figure 1 below: [Figure 1 not reproduced in this table] For those patients able to undergo surgical resection of their tumour, the patient experience can be characterised as an initial post operative period which is relatively free of symptoms and of relatively high utility represented by A to B or E. Once symptoms reoccur, at point B or E, there is a period of decline to death with progressively reducing quality of life. For simplicity, and in the absence of evidence this has been approximated linearly. Treatment with carmustine implants extends life. In the estimation of the QALY gain it is very important to determine if this extension to life comes before or after the onset of symptoms. If it is all after the onset of symptoms, then the QALY gain is given by the area BCD. If it is all before the onset of symptoms then the QALY gain is given by the area BEDC, which is twice the area. Use of neuroperformance data from Westphal gives an estimate represented by BEDC based on a longer symptom free survival period. The AG estimate is best represented by BCD with only a 1.3 week period of symptom free survival, i.e. most of the survival gain is implausibly after the onset of symptoms.	The Committee noted the difficulties in measuring progression free survival using imaging and measures of functional status – see FAD section 4.3.3. The assessment group conducted additional analyses using different measures of progression free survival – see FAD sections 4.2.7 and 4.3.15.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	2.2.2 Costs The cost estimates used in the ACD are based upon a value judgement which has been explicitly rejected in NICE methodology. The AG treated the incremental costs in the carmustine implant arm of the model as not being driven by any different (from placebo) symptoms caused by carmustine implants. The source of the extra costs in that arm arise from the fact that people live longer and receive standard care while doing so. The same logic could reject a free drug which extended survival of dialysis patients by twenty years because dialysis has a cost/QALY of c.£80k. Similarly, the same logic would find a drug to be cost-effective if it shortened the life of dialysis patients. Appraisal Committees can easily see the absurdity of the latter but seem to have missed it in its former manifestation. The principle is that if patients are kept alive who go on to receive standard care that is a good thing. The AG should not incorporate what is effectively a cost effectiveness analysis of those subsequent treatments. They are regarded as separable. 2.2.3 Cost/QALY estimate for Westphal ITT population Considering the above points (time to onset of symptoms of 7.4 weeks, no incremental costs and mean survival calculated from individual patient survival data of 2.45 months) Link presents a cost/QALY for the total Westphal patient population of £27,900. The data supporting this ICER are presented in Appendix 1.	The Committee noted that the evidence on effectiveness from the RCTs included the use of subsequent chemotherapy treatment and concluded that it was appropriate to consider this in the economic analysis – see FAD section 4.3.22. It is standard practice to consider all the costs directly associated with treatment of the disease, including those occurring in additional years of life, in an appraisal. The Committee considered the reanalysis provided by Link – see FAD section 4.3.11. It concluded that the Assessment Group's analysis was the most appropriate – see FAD sections 4.3.11 and 4.3.13.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	2.2.4 Cost/QALY estimate for subgroup of Westphal ITT population (maximal resection) The ACD indicates that subgroups in whom the treatment may be particularly effective should be considered. Link is therefore taking this opportunity to present data on such a subgroup, patients undergoing a maximal resection. This is considered a valid subgroup as it comprises 111 patients balanced between the two study arms. The difference in median survival between the carmustine implants and placebo arms was 2.15 months (p=0.006, unstratified log rank analysis) and the calculated mean survival gain was 4.2 months. Unlike the ITT patient population, if only GBM patients (n=101) in the maximal resection subgroup are considered the median survival at 2.10 months remains statistically significant (p=0.0191 unstratified log rank analysis). These impressive survival benefits give further hope to those patients receiving a maximal resection.	The Committee considered the additional analysis submitted by Link Pharmaceuticals – see FAD section 4.3.11. The Committee considered whether there would be subgroups of people for who carmustine implants may be particularly effective and cost effective, including the analyses performed by Link Pharmaceuticals and by the Assessment Group. It considered the difficulties of quantifying the extent of tumour resection and concluded that there were insufficient data to recommend the use of carmustine implants in a clinically identifiable group of patients – see FAD sections 4.3.16 and 4.3.17.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	Link has modelled these maximal resection results using the AG's incremental costs (which are incorrect in Link's opinion), to calculate cost/QALY. Link demonstrates below how these costs change with differing lengths of time to the onset of symptoms: • ICER of £36,700 for a 0.3 month gain in symptom free survival using radiological imaging to determine progression free survival. • If a 1.31 month gain in symptom free survival is assumed the ICER is £30,000. • ICER of £22,900 for a 3.0 month gain in symptom free survival using the mean of the 11 neuroperformance measures for the subgroup. The Appraisal Committee will see that only at implausibly short periods of less than 1.31 months, given a mean survival gain of 4.2 months, would carmustine implants be found not to be cost-effective. If the incremental costs are removed the ICER would be substantially lower. 2.3 Resource impact and implications for the NHS The preliminary ACD recommendations have no resource impact for the NHS. However a recommendation allowing the use of carmustine implants on the NHS has only a small resource impact. There are 1,860 new patients with high-grade glioma each year in England and Wales accounting for less than 2% of all primary cancers. However for individual patients a high-grade glioma on average results in 20 years of lost life. The direct costs to the NHS of funding carmustine implants for all eligible patients would be less than £2 million per annum.	The Committee considered the additional analysis included in Link's response to the ACD. It concluded that AG model was the most appropriate analysis on which to base its decisions – see FAD section 4.3.13. In addition the Committee considered the difficulties of quantifying the extent of tumour resection and concluded that there were insufficient data to recommend the use of carmustine implants in a clinically identifiable group of patients – see FAD sections 4.3.16 and 4.3.17. A costing report and template will be available when the guidance is published.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	**3.** Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS Link does not agree with the preliminary recommendations of the Appraisal Committee. As discussed in this response document the interpretation of the clinical and cost effectiveness evidence for carmustine implants are flawed resulting in an unsound and unsuitable basis for guidance to the NHS because: • The body of clinical evidence confirms that carmustine implants provide physicians and their patients suffering from high-grade glioma an opportunity to significantly extend survival and, importantly, improve symptom free survival. • Implementation of the preliminary recommendations would deny patients the opportunity for a five fold increase in 3 year survival with carmustine implants. • The NHS cancer plans aims to improve survival rates in line with other European countries. Denying UK patients access to carmustine implants which are in common clinical practice and fully reimbursed in the US, Australia (PBAC, April 2006) and many parts of Europe will be in conflict with this objective. • The benefits of NHS treatment with carmustine implants can be offered on a cost effective basis to the relatively small number of eligible patients suffering from this devastating condition. Carmustine implants provide a real and tangible benefit for patients with this devastating disease. The final recommendations of the Committee should therefore support the use of carmustine implants in newly-diagnosed high-grade glioma patients which have been shown to improve median and long term survival and to be cost effective to the NHS.	On the basis of the evidence presented, the Committee concluded that carmustine implants for the treatment of newly diagnosed glioma would not be a cost effective use of NHS resources – see FAD section 4.3.17.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	1. Whether you consider that all of the relevant evidence has taken into account 1.1 Efficacy data	
	The efficacy of carmustine implants has been studied in two phase III clinical trials, Valtonen and Westphal, both of which have been considered in the preparation of the ACD.	The Committee considered data from these RCTs – see FAD sections 4.1.2 to 4.1.8.
	However the long term follow up data from the Westphal study which has been accepted for publication in Acta Neurochirurgica, a peer reviewed journal, has not been given sufficient consideration in determining the efficacy of the product. These data demonstrate a statistically significant (p=0.017) non-stratified median survival benefit for carmustine implants of 2.2 months. In addition the opportunity for a five fold increase in long-term survival for a small number of patients with this devastating disease has not been recognised or put into a clinical context in the ACD.	The Committee considered the long term data from this trial – see FAD section 4.1.4.
	The AG has relied heavily on deliberations recorded in the minutes from an FDA meeting in 2001 on the subject of carmustine implants. This has introduced bias against carmustine implants in the Assessment Report. The main points arising from the FDA minutes are shown in the response to ACD Section 4.1.3 of this document. Subsequent deliberations by the FDA, which are not in the public domain and which include consideration of the long term survival data, led to the approval of carmustine implants for newly-diagnosed high-grade glioma.	The Committee carefully considered the criticisms by the FDA and the Assessment Group of the largest RCT. In addition it noted the response to these criticisms put forward by Link Pharmaceuticals – see FAD section 4.3.7 to 4.3.10.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	*1.2 Subgroup analysis (cost effectiveness of carmustine implants in patients undergoing maximal resection)* The ACD in Sections 4.3.13 and 5.2 ask that subgroups in whom the treatment with carmustine implants may be particularly effective should be considered. Link is taking this opportunity to present data on such a subgroup, patients undergoing maximal surgical resection. This subgroup analysis was not part of the original statistical analysis plan and has only been investigated now in response to the ACD request. Please see Appendix 2 for the full analysis.	The Committee considered the additional analysis submitted by Link Pharmaceuticals – see FAD section 4.3.11. The Committee considered whether there would be subgroups of people for who carmustine implants may be particularly effective and cost effective. It concluded that there were insufficient data to recommend the use of carmustine implants in a clinically identifiable group of patients – see FAD sections 4.3.16 and 4.3.17.
	2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	
	Link does not consider the summaries of either the clinical or cost effectiveness for carmustine implants to be reasonable interpretations of the evidence and therefore does not agree with the ACD preliminary recommendations. If these were to become final, clinicians, patients and carers would be deprived of carmustine implants, a product that has a demonstrated statistically significant improvement in median and 3 year survival. Both these outcomes are clinically meaningful in an area of medicine that has lacked any advances over the past 2 or 3 decades. In addition the cost impact to the NHS if all eligible patients were to receive carmustine implants is relatively small at less than £2 million annually.	The Committee noted that to date, this disease has had a poor prognosis – see FAD section 4.3.2.
	2.1 Clinical effectiveness	
	The clinical effectiveness of carmustine implants has been subject to intensive review by regulatory agencies leading to approval of the product in major international markets including USA, Canada, Europe (via the Mutual Recognition Procedure) and Australia.	Comments noted. Decisions are based on appraisal of data on both clinical and cost effectiveness.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	ACD Section 4.1.3 - *The AG reported that the Food and Drugs Agency (FDA) in the USA expressed several concerns when it evaluated the trial.* The concerns raised by the FDA appear to have been unconditionally accepted by the AG as being the definitive situation without recourse to any counter arguments or consideration of the points raised by Link in the response to the Assessment Report. Despite the initial FDA comments they, and many other regulatory agencies worldwide, have subsequently approved carmustine implants for the treatment of newly-diagnosed high-grade glioma patients indicating their satisfaction with the evidence for the efficacy of the product. Furthermore carmustine implants have received favourable reimbursement recommendations in a number of countries including the USA, via their Medicare/Medicaid health schemes, France, Spain and Greece. Most recently the PBAC in Australia has recommended that carmustine implants be made available in that country from April 2006. *In particular, it [the FDA] was concerned about:* *a) An imbalance between the types of tumours in study arms, which could have favoured carmustine implants.* The original histopathological diagnosis did not demonstrate an imbalance between study arms and the imbalance referred to in the ACD is solely based on the FDA analysis of the histopathology which is discussed below. The inclusion of grade 3 and 4 gliomas in the RCT reflects the reality of the clinical situation whereby it is not possible to make a definitive intra-operative diagnosis beyond classification of a glioma as high-grade. The mix of grade 3 and 4 gliomas in the carmustine implant and placebo groups is therefore by chance but is reflective of what will occur in clinical practice within the UK.	The Committee carefully considered the criticisms by the FDA of the largest study and the response to these put forward by Link Pharmaceuticals – see FAD section 4.3.7 to 4.3.10. The Committee considered the pragmatic evidence from the RCT as a reflection of the realities of current practice – see FAD section 4.3.10.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	*b) It [the FDA] was also concerned that the diagnosis made by one referee pathologist had been considered definitive, so recommended a sensitivity analysis using diagnosis from an alternative pathologist.* The statement that the final diagnosis was made by only one referee pathologist is simply incorrect. Given the prognostic significance of histopathology, its confirmation is critical to ensure correct diagnosis and subsequent treatment planning. However it is acknowledged that morphological assessment is confusing, even for trained pathologists and this point was raised by some of the clinical consultees responding to the Assessment Report. Knowing this, the histopathological diagnosis in the Westphal study was determined by a specific and robust methodology. This involved review by a local neuropathologist followed by confirmation by a central neuropathologist. Where there was disagreement, a third referee neuropathologist also reviewed the tissue sample. Consequently the final histological diagnosis was based on the agreement of at least 2 of the possible 3 neuropathologists and not on a single opinion. The results as presented in the study, based on the agreement of 2 specialists, can therefore be considered to be more robust than those based on just one pathologist's review as presented by the FDA. The Westphal data therefore shows a balance of grade IV gliomas between the two groups.	Section 4.1.3 has been amended to clarify this. The Committee recognised the difficulties in making definitive pathological diagnosis of high grade glioma and considered the pragmatic evidence from the RCT as a reflection of the realities of current practice – see FAD section 4.3.10.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	*c) Another concern was that the measurement of the time to decline of neurological symptoms and time of decline of KPS included death as an event rather than as censored data.* The collection of clinical data is in part controlled by the timing of planned visits within the study protocol combined with unscheduled visits due to complications or patient deterioration. Consequently the actual number of time points to base an analysis upon may be fairly low. In this situation a decision must be made as to the best way to handle events such as death to ensure that any data collected is meaningful. Westphal measured the time to decline of neurological symptoms and KPS and included death as an event whereas the FDA analysis censored data before death. Both methods of censorship are valid and neither is implicitly right or wrong. The limitations of the FDA approach, censoring patients for death, results in insufficient data to derive any meaningful differences between treatment arms due to insufficient patient observations and this will have the effect of underestimating the data. In the FDA minutes the example given of visual status clearly demonstrated that their approach lost 75% of the data. The Westphal methodology overcomes this potential loss of data, which risks losing any relevance of the parameter, by including death as an event. Whilst this is an equally valid approach, it may have the potential to overestimate the outcomes. In reality the true situation lies between these two extremes but this uncertainty is not taken into consideration in the ACD.	The Committee considered additional analyses performed by the Assessment Group and by Link Pharmaceuticals using time to decline of neurological symptoms as an outcome measure – see FAD sections 4.2.7 and 4.3.15.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	*d) The AG noted that three patients withdrew from the RCT and that it was unclear from which arm of the trial the patients withdrew.* Three patients were lost to follow up during the original phase of the Westphal study. However when the long-term follow up data was collected the outcome of two of these patients was known and only one patient, in the placebo arm, remained lost to follow up. This had the effect of changing the median survival gain from 2.3 to 2.2 months. *e) In addition, the manufacturer analysed the data which included stratification by country, and the FDA reanalysed this data without stratification.* The statement by the AG that stratification was not a pre-specified analysis is simply incorrect. Stratification by country as a potential covariant was pre-specified in the statistical analysis plan for the Westphal study at the request of the FDA following their review of the protocol in 1997 and is therefore a valid analysis of the data. A copy of the original statistical analysis plan can be made available to the Appraisal Committee if this provides the necessary reassurance on this point. In the Westphal study stratification by country is a logical analysis given the study design. A review of the survival data for the placebo arm at a country level, presented in Figure 2 below, demonstrates a degree of scatter with a median survival range between approximately 6 and 15 months. This variability is potentially greater than the anticipated treatment affect. Country as a variable must therefore be accounted for in the final analysis. Figure 2: is not reproduced in this table	The FAD has been amended to reflect that information has been provided by Link Pharmaceuticals - see FAD section 4.1.3 The Committee noted that stratification by country was an analysis specified in the statistical analysis plan – see FAD section 4.3.8.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	*It is important to note that the estimated hazard ratio of 0.71 for survival by the Kaplan Meier method is the same regardless of stratification or non-stratification and represents a 29% mortality risk reduction. The estimate of absolute clinical benefit of carmustine implants is therefore not affected by stratification only its variance thereby affecting its estimated statistical significance.* In addition the long term survival analysis, conducted at least 36 months after the recruitment of the last patient, showed a statistically significant survival benefit for carmustine implant compared to placebo (p=0.017 unstratified log-rank analysis) thus validating the results from the original phase of this study. A statistically significant (p=0.01 unstratified log rank analysis) 5-fold increase in 3 year survival (9.2% vs. 1.7%) was also shown in favour of carmustine implants. This potential for long term survival, albeit in a small number of patients is extremely important for patients, carers and their doctors alike.	The hazard ratios reported in the FAD reflect those reported in the assessment report and by the FDA. The Committee considered the long term data from this trial – see FAD section 4.1.4.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	ACD Section 4.1.4 *[The data reported below relate to the unstratified analysis unless otherwise stated.] The median survival was 13.8 months (95% CI: 12.1 to 15.1) in the carmustine implant group, and 11.6 months (95% CI: 10.2 to 12.7) in the placebo group. The Kaplan–Meier hazard ratio was 0.77 (log rank statistic: p = 0.08). Based on data from longer-term follow-up, the Kaplan–Meier hazard ratio was 0.73 (log rank statistic: p = 0.02). At 12 months 59.2% of the carmustine implant group and 49.6% of the placebo group were alive, at 24 months survival was 15.8% and 8.3%, and at 36 months survival was 9.2% and 1.7% in each group respectively (all estimates calculated on the basis of survival data censored at the relevant time period).* Using the pre-specified stratification by country as a valid statistical tool yields the following data for the original phase of the study: • Gain in median survival 2.2 months (p=0.03 stratified log rank analysis) • Hazard ratio of 0.71 (p=0.03 stratified log rank analysis). Please note that Link believes the 0.77 value given in Section 4.1.4 to be a typographical error. The long term follow up data is unstratified and therefore these data do not change from that given in the ACD. Survival at 3 years is statistically significant between the two treatment arms, p=0.01 log rank analysis.	The hazard ratios relating to unstratified analysis reported in the FAD reflect those reported in the assessment report and by the FDA.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	ACD Section 4.1.5 – *There was no difference in progression-free survival [PFS] between treatment groups. The median time to progression was 5.9 months (95% CI: 4.4 to 8.3) in the carmustine implant group and 5.9 months (95% CI: 4.7 to 7.4) in the placebo group.* This comment touches on some very important issues of principle, which in turn have profound implications for the estimation of the cost effectiveness of carmustine implants. Progression free survival (PFS) is taken as having two meanings: 1. the absence of symptoms 2. no evidence of tumour regrowth The AG use of PFS in their cost effectiveness analysis relates to the absence of symptoms as stated on page 91 of the Assessment Report "the model takes progression to relate to symptomatic, rather than pathological, disease progression". Link is in agreement that this is the correct way to estimate patient utility. However the AG has used radiological imaging which relates to pathological disease progression rather than being a measurement of symptom onset. This is in direct contradiction to their statement above. For the reasons previously provided in Link's response to the Assessment Report and laid out again below, PFS measured by radiological imaging cannot and does not provide an accurate measure of symptom free survival. *Indication of tumour recurrence on radiological imaging does not necessarily predict the onset of new symptoms. A high-grade glioma will be symptomatic when there are about 10^{10} tumour cells. A maximal resection removing at least 90% of the tumour mass will reduce this cell number to 10^{9}. Progression as defined by an increase in the mass by 25% will not in many cases reflect the growth of a tumour to a size likely to cause reappearance of symptoms. This is not likely to occur until the residual cells have doubled at least 4 times.*	This statement reflects the reported results from the largest RCT of carmustine implants. No change. The Committee considered additional analyses performed by the Assessment Group and by Link Pharmaceuticals using time to decline of neurological symptoms as an outcome measure – see FAD sections 4.2.7 and 4.3.15.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	*Radiological imaging is not the most meaningful measure of progression from the clinicians' or patients' perceptive. Therefore using measures that correlate with the onset of symptoms is more appropriate than a simple increase in tumour size. Neurologic status and functional impairment are deemed to be equally appropriate measurements of tumour activity and therefore onset of symptoms, especially in the palliative care setting where the aim of new therapy is prolongation of functionally independent survival.* *Generally tumour activity or progression is assessed by radiological imaging and indeed in the Westphal study, PFS was determined by radiological means in 70% of patients. However there are a number of factors related both to patients with high-grade glioma generally and the use of carmustine implants specifically that make measurement of PFS by radiological methods problematic and subject to a high degree of inaccuracy. This was acknowledged by the FDA who stated that PFS is difficult to assess in this patient population previously treated with surgery, radiotherapy or steroids.*	The Committee considered additional analyses using time to decline of neurological symptoms as an outcome measure – see FAD sections 4.2.7 and 4.3.15

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	*PFS measured by imaging techniques is assessed as the change in size of a tumour (or the development of a new lesion) on CT or MRI. The definition of tumour progression is an increase of more than 25% in the size of an enhancing abnormality in relation to previous scans. Different PFS results between studies may reflect the varying interpretations of progression on imaging. However accurate measurement may be confounded by several factors making it difficult to reliably assess these scans, even in the absence of implants. The size of an enhancing glioma following surgery and radiotherapy might represent a loss of tumour cells or an alteration in the properties of the blood-tumour barrier or blood brain barrier. Even if there has been some tumour cell kill a number of factors make the interpretation of imaging response in glioma difficult. A high-grade glioma has complex shapes with apparent projections and margins may be indistinct. Different scanning techniques have a major influence on interpretation of images. The timing of the scan following injection of an imaging medium alters the apparent size of an enhancing lesion. In addition, surgery, corticosteroids and excessive doses of radiation all affect the region of enhancement, making an objective assessment of progression difficult.* *This is particularly true for carmustine implants where radiological progression in the presence of the implants may be further confounded by the immediate post-operative oedema and enhancement that the implants themselves may produce. Furthermore, Kleinberg et al have demonstrated that treatment effects such as necrosis can radiographically mimic the findings of recurrent tumour in a proportion of patients and De Wit et al have demonstrated the problems with interpretation of radiological imaging.* *In conclusion radiological imaging is not the most appropriate measure for onset of symptoms for patients with high-grade glioma and especially where carmustine implants have been inserted. Consideration of alternative measurements for the onset of symptoms must therefore be used.*	See above

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	ACD Section 4.1.5 – *The manufacturer's analysis suggested that the time to decline of KPS and time to progression on neurological indices were statistically significantly improved in the carmustine implant group. However, a reanalysis of these data was conducted, which treated deaths as censored. This reanalysis found that the differences were a result of survival times between the treatment arms, which suggests that there was no independent effect by treatment on the time to decline of neurological indices and KPS.* See Link's response to ACD Section 4.1.3. part c. 2.2 Cost effectiveness ACD Section 4.2.3 - *The AG expressed concern about the estimation of time to symptoms using this approach because it was based on median values rather than mean values.* Following criticism in the Assessment Report on the use of a mean of medians (8.2 weeks) for the 11 neuroperformance measures this was recalculated based on the mean of mean data (7.4 weeks) in Link's response to the report. The cost effectiveness model was only moderately sensitive, in this instance, to the choice of means or medians. ACD Section 4.2.3 - *No statistically significant differences were found between treatment arms in the time to decline of functional status and time to deterioration of neurological performance scores in 10 of 11 indices when the data were reanalysed by the FDA.* Neither the approach taken by the FDA nor that taken in the Westphal study is intrinsically correct. The reality lies somewhere between these two extremes as discussed in the response under ACD Section 4.1.3. part c.	The Committee carefully considered the issues regarding the analysis of data on the time to neurological decline. It noted that this added to the uncertainty regarding progression free survival, but considered the analyses including measurement of PFS using neuroperformance data. The Committee concluded that carmustine implants would not be a cost effective use of NHS resources – see FAD section 4.3.15. Comments noted. The Committee carefully considered the issues regarding the analysis of data on the time to neurological decline. It noted that this added to the uncertainty regarding progression free survival, but considered the analyses including measurement of PFS using neuroperformance data. The Committee concluded that carmustine implants would not be a cost effective use of NHS resources – see FAD section 4.3.15.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	ACD Section 4.2.3 - *It was assumed that the only difference in costs between the two treatment groups was the cost of the implants themselves (mean: 6.54 wafers per patient).* The Assessment Report criticises the approach taken to costing treatments on grounds of principle. The approach recommended by the AG was considered by the NICE Methodology Committee at its most recent review of methodology and explicitly rejected (Personal Communication, Prof Mark Sculpher, Chair of Committee). The committee argued that the decision to treat someone, and thus keep them alive, should not be contingent on subsequent, separable decisions. It is quite possible that use of carmustine implants will enable a few patients to live very much longer than they otherwise would and therefore to incur a variety of health care costs, some related to management of glioma and some not. These incurred expenditures are a consequence of success in keeping the patient alive and should not be used to penalise the drug. The extension of the AG logic could lead to new technologies that keep people alive into old age not being found to be cost-effective because of the high costs of care in old age	The Committee considered the estimates of costs included in the AG model and concluded that they were appropriate – see FAD section 4.3.13. It is standard practice to consider all the costs directly associated with treatment of the disease, including those occurring in additional years of life, in an appraisal. This was not rejected by the review on methodology. It is noted that there is controversy around the issue of whether to include the costs incurred in life years gained that are unrelated to treatment of the disease being assessed. The AG analysis did not include costs unrelated to the treatment of glioma.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	ACD Section 4.2.4 - *The estimated mean incremental cost of carmustine implants was £4250 and estimated mean QALYs gained were 0.16. The base-case incremental cost-effectiveness ratio (ICER) was £28,000 per QALY gained. A probabilistic sensitivity analysis suggested that if the maximum acceptable amount to pay for an additional QALY is £20,000, then the probability of carmustine implants being cost effective is 0.28. This probability rises to 0.57 if the maximum acceptable amount was £30,000 per additional QALY. ……. The AG considered the model structure to be sound, but concluded that the main ICER of £28,000 per QALY gained was underestimated because of the assumptions used to estimate survival and the omission of treatment costs other than those of the implants.* By contrast Link contend that the assumptions embodied in the AG model, particularly in respect of the time to the onset of symptoms, the estimation of mean and median survival and the inclusion of incremental costs, are extreme, unreasonable and in part methodologically unsound. When constructing a cost effectiveness model a number of assumptions must be made in building the base case. The assumptions made by Link are based on the clinical evidence and are no less robust or valid than those made by the AG. The same data set is used for both base cases and the differences reflect the uncertainties surrounding the data. Link would criticise the AG for using the worst case values and Link may have been open for criticism for using values at the other extreme. The reality lies between these two sets of assumptions and this level of uncertainly in the models should be recognised by the Appraisal Committee. Whilst Link's ICER may be an underestimation the ICER estimated by the AG is certainly an overestimation.	The Committee carefully considered the analyses provided by Link and the Assessment Group. It concluded that the analysis provided by the Assessment Group was the most appropriate analysis on which to base its recommendations – see FAD section 4.3.13. See responses to specific criticisms above.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	ACD Section 4.3.1 - …… *It [the Committee] considered evidence on the nature of the condition and the value placed on the benefits of carmustine implants and temozolomide by carers of people with glioma, those who represent people with glioma, and clinical experts.* The comments on the Assessment Report received from clinician consultees do not appear to Link to have been given sufficient weight in the preliminary ACD recommendations.	The Committee considered the evidence provided by the clinical experts and all consultees, including those representing professional groups.
	ACD Section 4.3.6 - …… *However, it [the Committee] concluded that the gain in overall survival shown in the trial was small, irrespective of the concerns expressed by the FDA.* In a disease with such a poor prognosis where little survival benefit has been demonstrated in the past 20 years a 2.2 month increase in median survival is a clinically meaningful outcome. This is comparable to the 2.5 month increase seen with temozolomide and in both cases this represents approximately a 20% increase in survival compared to the respective control arm. The 1 year survival rates for the carmustine implants and temozolomide study arms are also comparable at 59.2% and 61.1% respectively. Furthermore the long term survival data for carmustine implants are even more impressive, representing a 5-fold increase in survival at 3 years, (p=0.01 unstratified log-rank analysis). In this context the overall survival gain in not small.	The Committee noted that patients with high grade glioma have a relatively short life expectancy. It also considered the long term data from this trial – see FAD section 4.1.4.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	ACD Section 4.3.7 - …… *The Committee concluded that the evidence to illustrate a beneficial impact on progression-free survival of carmustine implants was weak.* Carmustine implants have been shown to increase median survival by 2.2 months compared to placebo. The AG and the ACD suggest that the majority of this survival is post progression. However this implicit conclusion that symptom free survival was approximately one week out of the 2.2 months median survival gain is clinically implausible. How can carmustine implants which are administered at the time of the surgical resection and which are active for about 3 weeks have no impact on slowing disease progression or development of symptoms over the next six months yet provide a survival benefit in the progressive state, a time when no drug can possibly be present? The Assessment Report stated: *"We also considered post-progression survival (estimated by subtracting median PFS from median overall survival). From the data reported by Westphal and colleagues 2003, we calculated a median life expectancy following recurrence of 8 months for patients treated with BCNU-W compared to 5.7 months for those who received placebo wafers. In the trial reported by Valtonen and colleagues 1997, post-progression survival was doubled in the BCNU-W group at 5.6 v. 2.5 months.* *We are unable to undertake significance testing on these second-order measures without access to more extensive data. As neither RCT demonstrated a benefit in terms of PFS, any claimed treatment effect must be due to differences in survival after disease progression." [page 47]*	The Committee noted the difficulty of assessing progression free survival in patients with high grade glioma – see FAD section 4.3.3. The Committee noted that the largest RCT of carmustine implants demonstrated a benefit in progression free survival using measures of functional status, but demonstrated no benefit when using measures based on neurological imaging – see FAD section 4.3.15. Comment on Assessment Report.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	With regard to progression free survival AG state *"there is no good evidence that …. any (other) chemotherapy treatment delivered as first-line therapy for newly diagnosed tumours offers any benefit in slowing the rate of disease progression after recurrence*." *[page 87]* These two statements on pages 47 and 87 of the Assessment Report appear to directly contradict each other. Link agrees with the statement on page 87 and considering the pharmacology and clinical use of carmustine implants it is intuitive that the greatest clinical benefit will occur while carmustine is actually present i.e. in the period immediately following implantation and the benefit must therefore be prior to disease progression. The biological basis for this is discussed below. The infiltrative nature of gliomas means that despite maximal surgical resection there are inevitably residual tumour cells either at the margins of the resection cavity or within 2 or 3cms of the margin. Tumour regrowth over time therefore occurs in virtually all patients. The aim of chemotherapy and radiotherapy is to slow the rate of tumour regrowth and prolong symptom free survival. Carmustine is an alkylating agent that acts by disturbing the fundamental mechanisms concerned with cell proliferation, in particular DNA synthesis and cell division. Carmustine can act on cells at any stage of the cell cycle however cytotoxicity usually occurs when cells enter the S phase and hence progression through the cycle is blocked. The effects of applying carmustine locally will therefore result in apoptosis of tumour cells only while carmustine is present to produce its cytotoxic effects i.e. during the period of carmustine release from the implant. Given that 70% of carmustine is released within 3 weeks of implantation and that once released it has a short half-life of 22 minutes, the duration of chemotherapeutic action is likely to be in the region of 5 to 6 weeks. Full pharmacokinetic information was provided in Link's original submission.	Comment on Assessment Report. Comments noted.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	This immediate cytotoxic action at the time of surgery retards tumour regrowth and permits the patient to present for radiotherapy with a lower residual tumour burden than would otherwise be the case. This should enhance the efficacy of subsequent radiotherapy as the tumour burden has been minimised. Therefore the 2.2 month increase in median survival produced by carmustine implants must be prior to tumour progression as by this point there cannot possibly be any remaining chemotherapeutic activity due to carmustine. Intuitively, and as intimated by the AG, carmustine implants cannot affect the course of tumour progression several months after implantation. The ACD takes an extreme position in assuming that virtually all survival benefit is post progression, an assumption that is pharmacologically counterintuitive. This is the worst case scenario for carmustine implants. The best case scenario would be if all the survival gain were symptom free. The reality must fall somewhere between the two extremes and a sensitivity analysis of this variable is presented in the modelling discussion presented in the subgroup analysis in Appendix 2. ACD Section 4.3.9 - *…… The Committee concluded that the economic analysis submitted by the AG was the most appropriate. This was because estimates of survival were based on measures of overall survival from the two largest RCTs. Additionally, this economic analysis incorporated an estimate of the effect of the disease on health-related quality of life.* Link agree that the Markov model submitted by the AG is valid and accept that the mean survival advantage, the proportion of that survival which is progression (i.e. symptom) free and the relevant extra costs of treatment are all important determinants of the estimated cost effectiveness. However:	Comments noted. The Committee noted that the largest RCT of carmustine implants demonstrated a benefit in progression free survival using measures of functional status, but demonstrated no benefit when using measures based on neurological imaging – see FAD section 4.3.15. It considered additional analyses based on time to neurological decline and concluded that carmustine implants would not be a cost effective use of NHS resources – see FAD section 4.3.15.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	The AG's estimation of the mean survival gain provided by carmustine implants is wrong, and an underestimate. It is based on a modelled Weibull curve that, despite the claims of the AG, is a poor fit in crucial part to the real life data. A fuller commentary on this point was presented in Appendix 3 of Link's response to the Assessment Report but in summary the AG model underestimates median survival by 27% and also results in an estimated mean survival gain smaller than the median survival gain actually observed in the Westphal study for carmustine implants. The fit of the Weibull curve is particularly poor at the tail which is most important for estimating mean survival. The way in which symptom free survival has been estimated by the AG presents the most disadvantageous case for carmustine implants. Link has argued in the response to the Assessment Report and in this ACD response that PFS estimated on radiological changes is misleading, and even more so when implants are present to further confound the images. Link has also argued that a better PFS estimate would use time to neuroperformance decline. The AG note that the statistical significance of the eleven neuroperformance measures depends on the way in which the measures are censored at death and this has been discussed under ACD Section 4.1.3.c above. In summary censorship at the last observation before death underestimates any advantages achieved in this final period before death while censorship at death probably assumes too generous a benefit during that period. As a consequence of their deliberations the AG assume in their modelling that there is only 1.3 weeks advantage to carmustine implants over placebo in progression free survival. Given the accepted (albeit underestimated) advantage in overall survival, this is implausible. As argued above, the nature of the treatment with carmustine implants is such that its effects must come soon after surgery, i.e. well before progression, and it is likely that most of the survival advantage will therefore be symptom free.	The Assessment Group fitted a Weibull curve to the data on survival from the largest RCT. The Committee noted that this led to a slight underestimate in survival gain for carmustine implants in the analysis. However it also noted that sensitivity analyses suggested that this did not significantly affect the estimates of cost effectiveness was not a concern. See Assessment Report Appendix 12 and FAD sections 4.3.12 and 4.3.21. The Committee carefully considered the data on progression free survival using measures of functional status and radiological imaging – see FAD section 4.3.15. It considered additional analyses based on time to neurological decline and concluded that carmustine implants would not be a cost effective use of NHS resources – see FAD section 4.3.15.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	The Assessment Report criticises the use of the mean of medians in the measurement of neuroperformance decline. Link accepts that in principle, means are more appropriate and therefore included a calculation based on the mean of means (7.4 weeks) of neuroperformance outcomes rather than mean of medians (8.2 weeks) in the response. The results are only moderately sensitive, in this instance, to the choice of means or medians.	The Committee noted the additional information.
	Importantly, the AG criticises the approach taken to costing treatments on grounds of principle. The approach recommended was considered by the NICE Methodology Committee at its most recent review of methodology and explicitly, see discussion under ACD Section 4.2.3 above.	The Committee considered the estimates of costs included in the AG model and concluded that they were appropriate – see FAD section 4.3.13.
	Link therefore feels that the AG's criticism of the costings used are unfounded and restate the results obtained using Link's cost effectiveness model.	It is standard practice to consider all the costs directly associated with treatment of the disease, including those occurring in additional years of life, in an appraisal. This was not explicitly rejected by the review on methodology. It is noted that there is controversy around the issue of whether to include the costs occurred in life years gained that are unrelated to treatment of the disease being assessed. The AG analysis did not include costs unrelated to the treatment of glioma.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	ACD Section 4.3.10 -…… *The Committee considered that fitting a Weibull curve to the RCT survival data resulted in a slight underestimate of the median survival gain from carmustine implants, and slight overestimate of the survival gain from temozolomide.* The median survival gain attributable to carmustine implants from the Westphal study is 9.97 weeks whereas the predicted median survival gain from the Weibull model is only 7.31 weeks, page 218 of Assessment Report. This represents a 27% error in favour of the placebo arm and Link contends this is not a slight underestimation of the median survival gain from carmustine implants. Furthermore the mean survival gain estimated by the AG from carmustine implants is given as 9.7 weeks (page 141 of Assessment Report) compared to a mean survival gain derived from the Westphal data of 10.6 weeks (2.45 months). This represents an 8% error again in favour of the placebo arm. As the mean gain is driven by a small number of long-term survivors this value must be larger than the median gain. Taking this into consideration Link contends that the assumptions used in the AG's economic model are inaccurate and add to the general detriment to the estimation of ICERs for carmustine implants.	The Committee noted that the Assessment Group analysis underestimated the survival gain from carmustine implants. It considered the sensitivity analyses provided by the Assessment Group and concluded that the Assessment group's approach was appropriate and that the underestimate of survival gain would not alter its conclusions – see FAD section 4.3.12 and Assessment Report p 116.
	ACD Section 4.3.10 - …… *It [the Committee] also concluded that the results of the sensitivity analyses showed the survival gain from treatment would have to increase considerably for the incremental cost-effectiveness ratios to decrease substantially.* The AG only conducted a series of one way sensitivity analyses varying a single factor whilst fixing all the others. In reality the uncertainties of the data (as noted in the Assessment Report on page 135 to 136) suggests that this is not a robust method of testing. A multi-variant analysis would be more appropriate given the uncertainties surrounding many of the base case assumptions. Link did perform such an analysis in the original submission. Relatively modest changes in cost estimates and symptom free survival together affect the estimate of cost per QALY	The Committee noted that the analysis submitted by Link was sensitive to assumptions regarding costs. It concluded that the estimates of costs included in the AG analyses were the most appropriate as it included all the relevant costs of treating high grade glioma.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	ACD Section 4.3.11 - ……*The Committee concluded on the balance of the economic evidence, including the consideration of 'second and subsequent line' treatments (as far as was possible), that the use of carmustine implants and temozolomide for the treatment of newly diagnosed glioma would not be a cost-effective use of NHS resources.* This conclusion is based on inappropriate assumptions which Link does not agree with.	It is noted that Link does not agree with approach taken by the AG regarding the assessment of costs.
	ACD Section 4.3.13 - *The Committee considered whether there might be subgroups of patients for who the use of treatments may be more effective and cost-effective. ……* In response to the suggestion in the ACD a subgroup analysis of patients who have undergone a maximal surgical resection has been undertaken and is presented in Appendix 2. This subgroup contains 111 patients (approximately half of the ITT population in the original trial) and is therefore of sufficient size to allow meaningful conclusions to be drawn, although this analysis was not pre-specified in the original protocol.	The Committee considered the information provided by Link. See FAD section 4.3.11, 4.3.16 and 4.3.17.
	2.3 Resource impact and implications for the NHS The ACD states that there are 1860 new cases of high-grade glioma annually in England and Wales. According to Whittle only 25% of patients will meet the criteria of the Westphal study which represents the evidence base for carmustine implants. Using this value only 465 patients annually will be eligible to receive carmustine implants at a total cost to the NHS based on 6.5 implants per operation of £1,966,000. Furthermore if only patients who undergo maximal surgical resection are treated with carmustine implants (see Appendix 2) then the cost to the NHS would be halved to less than £1 million per annum.	Commonness or rarity of the condition is not considered by the Committee.

Consultee	Comment	Action/response
Link Pharmaceuticals Ltd (continued)	3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS The preliminary recommendations do not constitute a suitable basis for guidance to the NHS because: • The body of clinical evidence confirms that carmustine implants provide physicians and their patients suffering from high-grade glioma an opportunity to significantly extend survival and, importantly, improve symptom free survival. • Implementation of the preliminary recommendations would deny patients the opportunity for a five fold increase in 3 year survival with carmustine implants. • The NHS cancer plans aims to improve survival rates in line with other European countries. Denying UK patients access to carmustine implants which are in common clinical practice and fully reimbursed in the US, Australia (PBAC, April 2006) and many parts of Europe will be in conflict with this objective. • The benefits of NHS treatment with carmustine implants can be offered on a cost effective basis to the relatively small number of eligible patients suffering from this condition. In this devastating disease the recommendations of the committee should be to support the use of carmustine implants which have been shown to improve median and long term survival and to represent cost effective use of NHS resource.	See responses to specific comments above.

Consultee	Comment	Action/response
Schering Plough	Schering-Plough welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for temozolomide (TMZ) in newly diagnosed glioblastoma. It is a matter of great concern that NICE has drafted an ACD with a preliminary recommendation that TMZ should not be used within the NHS for the treatment of newly diagnosed glioblastoma. This constitutes an alarming denial of patient access to a treatment that represents a major breakthrough in malignant glioma. Schering-Plough's principal comments in relation to the ACD are as follows: 1. The EORTC study unequivocally demonstrates the superior efficacy, acceptable toxicity, and preservation of quality of life by TMZ in the treatment of newly-diagnosed glioblastoma. Recommendations for further research, as set out in section 5 of the ACD are therefore perverse. 2. The suggestion to conduct a head-to-head trial of TMZ versus PCV in this patient population is wholly inconsistent with published clinical trial evidence. 3. The Assessment Group (AG) economic model contains critical errors. Recommendations based on the results of the AG model are unreliable. 4. Contrary to the final scope for this appraisal, the AG failed to consider the cost-effectiveness of TMZ in subgroups that are easily defined according to the scientific literature. Consistent with current UK clinical practice, patients with known poor prognostic factors (WHO performance status >2) are unlikely to receive aggressive therapy. Schering-Plough believes that the AG model contains a number of critical errors and that the estimates of cost-effectiveness generated are therefore unreliable. However, with respect to the overall recommendations set out in the ACD, Schering-Plough requests that NICE reconsider these in the context of important and relevant precedents for recommending end-stage cancer treatments with ICERs exceeding £30,000/QALY. NICE has previously accepted an ICER of £49,000/QALY for the treatment of the blast crisis phase of chronic myeloid leukaemia with imatinib (Rawlins and Culyer, 2004).	See responses to specific comments below. Following consideration of the evidence for subgroups of patients, the guidance has been amended to recommend TMZ for patients with a WHO performance status of 0.

Consultee	Comment	Action/response
Schering Plough (continued)	In addition NICE has previously issued positive guidance for other oncology treatments, where the cost/QALY has exceeded an incremental £30,000/QALY, and additionally in the *absence* of an incremental cost per QALY. In these cases, the economic outcome was incremental cost per life year gained (as was used in the Schering-Plough submission for this appraisal) or incremental cost per year of disease free progression. The AG concludes that treatment with TMZ yields an ICER of £46,000/QALY and suggests that TMZ may not be cost-effective. Given the precedent of NICE accepting ICERs exceeding £30,000/QALY for other treatments of end-stage cancers, the preliminary ACD recommendation should be re-considered.	Above an ICER of £30,000/QALY, the case for supporting a technology has to be increasingly strong in relation to specific factors as clearly set out in Section 6.2.6 of the Guide to the Methods of Technology Appraisal (Available from URL http://www.nice.org.uk/page.aspx?o=201974).
	Schering-Plough requests an explanation as to why the AG failed to respond to our final comments regarding the HTA report, as set out in our letter of November 11th. This was previously agreed with the Institute. In our letter of November 11th, we requested that the AG respond to specific issues in relation to the HTA report including the failure to evaluate cost-effectiveness in established patient subgroups, and a number of errors in relation to the estimation of treatment costs by the AG. We request feedback on this matter as soon as possible. **SCHERING-PLOUGH RESPONSE TO ACD** **Section 1.3** **The ACD states that 'Clinical studies on …temozolomide for the treatment of newly-diagnosed high-grade glioma in adults and children should include research into: impact on quality of life, long-term effectiveness, subgroups for which the treatments may be particularly effective, and comparison with other chemotherapy regimens.'** **Schering-Plough Response:** While further research is always useful, we would encourage the Appraisal Committee to consider the following:	The comments provided by Schering-Plough in their letter of 11th November were provided to the Assessment Group and the Appraisal Committee. The Assessment Group are provided with the opportunity to respond to comments on the Assessment Report at their discretion.

Consultee	Comment	Action/response
Schering Plough (continued)	**Re: Quality of life** A quality of life analysis of EORTC 26981 was published in November, 2005 in *Lancet Oncology* by Taphoorn et al. These data were submitted as "Academic in Confidence" as part of our original dossier. In this study, quality of life was not impaired with the addition of TMZ to radiation. More important, as progression-free survival was also significantly improved by the combined treatment, it indicates that the survival benefit conferred on patients was in time without progression. That is, the treatment does not merely lengthen disease progression, it provides meaningful, quality of survival.	The Committee considered the quality of life data from the EORTC trial – see FAD sections 4.1.15 and 4.3.20.
	Re: Long-term effectiveness In a patient population where the average survival was historically less than 12 months, the EORTC study median follow-up of 28 months, with 26% of TMZ patients alive at 2 years, represents long-term effectiveness.	Comments noted.
	Re: Subgroups that derive substantial benefit We would like to make the Appraisal Committee aware of the Appendix 1 to this letter, which contains Supplemental Table 1 and Supplemental Figure 1, originally published in the on-line version of the NEJM article. In the study, virtually all subgroups derived significant benefit from TMZ/RT versus radiotherapy alone, attesting to the robustness of the study data. Patients with poor prognostic factors (i.e., poor performance status; WHO PS = 2) did not derive substantial benefit from combined modality treatment.	This information on subgroups has been considered by the Committee – see FAD sections 4.1.13, 4.2.13, 4.3.23, 4.3.24, 4.3.26. Temozolomide is recommended for patients with performance status of 0.

Consultee	Comment	Action/response
Schering Plough (continued)	**Re: Comparison with other chemotherapeutic regimens** We would like to make the Appraisal Committee aware of the study published in 2001 in the *Journal of Clinical Oncology* by the MRC Brain Tumour Working Group. The UK MRC trial categorically demonstrated no survival benefit with PCV plus radiotherapy compared to radiotherapy alone in patients with high-grade astrocytoma, Grade III and Grade IV (*see Appendix 2, Figures 2 and 4*). Therefore, there is absolutely no basis for subjecting patients with grade IV glioblastoma to the toxicities of PCV, an ineffective regimen, as proven by the UK MRC trial. In fact, this trial provides complete and total support for the study design used in the EORTC trial, i.e. a control arm with radiotherapy only. **Section 2.6** **The ACD states: 'Adjuvant chemotherapy is not considered part of standard therapy in the UK, but is used more routinely in the USA.'** **Schering-Plough Response:** We agree that, in light of the MRC trial, adjuvant chemotherapy with PCV is not considered part of standard therapy in the UK. However, this statement contradicts the Appraisal Committee's recommendation that TMZ be studied in conjunction with other chemotherapies (see Response to Section 1.3) in this patient population of newly-diagnosed glioblastoma. We are unclear as to why the Appraisal Committee would recommend a head-to-head trial versus a regimen that has been demonstrated to show no survival benefit and is admittedly not standard of care in the UK.	Noted. The research recommendations have been amended.

Consultee	Comment	Action/response
Schering Plough (continued)	**Section 4.1.10** **The ACD states: 'Median survival was 14.6 months (95% CI: 13.2 to 16.8 months) in the radiotherapy plus temozolomide group and 12.1 months (95% CI: 11.2 to 13 months) in the radiotherapy only group.'** **Schering-Plough Response** The AG and the ACD fail to address the results of the subgroup analysis as reported in the NEJM publication by Stupp et al. We would like to draw the Appraisal Committee's attention to Appendix 1 in this letter, which contains Supplemental Table 1 and Supplemental Figure 1, originally published in the on-line version of the NEJM article. In this study, virtually all subgroups derived significant benefit from temozolomide/RT versus radiotherapy alone, attesting to the robustness of the study data. Patients with generally accepted poor prognostic factors, i.e. poor performance status (WHO PS = 2), did not derive substantial benefit from combined modality treatment. **Section 4.1.11** **The ACD states: 'Patients with reduced MGMT activity…In the group with normal MGMT activity.'** **Schering-Plough Response:** We would like to correct the inaccurate terminology contained in the Appraisal Committees assessment. The analysis conducted by Hegi et al. studied MGMT promoter methylation. They did not measure activity of the MGMT enzyme. Furthermore, there is no established definition of "normal" MGMT activity. As this was a post-hoc, retrospective analysis, the only appropriate conclusion that can be drawn is with respect to the methylation or non-methylation of the MGMT promoter. Inferences with respect to treatment response or relative activity of the MGMT enzyme are not reliable.	The data regarding subgroups has been considered by the Committee – see FAD sections 4.1.13, 4.2.13, 4.3.23, 4.3.24, 4.3.26. Temozolomide is recommended for patients with performance status of 0. The text in this section has been amended.

Consultee	Comment	Action/response
Schering Plough (continued)	**Section 4.2.9:** **The ACD states: '…the mean incremental cost of temozolomide plus radiotherapy compared to radiotherapy alone was £8,560…A speculative analysis of patients with better prognosis found that the mean incremental cost per QALY was just under £43,000.'** **Schering-Plough Response:** Estimates of cost-effectiveness derived by the AG model, both in the base case and the 'speculative analysis' are unreliable for a number of important reasons and these are summarized below.	See responses to specific comments below.
	Drug-acquisition costs for TMZ as concurrent chemotherapy are incorrect. The recommended length of concurrent chemotherapy is 42 days as stated in the product SPC and not 49 days as assumed in the AG model. Section 3.7 of the ACD acknowledges this to be the correct dosage regimen. The EORTC trial data supports 42 days as the median treatment duration.	The drug acquisition costs included in the model are based upon 42 days of concurrent chemotherapy and are correct. However it is noted that part of the Assessment Group's spreadsheet was labelled incorrectly. This does not affect the results of the analysis.
	The AG model underestimates costs associated with treatment at first relapse. Schering-Plough market research, conducted among clinical experts in the UK, indicates that in clinical practice approximately one third of patients receive TMZ at first relapse. Notwithstanding the uncertainty surrounding the exact proportion of patients in question, excluding this cost entirely from an economic evaluation is plainly inappropriate and results in an unreliable estimate of the cost-effectiveness of TMZ.	Additional analyses were performed using different assumptions about second-line treatment. The Committee carefully considered the evidence and existing NICE guidance regarding appropriate treatment at relapse – see FAD sections 4.2.12, 4.2.13 and 4.3.22.

Consultee	Comment	Action/response
Schering Plough (continued)	**The AG failed to conduct relevant sub-group analyses, as set out in the Final Scope for this appraisal.** Clinical benefit in well-defined patient sub-groups exceeds that observed in the overall patient population. Cost-effectiveness estimates in patient sub-groups would be substantially lower than that reported in the AG reference case. A recommendation regarding TMZ that does not consider available sub-group data is perverse (see Appendix 1: Additional subgroup survival analyses from Stupp et al, NEJM). **The AG has overestimated the cost of TMZ as adjuvant chemotherapy**. Whilst the AG model is difficult to validate and lacks transparency, it would appear that patients receiving TMZ as adjuvant chemotherapy are allocated 6 cycles of treatment. In contrast, the Stupp study reported that patients received a median of 3 cycles of adjuvant chemotherapy. These four points detailed above, when considered in combination, invalidate the reference-case and the 'speculative analysis' conducted by the AG. An ACD recommendation that relies upon these cost-effectiveness estimates is therefore not an appropriate basis for a recommendation. It is clear that in a subgroup of patients, where clinical benefit is markedly greater, the cost-effectiveness ratio for TMZ would be considerably lower than the reported AG reference-case, particularly in view of the incorrect modelling of treatment costs for both concurrent chemotherapy and second-line chemotherapy.	The data regarding subgroups has been considered by the Committee – see FAD sections 4.1.13, 4.2.13, 4.3.23, 4.3.24, 4.3.26. Temozolomide is recommended for patients with performance status of 0. The Assessment Group's economic analysis does not assume all patients receive 6 cycles of chemotherapy. The median number of cycles included in the analysis is 4. See specific responses above.

Consultee	Comment	Action/response
Schering Plough (continued)	**Section 4.3.3** **The ACD states: '…that there was some evidence suggesting that chemotherapy with the PCV regimen may also be an effective treatment option. It acknowledged that there were no trials comparing temozolomide to other regimens such as PCV.'** **Schering-Plough Response:** We are unaware of any data to suggest that PCV is an effective treatment option in newly-diagnosed glioblastoma. Substantial evidence exists to the contrary. A large (N = 674) randomized trial conducted in 15 centres throughout the UK showed no benefit to PCV chemotherapy used in conjunction with radiation in patients with glioblastoma. For patients receiving RT alone, median survival was 9.5 months. For those receiving RT-PCV, median survival was 10.0 months. The authors concluded that the trial "failed to demonstrate a place for adjuvant chemotherapy with PCV in the treatment of high-grade astrocytoma" and that "no-chemotherapy control arms remain ethical in randomized trials of high-grade astrocytoma." Consequently, there is no rational basis for recommending that TMZ be compared to PCV or other such chemotherapy.	This information has been clarified in the FAD – see FAD section 4.3.6.

Consultee	Comment	Action/response
Schering Plough (continued)	**Section 4.3.4** **The ACD states: '…that the length of survival of patients in the control arm of the largest RCT for temozolomide was better than is currently the norm in UK clinical practice.'** **Schering-Plough Response:** The MRC trial has shown that, in routine clinical practice throughout the UK, the median overall survival for patients with high-grade astrocytoma (grade III or IV) receiving RT alone is 9.5 months. In the EORTC trial, the control arm achieved 12 month overall survival. It is not surprising that the treatment results for RT are different in the MRC and the EORTC trial, as important prognostic factors are not consistent between the trials: e.g. Performance status 0 reported in 25% of the MRC trial and 38% of the EORTC trial; conversely Performance status 2/3 in 25% and 12% respectively; tumour biopsy or less 42% and 16% respectively. If, in the context of the trial, patients undergoing RT therapy performed better than expected (either in the UK or elsewhere) in the control arm, this would only mean that in regular clinical practice, the difference between patients receiving radiation alone versus TMZ as part of first-line treatment would be even greater. Of note, a recent study by Beresford et al from the Mount Vernon Cancer Centre and Charing Cross Hospital examined whether the results of the EORTC trial could be replicated in clinical practice in the UK. The records of 102 high grade glioma patients who received radiotherapy plus TMZ from 1998-2003 were reviewed. A regimen similar to the one in the EORTC trial was employed to these patients (radiotherapy at 60-65 Gy in 30-37 fractions over 6 weeks, TMZ administered at 75 mg/m^2 daily for 6 weeks during radiotherapy, followed by adjuvant TMZ for 6 cycles on days 1-5 of a 28 day cycle (150-200 mg/m^2/day). Patients treated with concurrent TMZ and radiotherapy demonstrated an improved median survival by log-rank comparison of 12.5 months, compared to 9 months for patients treated solely with radiotherapy (p=0.029). These results show that this combined modality regimen can be replicated in clinical practice, with significant clinical impact.	Information noted.

Consultee	Comment	Action/response
Schering Plough (continued)	We acknowledge that this data was not available at the time of the initial HTA; nonetheless it has an important bearing on the interpretation of clinical trial evidence for TMZ as set out in the ACD, section 4.3.4. **Section 4.3.7** **The ACD: '…it [***the Appraisal Committee***] considered evidence from experts that glioma can have a considerable impact upon the quality of life of patients, which may deteriorate rapidly after the onset of disease progression.'** **Schering-Plough Response:** We would like to draw the attention of the Appraisal Committee to the quality of life analysis of EORTC 26981 published in November, 2005 in *Lancet Oncology* by Taphoorn et al. These data were submitted as "Academic in Confidence" as part of our original dossier. We would also like to point out that there was an overall improvement in progression-free survival of approximately 2 months associated with TMZ treatment. It can then be inferred that patients lived longer, with improved quality of life, as the addition of TMZ did not negatively impact their quality of life.	The Committee considered the results of the study of the quality of life of patients in the EORTC trial – see FAD section 4.1.15.

Consultee	Comment	Action/response
Schering Plough (continued)	**Section 4.3.11** **The ACD states: '…The Committee concluded on the balance of the economic evidence, including the consideration of second and subsequent line' treatments (as far as was possible), that the use of carmustine implants and temozolomide…would not be a cost-effective use of NHS resources.'** **Schering-Plough Response:** As detailed elsewhere in Schering-Plough's response to the ACD, basic errors in the calculation of drug acquisition costs for TMZ and the failure to appropriately incorporate costs associated with TMZ treatment at first relapse render the cost-effectiveness estimates unreliable. Further, the AG failed to consider the cost-effectiveness of TMZ in clearly defined patient subgroups. An ACD recommendation, based upon the economic evidence set out by the AG, is therefore perverse.	See responses to specific comments.

Consultee	Comment	Action/response
Schering Plough (continued)	**Section 4.3.13** **The ACD states: 'The Committee considered whether there might be subgroups of patients for who the use of treatments may be more effective and cost-effective. It acknowledged the results of a retrospective analysis of patients with reduced MGMT activity… The Committee concluded that this early research [MGMT as a biological marker for better response] was promising and that further research into biological markers of chemosensitivity and the use of such markers to identify subgroups of patients in whom the treatments may be more effective should be pursued.'** **Schering-Plough Response:** In respect of 'subgroups of patients for whom the use of treatments may be more effective and cost-effective' the ACD makes no reference to subgroups, such as the groups outlined in the appendix of the Stupp et al NEJM paper. It is unclear as to why the AG has failed to consider these classical subgroups, particularly since the cost-effectiveness case in these populations can be substantially stronger than in the overall patient population (see Appendix 1 for subgroup survival analyses). Regarding further validation of the MGMT data, we believe the Appraisal Committee is aware of the large, randomized, phase III trial that Schering-Plough is supporting in order to validate this finding prospectively. However, until this hypothesis is proven and, until physicians are able reliably and consistently to identify those subgroups of patients who are clearly deriving substantial clinical benefit from the use of TMZ in combination with radiation, we strongly question whether it is ethical to deny such patients access to life-prolonging treatment, because a subset of patients may not derive as much benefit.	The data regarding subgroups has been considered by the Committee – see FAD sections 4.1.13, 4.2.13, 4.3.23, 4.3.24, 4.3.26. Temozolomide is recommended for patients with performance status of 0. The Committee rejected the notion of patient selection on the basis of this marker – see Section 4.3.25.

Consultee	Comment	Action/response
Schering Plough (continued)	**Section 5.2** **The ACD states: '…the Committee considered that further research into the effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed glioblastoma is required. Such studies should include:** • **A robust design, adequate sample size, and appropriate statistical analysis** • **Analysis of the effect of treatment upon health-related quality of life** • **A comparison of treatment regimens with other active chemotherapy treatments, such as the PCV regimen** • **A consideration of the effectiveness of treatments in children as well as adults** • **A consideration of the subgroups in whom the treatments may be particularly effective, such as those defined by biological markers.'** **Schering-Plough Response:** The EORTC study, an independent RCT of TMZ in newly diagnosed, glioblastoma achieved international acclaim as unequivocal evidence of the first major clinical advance in this patient population for 30 years or more. The data resulted in the first plenary session presentation ever on the topic of brain tumours at ASCO, the most significant cancer meeting in the world. This presentation was followed by 2 major publications in the most prestigious New England Journal of Medicine, and subsequently confirmed by other positive clinical trials.	The research recommendations have been amended.

Consultee	Comment	Action/response
Schering Plough (continued)	***A robust design, adequate sample size, and appropriate statistical analysis*** EORTC 26981 was designed by the EORTC Brain Tumour Group, an independent, academic research organization. The EORTC received an unrestricted educational grant and study drug from Schering-Plough. The results of the trial, when submitted for market authorizations, were granted priority review by the US FDA, the Canadian Ministry of Health and the Japanese Ministry of Health. There should be no remaining questions with respect to the trial design. This is the largest study of its kind in glioblastoma. The sample size and statistical analysis were deemed appropriate by both the EMEA and the US FDA, as market authorization was granted.	The Committee considered the EORTC trial of temozolomide to be of good quality. This recommendation related to future studies however the research recommendations have been amended.
	Analysis of the effect of treatment upon health-related quality of life Health-related quality of life was analyzed in EORTC 26981, and published in November 2005 in *Lancet Oncology*. The addition of TMZ to radiotherapy did significantly prolong relapse-free and overall survival and did not have a negative impact on patients' quality of life.	The Committee considered the results of the study of the quality of life of patients in the EORTC trial – see FAD section 4.1.15. The research recommendations have been amended.
	A comparison of treatment regimens with other active chemotherapy treatments, such as the PCV regimen We do not believe that PCV is an appropriate comparator given data from the phase III trial by the Medical Research Council. Furthermore, PCV, in combination, or as single agents, is not licensed for use in the treatment of newly-diagnosed glioblastoma. Current standard of care in the majority of industrialized nations has largely abandoned PCV due to its enormous toxicity. It is effectively not a therapeutic choice of any significance. As the Medical Research Council concluded, their own trial failed to demonstrate a role for PCV in the treatment of glioblastoma patients. We believe that any trial design that would randomize patients to receive RT-PCV would be unethical and further reduce the standard of care for glioma treatment in the UK, which currently lags substantially behind the other industrialized nations.	The research recommendations have been amended.

Consultee	Comment	Action/response
Schering Plough (continued)	***A consideration of the effectiveness of treatments in children as well as adults*** We agree that it is important to continue to investigate treatment options in children with brain tumours. However, any speculation with respect to the activity of TMZ in paediatric patients is outside the scope of the trial and outside the scope of the dossier prepared by Schering-Plough. We request therefore, that the review should only examine the appropriateness of use in those patients that meet the enrolment criteria of EORTC 26981.	The research recommendations have been amended. Children were not excluded from the scope of the appraisal.
Schering Plough (continued)	**A consideration of the subgroups in whom the treatments may be particularly effective, such as those defined by biological markers** We agree that the retrospective analysis by Hegi et al. is important in its hypothesis generation and are thus supporting the first, truly global, cooperative group trial in this patient population to prospectively investigate the finding with a reproducible, validated assay. However, until the results of the trial are available, as we note above, we strongly question whether it is ethical to deny all patients access to life-prolonging treatment because a subset of patients may not derive as much benefit as others.	The research recommendations have been amended. The Committee rejected the notion of patient selection on the basis of this marker – see Section 4.3.25.

NHS QIS (Scotland)

Consultee	Comment	Action/response
NHS QIS reviewer 1	I find the NICE ACD document unsatisfactory for the reasons listed below. I have expanded on these in the text where I concentrate on the technical issues. I leave it to others to expand on the impact that acceptance of the ACD conclusions will have on patients, service and research. 1. The endpoint chosen is inappropriate for this population of patients. 2. The endpoint has been developed by the investigators themselves, it has not been externally validated. There are likely flaws. 3. The economic model is complex, makes inaccurate assumptions, over-emphasises median survival and has not been convincingly validated in this group of patients. 4. The committee have accepted the economic model without providing criticism in the ACD and used it as the overwhelming criterion on which they base their recommendations. 5. The committee have concluded that the technologies should not be used outside of clinical trials without considering use limited to groups of patients (identified in the studies) who might particularly benefit and who, even on their economic model, may have a lower ICER. 6. The ACD has been written without direct input from an oncologist (and in particular no neuro-oncologist), and without input from a representative of brain tumour patients. 7. None of the NICE professional (neuro-oncology) experts, who advised the committee, accept the conclusions in the document. 8. The recommendations for further clinical study are of no value. These recommendations demonstrate the failure of the committee to understand the current state of research in this group of patients worldwide. This probably results from the lack of adequate neuro-oncology input to the document.	See responses to specific comments below.

Consultee	Comment	Action/response
NHS QIS reviewer 1 (continued)	**Introduction** I think it is unfortunate that the two technologies have been considered together. There are significant enough differences to make a joint assessment difficult. Gliadel (Carmustine) is a surgically applied treatment, restricted in application to those patients with tumours that are surgically removable in such a way as to leave favourable anatomy. The technology is applied to all high-grade gliomas fitting this description, including glioblastoma, anaplastic astrocytoma and anaplastic oligodendroglioma. Temozolomide is a treatment applicable to patients undergoing surgery or just biopsy and in whom a local pathologist has made a diagnosis of glioblastoma. There were differences in study design and differences in study outcome for these two technologies. I am not convinced that the committee fully appreciated this. For example in paragraph 4.3.5 they write 'it considered concerns regarding the estimates of effectiveness of Temozolomide (including the length of survival in the placebo arm)' Indeed there was no placebo arm used in this study!	Comments noted. The Committee carefully considered the clinical trials of both temozolomide and carmustine implants. This section has been amended. The Committee understood the design of the trial.

Consultee	Comment	Action/response
NHS QIS reviewer 1 (continued)	**1. Choice of endpoint** Whilst I appreciate the need for a parameter with which to compare different treatments in different diseases, I seriously question the use of QALYs in this particular instance. It is questionable whether the QALY model, which is based on members of the general public who are well assessing chronic, hypothetical health states, can apply to an explosive disease such as glioblastoma. Glioblastoma has virtually no chronic phase; its appearance is acute, and it is lethal in a short space of time. In such a situation, patients are much more likely to value an extension of survival, almost at any cost, and only secondarily value their 'symptomatic' health state. Further, this model takes no account of the value of extension of life to relatives. It is acknowledged that the use of QALY's in extreme health states is questionable and there are few more extreme states in oncology than glioblastoma. The economic group have not attempted to justify their choice of endpoint and this is difficult to accept.	The reference case stipulates that the health effects of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.3.4 (Available from URL http://www.nice.org.uk/page.aspx?o=201974). The QALY approach encapsulates the effect of treatment on both quantity and quality of life.

Consultee	Comment	Action/response
NHS QIS reviewer 1 (continued)	**2. Validity of endpoint** It was admitted by the Peninsula Group (Assessment report page 95 section 5.5.2.1) that they did not find a validated source of utility values for patients with high grade glioma from which to calculate their QALY's . They therefore developed their own, using a set of scenarios based on the EORTC QLQ-30 questionnaire. For this, 36 members of an original group of 93 patients from a general population were used to generate the data, which would eventually be fed into the QUALY analysis. Do we know how this subgroup of 36 was chosen. It is a severely minority subgroup - were there biases? Is it valid at all to use so small a group? The approach was not validated in any acceptable way. In a very limited attempt to seek validity the Peninsula group report '*validity of the health state descriptions was sought using 3 members of the expert advisory group'*. This group concluded that '*standardising the impact of gliomas was difficult….*' It must be concluded from this that the methodology has not been internally validated and has certainly not been subject to any external review or validation process. **Summary** I would conclude that the chosen endpoint is of doubtful applicability in this group of patients and that the validity of the endpoint, even if it were appropriate, has not been established.	Published utility data for patients with high grade glioma were not available. The Committee carefully considered the utility data included in the analyses and the results of sensitivity analyses (see Assessment Report Figures 16, 19, 20, 28, 31 and 32).

Consultee	Comment	Action/response
NHS QIS reviewer 1 (continued)	**3. Comments on the underlying model** The Peninsula Group have used a highly complex economic model and adapted it for brain tumour work. A number of assumptions have been made which are at best approximations and at worst possibly wrong. For example, the model is based on an assumption that transition states are time dependent rather than state dependent. They admit that this is counter intuitive and I would argue that it is actually erroneous. The length of time a patient with glioma is likely to live is certainly most closely related to their state (whether in remission or has progressive disease) rather than their time from diagnosis, as assumed in this model. Though the two parameters may be related the relationship is not necessarily simple. A relapsed patient is likely to die sooner than one who has not relapsed. This discrepancy in the model is likely to be most apparent at longer lengths of survival, which is where the greatest benefit from Temozolomide occurs.	The Committee carefully considered this assumption in the analysis and the results of a sensitivity analysis (see Assessment Report Figures 16 and 28). It concluded that the sensitivity analysis demonstrated that the results were not sensitive to this time dependency assumption – see FAD section 4.3.12 and Assessment Report pages 115 and 127.
	By their own admission, the model they have used is particularly sensitive to the median survival (Peninsula Group Assessment report page 5). When the more important parameter is survival at 2 years or later (as in the Temozolomide study) and when the median survival is less than 18 months, the model they have used may become particularly inappropriate and may underestimate the value of the technology.	The survival estimates in the economic model were based on the entire Kaplan-Meier survival curves and not just median survival – see Assessment Report section 5.5.1. The sensitivity analyses explored the effect of varying survival estimates on the ICERs.

Consultee	Comment	Action/response
NHS QIS reviewer 1 (continued)	A further criticism is that they appear to have calculated the costs of treatment at relapse based on an assumption that all patients receive PCV for relapsed disease. Certainly a significant number of patients who did not receive Temozolomide for their initial treatment will receive Temozolomide subsequently. (This has been recommended by NICE following a previous submission). This use of Temozolomide will increase costs in the radiotherapy only arm. It will act to decrease the cost differential and improve the ICER and the impact of this could be considerable.	The base case assumed that 70% of patients whose disease recurs would get PCV. NICE TA Guidance no.23 recommends that temozolomide should be considered for the treatment of people with recurrent brain cancer who's initial chemotherapy treatment has failed. The Committee considered the results of an additional analysis including differential post-progression treatment. See FAD sections 4.2.12, 4.2.13 and 4.3.22.
	4. Acceptance of the model Once again the only assessment of this model appears to have been from the NICE Group themselves and the issues discussed above have not been acknowledged in the ACD. The group have spent the great majority of the document discussing economic issues without criticising the models on which they are based. They have not considered the broader picture of what patients and their relatives might want as outcome from treatment and what improvement they might consider valuable. They have not considered the quality of life data published by Taphoorn and colleagues which uses *directly* the validated QLQ 30 instrument and not an unvalidated derivative of it as in the Peninsula model. Further, the report has been produced without input from a neuro-oncology clinician, which is very surprising. For these various reasons I have considerable reservations as to whether this model (despite the detail) can be considered a valid instrument on which to judge this technology in this group of patients.	The Committee considered the evidence submitted, including the AG's economic model and the comments from consultees in response to the Assessment Report. The Committee also considered evidence in the forms of submissions and comments from patients and organisations representing them, and the views of the patient representatives at the Committee Meeting. The Committee considered the quality of life data from the EORTC trial – see FAD section 4.1.15.

Consultee	Comment	Action/response
NHS QIS reviewer 1 (continued)	**5. Consideration of use in subgroups** I am concerned that the Committee has failed to comment on the possible use of either technology in sub-groups of patients. In the original publication from Stupp et al, it was clear that poor performance status patients and patients who did not receive a tumour resection, did not fair well either with or without chemotherapy. Conversely, those with the best performance status and the best resections had the greatest benefit from Temozolomide. If a further analysis had been done on this basis by the Peninsula group, it would undoubtedly have improved the ICER for patients in appropriate sub-groups. (Analysing a group of patients with a global 'better prognosis', as the Peninsula group does on their page 132 does not add to the debate and is a relative waste of time). Whilst I accept that numbers in the 'Stupp' sub-groups might be small, the differences never the less were strong (Data presented at numerous meetings inc ECCO 2005). I feel it is a mistake to fail to consider the evidence on sub-groups already available to the Committee and thereby to consider the possibility of limited prescribing on a selected basis.	The Committee carefully considered the issue of subgroups – see FAD sections 4.1.13, 4.2.13, 4.3.23, 4.3.24, 4.3.26. Temozolomide is recommended for patients with performance status of 0.
	6. Lack of specialist expertise on the appraisal committee A list of the members of the appraisal committee is given in Appendix A. I would express concern that although relevant clinicians have been used to advise the NICE Committee, no neuro-oncologist of any kind has been involved in the production of the ACD. Indeed I can see no evidence of an oncologist of any kind in the group. I find it difficult to understand how an adequate assessment can be made without such expert opinion. I believe this lack of expertise is demonstrated at many stages of the report, including the conclusions. Neither, as far as I can see, has a patient expert been involved at this stage. The only 'independent Patient Advocate' is Dr Ann Richardson. I would be keen to know what expertise this single individual brings with respect to the experience of patients with malignant glioma and their relatives.	The Appraisal Committee is a standing committee made up of people from a mix of backgrounds and specialist expertise. The Committee considered evidence provided by clinical experts who are specialist in treating people with high grade gliomas, and representatives of patients with high-grade glioma and their carers. Dr Ann Richardson is more correctly described as 'Lay member' in the FAD

Consultee	Comment	Action/response
NHS QIS reviewer 1 (continued)	**7. Lack of support from specialist advisors.** I accept that the committee did take evidence from chosen experts and that these experts are indeed eminent in their fields and represent, reliably, opinion in the UK. However these experts were not involved in the writing of the ACD. I find it of grave concern that each of these advisors (Professors Brada, Cruickshank, Walker and Dr Rees) have each since felt it appropriate to criticise the conclusions of the report. I believe it true that none of these experts supports the conclusions. I would ask how the Committee can justify the production of a document that contradicts the opinion of their own chosen experts and opposes the great majority opinion of neuro-oncologists in the UK. Does the committee feel comfortable in producing such a report where there is such united opposition and particularly from amongst their own selected advisors? I believe that similar remarks could be made with respect to the patient representatives advising the committee. **8. Recommendations for research** The recommendations on research made by the Committee show that they fail to understand the current situation with respect to this regimen, again demonstrating the lack of specialist input. The study itself has been viewed and reviewed by the international neuro-oncology and wider scientific community and has attracted very little criticism in its design, conduct or its conclusions. The regimen has been accepted as standard or care almost universally. The original study has been analysed in terms of quality of life and these data are available already. Hence to recommend further research in this area without acknowledging what has been done is inappropriate and neglectful. Current randomised studies in this area do include a QOL aspect, if the committee had taken notice of their advisors they would know this.	The Committee considered the perspectives of the clinical experts and patient representatives alongside the evidence on clinical and cost effectiveness when formulating its recommendations. The research recommendations have been amended in the FAD. Information on quality of life is not available from the principal RCT of carmustine implants.

Consultee	Comment	Action/response
NHS QIS reviewer 1 (continued)	A subsequent programme of research based on this regimen is already in place and includes an analysis of sub-groups, both clinical and chemical (including assessment of MGMT status). To suggest that we repeat this work in the United Kingdom based on a lesser regimen (radiotherapy alone), would attract no interest internationally and no funding nationally. I find it difficult to understand the recommendation to compare this regimen with other active chemotherapy treatments if this regimen is not accepted as 'standard of care'. On the other hand how can we justify using this regimen as a control arm, if the Committee say they cannot recommend its use routinely? In that situation we would be using as control a regime which the committee does not consider 'standard of care'. Scientifically this makes no sense.	The research recommendations have been amended in the FAD.
	It would be extremely difficult to interest researchers in an assessment of this regimen in children if we know that a result as positive as that found in adults (by Stupp) would be rejected by NICE. What possible interest can this attract from researchers who will feel that their efforts, even if positive, are likely to be rejected by such a Committee?	The research recommendations have been amended in the FAD.
	I would therefore welcome serious suggestions from the Committee as to how the UK research community could proceed in the light of a refusal from NICE to accept either of these regimens as standard of care. For the committee to 'recommend' research that is either already done, already underway or not feasible is not helpful.	The research recommendations have been amended in the FAD.

Consultee	Comment	Action/response
NHS QIS reviewer 1 (continued)	**Summary** The diagnosis of glioblastoma is an extreme situation in oncology. Death is inevitable and survivals are short. Such progress as we have has been achieved incrementally by the judicious, successive use of steroids, surgery, radiotherapy and now chemotherapy; which has extended median survival from 2-3 months to around 14 months and has generated a small, but significant number of longer term survivors. The disease affects across the age range including many in middle-life and gives little warning before its onset, bringing with it the imminent prospect of death. Clinicians and patients will know the value of even brief extensions of survival, almost independent of its quality. In these circumstances the uncompromising use of a model based on the assessment by healthy members of the general public of chronic health states is almost certainly inappropriate. The international, almost universal acceptance of the Temozolomide regimen is testimony to these sentiments. I think it would be appropriate for NICE to reconsider its assessment on the basis of the appropriateness of the evaluation and to consider at least limited use of either of these technologies in patients with newly diagnosed glioma. In summary therefore, I think that the basis on which the NICE decision has been made is questionable, both in terms of the endpoint and in terms of the model used to examine this endpoint. I would consider an approach based on survival and quality of life estimate, as has been done in the publications of Stupp 2005 and Taphoorn 2005 and an economic analysis based on these to be more appropriate.	The Committee took the limited life expectancy of these people into account in their decision – see FAD section 4.3.26. Temozolomide is recommended for patients with performance status of 0. Survival estimates were based on data from the EORTC trial. The reference case stipulates that the health effects of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.3.4 (Available from URL http://www.nice.org.uk/page.aspx?o=201974).
NHS QIS Reviewer 2	This ACD and the accompanying overview document are excellent and comprehensive summaries of the state of the evidence and fully justify the conclusions presented. The health economic arguments are always difficult and particularly so in a condition with such a poor prognosis as high grade glioma, but the unequal mix of cases in the major trials reviews invalidates their conclusions of benefit from treatments of, at most, marginal effectiveness.	Comments noted.

Department of Health and Welsh Assembly Government

Consultee	Comment	Action/response
Department of Health	Thank you for the opportunity to make comments on the appraisal consultation document on carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma. My colleagues at the Department of Health have no specific comments to make on the above consultation document.	No action required
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment on the document. We are content with the technical detail of the evidence supporting the provisional recommendations and have no further comments to make at this stage.	No action required