NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma

Responses to comments arising from consultation on the ACD from consultees, commentators and the public

Comment from	Nature of comment	Response
Link	Link is extremely disappointed that the Appraisal Consultation Document (ACD) issued in December 2006 does NOT recommend the use of carmustine implants for the treatment of newly diagnosed high-grade glioma patients undergoing maximal resection, thereby denying patients and clinicians access to this treatment. The case for recommending carmustine implants in this subgroup of patients rests upon it being a cost effective intervention, with an ICER below the willingness to pay threshold of £30,000. Link believes there is a compelling case for recommending carmustine implants in a small patient population (newly diagnosed high-grade glioma patients able to undergo a maximal resection - circa 450 patients per annum) which would result in direct costs to the NHS in the region of only £1 million p.a. (i.e. less than 0.01% of the total annual drug budget). In summary Link has grave concerns with this appraisal and its process as demonstrated by the four key issues raised below:	Comment noted. The FAD has been amended. See responses to specific comments below.

Comment from	Nature of comment	Response
Link	**1. Factual inaccuracies** We are concerned about the continued inclusion of major errors. Despite having been told that the price for carmustine implants was incorrect in the revised PenTAG model (as was also the case in the original model) giving rise to falsely high ICERs this error was NOT corrected in the reanalysis and thus incorrect ICERs were presented in the second ACD. Despite being informed of this error, the use of an incorrect price within the model has not been acknowledged nor corrected, by the Institute, at any stage of the process. Similarly, the second ACD contained the statement that the extent of tumour resection was assessed using post-operative imaging (section 4.3.18). This is incorrect as assessment was by the immediate recording of those data by the operating surgeon at the time of operation, a point made clear in the Link response to the PenTAG reanalysis. These errors have serious negative impacts on the assessment of carmustine implants and have not, as far as we can see from the recent minutes of 22 Nov 2006, been discussed by the Appraisal Committee.	The Committee was aware of the price change throughout the course of the appraisal and of the sensitivity analysis conducted by the Assessment Group around the price of the wafers. This has been clarified in the FAD (see Section 4.2.8). Comments noted. This section has been amended. This information came from the published paper relating to this trial (Westphal et al. Neuro-Oncology 5, Apr 2003, Pg 82.) that "the postoperative scan with enhancement was used to determine the extent of resection".
Link	**2. Inequity** We have several significant issues with the methodologies used in (effectively) comparing data from very different and non-contemporaneous clinical studies for temozolomide and carmustine implants, and applying them in the same cost-	The model is a representation of the disease process. The values of parameters are specific to each treatment where appropriate.

Comment from	Nature of comment	Response
	effectiveness model. In addition when the resultant ACD describes a 2.2 month median survival gain with carmustine implants as “a small gain”, while describing a 2.5 month median survival gain with temozolomide as “a gain”, serious doubts start to emerge about the even-handedness of the appraisal process that has been applied.	Changed in the FAD.
Link	**3. Compelling evidence in maximal resection** The evidence for the efficacy of carmustine implants in patients undergoing ≥90% surgical (maximal) resection is strong and statistically significant. Within the RCT discussed by the Appraisal Committee the assessment of resection was made by the neurosurgeon at the end of the surgical procedure at the point when carmustine implants are inserted and not, as stated in the ACD, by assessment of a post operative MRI scan. Surgeons are, a priori, good at selecting patients in whom they are likely to achieve maximal resection. This group of patients shows a significant survival gain compared to a partial resection subgroup (where no survival gain with carmustine implants can be seen). The ICER values for maximal resection patients lie well below the “willingness to pay” threshold. These clinical and cost effectiveness data should allow the Appraisal Committee to recommend carmustine implants for this patient subgroup.	This has been amended in the FAD (see sections 1.2, 1.3, 4.3.17 to 4.3.21.) The committee heard expert testimony from a clinical expert that, given sufficient expertise and with available technology, patients in whom maximal resection could be achieved could be identified pre operatively and maximal resection could be confirmed peri operatively. The FAD has been amended accordingly (see sections 1.2, 1.3, 4.3.17 to 4.3.21).

Comment from	Nature of comment	Response
Link	**4. Lack of choice for grade III glioma patients** A negative recommendation for carmustine implants denies grade III patients access to the only licensed chemotherapy option that has been shown to be effective in these patients. The RCT for carmustine implants recruited both grade III and IV high-grade glioma patients and the study outcomes led to a European Marketing Authorisation for use in all high-grade glioma patients. Conversely temozolomide is only licensed for use in grade IV patients. Overall, therefore, we believe these issues raise concerns regarding the thoroughness with which consultees comments have been reviewed and considered, and brings into question the robustness and fairness of the process used in this appraisal.	The Committee noted that the marketing authorisation for carmustine implants relates to 'high-grade glioma'. See FAD section 4.3.10.
Link	Link has provided this response under the three general headings recommended by the Institute. **Whether you consider that all of the relevant evidence has been taken into account** Link does not consider that all relevant information has been taken into account and is concerned that factual inaccuracies previously highlighted to the Institute have not been corrected in the current ACD. These issues are discussed under the second heading of this document. **Revised ICER values presented by Link** The ICER values presented by Link in response to the	The committee was aware of the ICER

Comment from	Nature of comment	Response
	PenTAG reanalysis have not been given due consideration in the ACD. The revised ICER values presented in Link's response to the PenTAG reanalysis were calculated using a reworked economic model that addressed the previous concerns of the Assessment Group. The adjusted Link model produces an ICER similar to that of the PenTAG reanalysis base case ICER, a fact that clearly validates the Link model. Section 4.2.4 continues to criticise Link's economic model for the omission of treatment costs other than those of carmustine implants. It is unclear from either the ACD (section 4.2.5) or the Appraisal Committee minutes for 22 November 2006 whether or not the use of Link's revised model, and the validity of the ICERs presented, were clearly conveyed to the Appraisal Committee to allow informed discussion to ensue. We are very concerned that the Appraisal Committee may instead have been allowed to continue to mistakenly believe that the Link model was not considered appropriate. Using this revised economic model, Link presented (within its response to the PenTAG reanalysis) new ICER values, incorporating the correct price for carmustine implants, which clearly demonstrated costs below the 'willingness to pay' threshold of £30,000 for the maximal resection subgroup of patients.	values presented by Link in response to the PenTAG reanalysis. This section of the ACD and FAD describes the economic model supplied in the Link submission in accordance with standard processes. Details of comments made by Link during consultation regarding the cost effectiveness of carmustine implants taking into account other treatment costs are noted in Section 4.2.5.
Link	**Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the**	

Comment from	Nature of comment	Response
	evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate For the following reasons Link does not consider the summaries of clinical and cost effectiveness to be reasonable interpretations of the evidence. **Price of carmustine implants** There has been a persistent pricing error in the analyses undertaken by the PenTAG Assessment Group for carmustine implants throughout this appraisal (see Appendix 1). The persistence of this error is of major concern. The original PenTAG model used a price for carmustine implants of £687.50 per implant. However due to a price reduction initiated through the PPRS scheme, this was reduced to £650.38 in January 2005, nine months before the Assessment Report was issued. The error persisted in the revised PenTAG model, as provided to Link in October 2006. Despite, again, being raised by Link in our response to the reanalysis, the ICER values considered by the Appraisal Committee remained as presented in the PenTAG reanalysis of October 2006 and had not been recalculated as requested by Link. Consequently the ICER values presented to and considered by the Appraisal Committee and documented within Section	The Committee was aware of the change in price of carmustine implants and of the sensitivity analysis around the price of the implants throughout the course of the appraisal. The FAD has been amended to clarify this (see Section 4.2.8)

Comment from	Nature of comment	Response
	4.2.8 of the ACD are, once again, incorrect. Correct ICERs were provided in the revised analysis conducted by Link and are referred to in Section 4.2.5. This revised analysis both mirrored the PenTAG approach and addressed the issues raised in the original ACD.	

Comment from	Nature of comment	Response
Link	**Maximal resection subgroup** Critically, the Appraisal Committee has misunderstood the measurement of maximal resection. This has a fundamental effect on the applicability of this subgroup in clinical practice. The Committee considered that "quantifying the extent of resection was difficult and open to considerable bias". (Section 4.3.18) and in the absence of clarification or transparency as to the exact discussions of the Committee, we have assumed that this is based on the fact that "…….The Committee noted that the extent of tumour resection as defined in the RCT was judged retrospectively on postoperative imaging……". This latter statement is simply incorrect. Westphal et al 1 do, indeed, present mean percent tumour resection values in the published report for the RCT, stating that these were measured by comparing the preoperative and postoperative MRI scans. However, as was clearly stated in section 3 paragraph 3 of Link's response to the PenTAG reanalysis, the degree of resection value used in the subgroup analysis provided by Link was determined by the neurosurgeon intraoperatively and recorded in the Case Report Form at the time (see Appendix 2). This methodology and the resulting data clearly reflect clinical practice. The RCT was conducted across 38 centres in 14 countries and any variability in this subjective estimation, both under and overestimation is therefore indicative of that which would occur in routine clinical practice. In addition, letters from UK neurosurgeons (Appendix 4) confirm that all UK neurosurgery units have neuro-navigation and/or intra-operative ultrasound available to them allowing objective intra-operative confirmation of maximal resection.	Comments noted. This section has been amended. This information came from the published paper relating to this trial (Westphal et al. Neuro-Oncology 5, Apr 2003, Pg 82.)

Comment from	Nature of comment	Response
Link	**Inappropriate measurement of progression free survival by radiological imaging** We are concerned that the Appraisal Committee has taken radiological imaging to be the definitive measure of progression free survival (PFS) regardless of any problems that may be associated with this measure for a local treatment modality such as carmustine implants (see Appendix 5 for supporting testimonies from five UK clinical experts). Throughout this appraisal Link has asserted that the confounding factors of surgery, carmustine implants and radiotherapy make measurement of PFS by radiological methods problematic and subject to high degrees of inaccuracy and uncertainty. The ACD in section 4.3.3 states "The committee was persuaded that quality of life is paramount……" This statement clearly supports the use of measures that are surrogates for quality of life to determine progression of the disease. It is the point at which functional progression occurs that determines when patients can no longer completely care for themselves or carry out normal activities. This is of the greatest importance to patients and their families, and is also a key driver of subsequent healthcare costs. Data on the functional measures of progression for both the maximal resection and partial resection patient subgroups are presented in Table 1, below, and compared to radiologic imaging and overall survival. There is clear correlation for both	The Committee was aware that the clinical trial used a composite measure (radiological and clinical) to define disease progression and that this was used in the base case of the Assessment Group's economic analysis. The committee was also aware of the ICERs that resulted from using other measures to determine progression. The Committee carefully considered the issues regarding the measurement of disease progression (see FAD sections 4.3.4, 4.3.9, 4.3.11, 4.3.14 and 4.3.21)..

Comment from	Nature of comment	Response
	subgroups between survival gain and PFS gain as measured by functional status i.e. for the maximal resection patients who experience a 4.2 month mean survival gain there is a PFS gain of 2.6 to 3.0 months. However, for the partial resection subgroup the corresponding survival gain and PFS gain are 0.1 months and –0.2 to –0.9 months. Link recognises the concerns of the Appraisal Committee (expressed in ACD section 4.3.14) that "The Committee was mindful that the measure of neurological performance decline was not based on a validated instrument." However, the above data and discussion cast significant doubt on the validity of PFS by radiologic imaging as a measure of treatment effect, and in the absence of anything else, support the use of functional measures for this purpose in this patient group.	
Link	**Inequality in the appraisal between carmustine implants and temozolomide** **a) Interpretation of survival gain** The ACD (section 4.3.7) describes a statistically significant 2.2 months survival gain with carmustine implants in the ITT group as "a small gain", while describing the corresponding 2.5 months median survival gain with temozolomide simply as "a gain" (ACD section 4.3.20). Link believes this misrepresents the clinical effectiveness of carmustine implants which is clearly comparable to that of temozolomide, as demonstrated in Table 2, below.	Changed in FAD

Comment from	Nature of comment	Response
Link	**b) Post-progression treatment costs** The ICER value for temozolomide is only below the "willingness to pay" threshold when alternative assumptions to the original PenTAG base case model on post progression costs, derived from the RCT, are considered. In the interests of fairness a similar approach should be adopted for carmustine implants. However this is difficult as carmustine implants are effectively penalised for having a superior double-blinded study design that meant treatment at recurrence could not be decided based on a knowledge of how the condition was initially managed. It is unclear from the ACD (section 4.3.13) if this difficulty was appreciated and fully discussed by the Appraisal Committee. In light of this problem Link presented a range of ICER values using alternative post progression costs (section 4.2.5) in line with the post progression costs within the Stupp RCT and as applied to temozolomide. However the Appraisal Committee has decided that the Assessment Group's post progression costs (as used in the base case) are the most appropriate (section 4.3.13) despite receiving "testimony from clinical specialists that there is considerable uncertainty about the appropriate treatment for patients whose disease progresses after chemotherapy after initial diagnosis" (Section 4.3.24) and despite existing NICE guidance on the use of temozolomide in recurrent glioma. Furthermore at the time the RCT was carried out there were	The Committee was aware of existing NICE guidance on the use of temozolomide for the treatment of recurrent glioma and that temozolomide is used routinely in this setting. The Committee considered that the use of temozolomide as part of initial treatment that current practice could lead to a reduction in the subsequent use of temozolomide at disease progression (see FAD section 4.3.26). However, based on the re-analysis conducted by the Assessment Group, the Committee did not consider it necessary to issue guidance on the subsequent use temozolomide. The Committee did not consider that the use of carmustine implants as part of initial treatment would reduce the need for other routinely used chemotherapy, such as temozolomide, at disease recurrence (see Section 4.3.13).

Comment from	Nature of comment	Response
	no licensed medications available specifically for the treatment of recurrent high-grade gliomas as neither carmustine implants nor temozolomide had gained European regulatory approval for this indication. Post-progression options in the base case (as applied to carmustine implants) are therefore not realistic in light of the subsequent approval of these two agents. The uncertainty about post-progression treatments serves to add further uncertainty to the validity of the ICER calculation for carmustine implants. As demonstrated by Link's response to the PenTAG reanalysis, it is likely that any alternative post progression treatment costs to the base case will reduce the ICER value, and in many cases this will fall to below the "willingness to pay" threshold for both the ITT and maximal resection groups.	
Link	**Therapeutic restriction** **a) Grade III gliomas** The RCT for carmustine implants recruited both grade III and IV high-grade glioma patients and the study outcomes led to a licence for use in all high-grade glioma patients. Conversely temozolomide is only licensed for use in grade IV glioma patients. A negative recommendation for carmustine implants denies grade III patients access to the only chemotherapy option that has been shown to be effective in this patient group.	The Committee noted that the marketing authorisation for carmustine implants relates to 'high-grade glioma'. See FAD section 4.3.10.

Comment from	Nature of comment	Response
Link	**b) At recurrence** The Appraisal Committee recognised the views of clinical specialists with regard to the benefits of carmustine implants, e.g. section 4.3.13 “It also considered the testimonies from clinical specialists that a potential benefit of carmustine implants is that temozolomide could be used to treat disease progression ” However, we remain disappointed that these views were not developed and an appropriate positioning for carmustine implants has not been defined e.g. in patients undergoing a maximal resection (for whom data have been presented). The current recommendation denies such patients any treatment option with this drug. With only two licensed therapies available for high-grade glioma patients at either initial diagnosis or at recurrence any recommendation restricting the use of either or both of the products severely limits treatment options upon recurrence. If carmustine implants are not recommended at initial diagnosis, even for a subgroup of patients, these patients will have lost the opportunity to receive another effective product (i.e. temozolomide) at recurrence.	The use of carmustine implants at recurrence is in the process of undergoing a NICE appraisal.
Link	**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. However only 25% of patients3 meet the entry criteria of the RCT that represents the evidence base for carmustine implants. Using these values, only 465 patients annually will be eligible to receive	The committee does not take the rarity of a condition into account when formulating its recommendations.

Comment from	Nature of comment	Response
	carmustine implants, at a total cost to the NHS (based on the mean 6.5 implants per operation) of £1,966,000. Furthermore, if only those patients who undergo maximal surgical resection (less than 50% of patients in the RCT) are treated with carmustine implants, then the cost to the NHS would be halved to less than £1 million per annum – or less than 0.01% of the total annual drugs budget.	
Link	**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** For the reasons documented above Link does not consider the provisional recommendations to be sound, on the basis that: Patients and clinicians are denied carmustine implants when the body of evidence confirms the benefits of carmustine implants in patients undergoing maximal resection. Carmustine implants have been shown to be cost effective in patients undergoing maximal resection. Carmustine implants are the only licensed chemotherapy agent for grade III gliomas. The ACD contains persistent factual inaccuracies and cannot be regarded as a robust consideration of the evidence. The processes used in making the determination and presenting its findings are also subject to significant criticism,	See above responses to specific comments. The FAD recommends carmustine implants as an option for the treatment of patients undergoing maximal resection (>90%).

Comment from	Nature of comment	Response
	thus undermining the credibility of both the determination and NICE itself. The NHS cancer plan aims to improve survival rates in line with other European countries. Denying patients access to carmustine implants which are commonly used (and fully reimbursed) in many parts of Europe (plus the US and Australia) will be in conflict with this objective.	The Committee is charged determining the most cost effective use of NHS resources.
Schering-Plough	Schering-Plough welcomes the opportunity to comment on the revised Appraisal Consultation Document (ACD) for carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma. We are pleased to see that, following appropriate and important amendments to the Assessment Group's modeling, temozolomide is now demonstrated to be cost-effective for the treatment of the majority of patients with newly diagnosed glioma.	Noted
Schering-Plough	In general, we concur with the Committee that WHO performance status is not an appropriate means of selecting patients for treatment, particularly since it is very difficult to differentiate between patients rated as WHO PS 0 and 1. We are therefore confident that the draft guidance, to recommend temozolomide for patients with either WHO PS 0 or 1 is appropriate.	Noted
Schering-Plough	We agree with the Committee that the Assessment Group's estimates of cost-effectiveness represent a highly conservative scenario since longer-term follow-up data	Noted

Comment from	Nature of comment	Response
	suggest a proportion of patients treated with temozolomide survive beyond 5 years, the point at which the AG model analyses are truncated. Over longer time-horizons we expect the mean survival benefit associated with temozolomide will continue to increase and the ICERs to reduce further.	
Schering-Plough	The appraisal of newly diagnosed glioma has unfortunately already been subject to considerable delays, in part as a result of important errors in the Assessment Group's modeling. Given the short life-expectancy of patients diagnosed with glioblastoma and the significant need for effective treatments, we would encourage the Institute to avoid further any further delays and ensure this positive guidance reaches the NHS as quickly as possible.	Noted
Association of British Neurologists and Royal College of Radiologists	We would like to comment on behalf of the Association of British Neurologists and the Royal College of Radiologists on the Appraisal Consultation Document concerning Carmustine Implants and Temozolomide for the Treatment of Newly Diagnosed High Grade Glioma.	
Association of British Neurologists and Royal College of Radiologists	Regarding Temozolomide, we consider that all of the relevant evidence has been taken into account and that the preliminary views on the resource impact and implications for the NHS are appropriate. We feel that the provisional recommendations are sound and provide a suitable basis for the preparation of guidance to the NHS.	Noted.
Association of British Neurologists and	Regarding Carmustine Implants, the majority view of the ABN Panel Members and the RCR is the same as that outlined	Noted.

Comment from	Nature of comment	Response
Royal College of Radiologists	above for Temozolomide. However, one ABN Panel member takes a very different view which is expressed in the attached document. The ABN Panel is therefore unable to reach a unanimous view and we will expect that the dissenting view is also given full consideration by the Appraisal Committee.	
ABN – comments from single panel member	I have seen and have admired the thoroughness of the PenTAG Report when assessing effectiveness of these agents. Nevertheless, I strongly feel, these drugs have to be put in clinical context and not just considered on cost-effectiveness, where the difference between the drugs is at best marginal. Neither drug is a dramatic advance, but any advance in this condition may be important. With respect to concomitant and adjuvant Temozolomide, I think that NICE current re-assessment is fair. It is not the same, as the Scottish Medicine's Consortium view, but is similar, therefore smoothing out postcode prescribing in the UK.	The committee considers which technologies are a cost effective use of NHS resources. Hence it needs to look beyond just effectiveness NICE arrives at it's decisions by a rigorous process that is different from the SMC. Hence the decisions can be expected to vary.
ABN – comments from single panel member	My real concern is with the NICE recommendation regarding Gliadel. Gliadel has been accepted by Scottish Medicines Consortium, supported by me and others – so I can't not recommend it in England and Wales. I have personal experience of many patients who have been treated with Gliadel and experience of many who have had concomitant and adjuvant Temozolomide. I should say that I have never received any research or personal funding from Link Pharmaceuticals. I have not received any payment for presentations at meetings supported by Link Pharmaceuticals,	Noted.

Comment from	Nature of comment	Response
	therefore no competing interests to declare. The Gliadel RCT, I believe was well designed (and the only placebo controlled trial). The company rather stupidly placed too much emphasis on imaging change which has come back to haunt them.	
ABN – comments from single panel member	a) The effect of local therapies on appearance of gadolinium enhanced scans is uncertain, but most likely most local therapies are associated with higher frequency of local contrast enhancing changes.	Agreed. The committee appreciated this point.
ABN – comments from single panel member	b) The tumours were to be maximally resected. Therefore imaging progression presents at a very early stage. One voxel enhancement increasing to 2 voxels = imaging progression. (compare 4cm mass has to get to >5cm to progress)	Noted. The committee were aware that degree of resection could alter the duration of non-progress clinically determined.
ABN – comments from single panel member	Based on point a), a clinical time to progression endpoint would have been better (Karnofsky Performance Scale and Neurological Performance Scale did favour treatment). The trial showed an approximately 2 month survival advantage, similar to Temozolomide.	Noted.
ABN – comments from single panel member	The survival in the placebo and RT group of Gliadel is similar to the RT alone arm of Temozolomide, therefore one can assume that patients entering both trials are broadly similar. Approximately 16% of Gliadel patients are alive at 2 years vs 26.5% with Concomitant and adjuvant Temodal, but the side effect profile of Gliadel “up front” is hugely less toxic and I remain uncertain of the effect of C+A Temodal on long term survivors.	The trials had differing inclusion and exclusion criteria. The side effect profiles of both interventions and drop out rates are incorporated within the economic model.
ABN – comments	My personal view is that there are cases in our MDT meetings	It is good practice to discuss patients in

Comment from	Nature of comment	Response
from single panel member	where we would favour Gliadel over concomitant and adjuvant Temodal and the median survivals gain are similar. Since we were allowed to prescribe Gliadel, more cases are discussed at MDT meetings prior to surgery (an aim of the NICE Commissioning Guidance). In uncertain cases, patients have more say in their treatment – a tenet of this Government! The drugs are not be used in sequence (e.g. Gliadel then concomitant and adjuvant Temodal), therefore the cost would be similar.	an MDT meeting regardless of the treatments options available – as recommended in the Improving Outcomes Guidance. NICE appraises the cost effectiveness of interventions – patient choice is important but does not improve the cost effectiveness of an intervention.
ABN – comments from single panel member	Essentially banning Gliadel at initial tumour resection, reduces patient's and doctor's options from the onset, works against the value of MDT meetings and is forever, getting rid of an effective treatment. At worst, NICE should negotiate with the makers of Gliadel on a cost reduction to fit into the NICE envelope. It has been done with beta interferons.	The arrangement for beta interferon was made between the manufacturer and the Department of Health.
ABN – comments from single panel member	Finally, NICE's recommendation not to fund effective cancer therapies in patients with malignant glioma in the UK, I believe will prove to be a hurdle for future drug company research in this area, which will result in UK research falling even further behind.	NICE's remit is to issue guidance after consideration of the most cost effective use of NHS resources and not to facilitate clinical research in the NHS.
ABN – comments from single panel member	I have supported the use of Gliadel to the SMC and it would not be correct of me therefore to agree with the ABN recommendation, that it should not be used in England and Wales.	Noted

Comment from	Nature of comment	Response
Brain Tumour UK	**Temozolomide** We welcome the preliminary guidance that this therapy is now recommended for the treatment of newly-diagnosed gliomablastoma multiforme (GBM) in patients with a World Health Organisation (WHO) performance status of 0 or 1. We are pleased that NICE has recognised the limitations of restricting access to Temozolomide to patients assessed as WHO performance status 0, and has therefore extended the therapy to include WHO performance status 1.	Noted
Brain Tumour UK	**Carmustine Implants (Gliadel)** While we embrace the positive recommendation for temozolomide, the decision not to recommend Gliadel is disappointing. The treatment options currently available for brain tumour patients are very limited. Also there appears to be no mention of the following important points regarding Gliadel (carmustine implants):	
Brain Tumour UK	That Gliadel is the only approved chemotherapy treatment that has improved patient survival. As it is licensed to treat both grade 3 and grade 4 gliomas, it can be used for a wider range of patients than other products. Also, it provides the opportunity to give additional treatment to grade 3 gliomas at time of surgery. There is no comparable treatment.	The guidance has been amended (see Section 1.2 and 1.3.
Brain Tumour UK	That Gliadel (to our present knowledge) is the only licensed anti-tumour therapy which can be used between neuro-surgery and radiation treatment against remaining cancer	Noted.

Comment from	Nature of comment	Response
	cells following full or partial re-section	
Brain Tumour UK	That it is administered as a single treatment (during surgery), therefore patients do not need repeated visits to hospital or clinic with the costs (and the patient stress) associated with these visits.	These costs are incorporated in the model.
Cancerbackup	Cancerbackup is pleased that the Appraisal Committee's initial decision is that temozolomide should be recommended for the treatment of newly diagnosed glioblastoma multiforme (GBM) in patients with a World Health Organisation (WHO) status of 0 or 1. Temozolomide can improve survival while improving patients' quality of life, and offers a significant option for a group of patients with few treatments currently available to them.	Noted
Royal College of Nursing	**Temozolomide** We are pleased that NICE has decided to include newly diagnosed patients with GBM with NPS performance status 1 and not limit this to performance status 0 as previously. As generally, patients with GBM do not have NPS performance status 0. It is also difficult a times to distinguish between NPS 0 and 1 and often reflects the clinician's views which may vary from clinician to clinician given their expertise.	The guidance recommends use in patients with a WHO performance status of 0 and 1.
Royal College of Nursing	With reference to Point 4.3.10 and 4.3.21 of the Appraisal Consultation Document, which discusses the difficulties of at times in distinguishing between a grade 3 and 4 HGG and concluded that the guidance for the use of Temozolomide	The difficulties of a histological differentiation of grade 3 and grade 4 glioma was appreciated by the committee. The guidance is in accordance with the

Comment from	Nature of comment	Response
	should apply to grade 4 (GBM) - We are concerned with and have no doubt that this has been discussed in detail, the fact that it is possible for a patient who undergoes a tumour biopsy rather than resection that the histology could be reported as a grade 3 simply because of where the tumour tissue was obtained at biopsy i.e. other parts of the tumour could be a grade 4.	marketing authorisation for temozolomide.
Royal College of Nursing	**Carmustine implants** We have no further comments to submit at this stage on the recommendations relating to the use of carmustine implants for the treatment of newly diagnosed high-grade glioma.	
Samantha Dickson Brain Tumour Trust	**Temozolomide** SDBTT welcomes the revised draft guidance from NICE for patients with newly diagnosed gliomas. We are pleased that Temozolomide (Temodal), within its licensed indications, is now recommended for the treatment of newly diagnosed High Grade Glioma patients with a WHO performance status of 0 or 1	Noted
Samantha Dickson Brain Tumour Trust	**Carmustine Implants (Gliadel wafers)** We are disappointed that Carmustine Implants are not being recommended for use by NICE at the second ACD stage. We would like to put forward the following points for consideration with regard to Carmustine: (i) whether you consider that all the relevant evidence has been taken into account	

Comment from	Nature of comment	Response
	We would like to suggest that when looking at data for median survival and the disease/symptom-free interval, NICE take into account Karnofsky measures and performance measures as well as relying on imaging. Radiological imaging is an insufficient measure for Gliadel as the implants have an effect on the imaging process and imaging results alone can be unreliable and misleading	The committee considered varying definitions of progression free survival and was aware of their implications for the cost effectiveness of the intervention.
Samantha Dickson Brain Tumour Trust	(ii) 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 Patients with grade 3 gliomas (who account for about 25% of newly diagnosed gliomas each year – around 400 people) will have no approved treatment option available to them if Carmustine is not recommended.	The rarity of a condition is not considered by the committee.
Samantha Dickson Brain Tumour Trust	As 72% of patients requiring radical radiotherapy wait longer than the maximum acceptable guideline of 4 weeks, Gliadel can reduce the risks of tumour growth during this period as it starts to kill residual tumour cells after surgery and prior to radiotherapy when no alternative treatment is available. The action of Carmustine lowers the tumour burden for radiotherapy to deal with.	The committee appreciated the fact that overall care, including the timing of radiotherapy, would impact on survival (see FAD section 4.3.5).
Samantha Dickson Brain Tumour Trust	Gliadel treatment is not associated with the risks of systemic toxicity and allows patients to start chemotherapy immediately following surgery.	Noted.
Samantha Dickson	The cost of Gliadel is just over £5,000 per patient. If all	The committee does not consider the

Comment from	Nature of comment	Response
Brain Tumour Trust	patients suitable for Gliadel received the treatment, the cost to the NHS would be around £2 million per annum – a relatively small amount for a treatment which can prolong meaningful quality of life and significantly increase survival rates for an identifiable patient group	rarity of the condition.
Society of British Neurological Surgeons (SBNS)	The SBNS welcomes the new draft recommendation on the use of Temozolomide and Carmustine wafers in the treatment of newly diagnosed high grade gliomas and commends the very thorough approach that NICE have now taken (evaluation document). The Society is pleased to see that the ICER banding has been expanded to include WHO 0 and 1 access to this important treatment and believes that this will provide a much improved framework to manage these difficult tumours. However the Society remains very concerned over a number of issues that are not accurately addressed in the Draft. 1. That the role of resective surgery has been misrepresented 2. The cost benefit analysis of the impact of recurrent treatments is incorrect 3. The appropriate use of the two treatments neglects current experience 4. A number of patients who would fit within the ICER band spread are excluded	
Society of British Neurological	**The role of resective surgery has been misrepresented** Evidence submitted to NICE indicates that where surgeons	The committee heard from a clinical expert during the FAD meeting that

Comment from	Nature of comment	Response
Surgeons (SBNS)	have noted that maximal resection has been achieved the survival including progression free survival, after Carmustine wafers has been greater than that for limited resection. The recent IOG for Brain and CNS tumours has clearly indicated that specialist surgeons in this area using appropriate technology can prospectively identify patients in whom maximal resection is possible and are able to confirm this situation at operation, by virtue of the end operative appearances. Note that the difference in survival with implanted Carmustine wafers, related to resection result, was made in real time but has true value as a surrogate marker for response to Carmustine, even where we are certain that maximal observed excision is almost certainly less than the biological tumour mass. It is also true that analysis of patient records from the Westphal trial that there was very good concordance between surgeons claim of excision and postoperative degree of excision determined by post operative MRI. There is a considerable literature on the relationship between tumour excision and survival. There is however great difficulty in these studies, separating the much greater effects of obligatory post-operative radiation, from the lesser effects of pre-radiation surgery in their contribution to survival. Nonetheless there is considerable data to support the conclusion that tumour mass reduction enhances the effect of chemotherapy. The argument proposed by NICE is that at operation the extent of resection cannot be determined. In practise the degree of resection as determined by post	maximal resection could be reliably and routinely achieved in carefully selected patients. This would be within an MDT and on the basis of preoperative imaging. Maximal resection could then be obtained by an experienced surgeon with access to the requisite technology intraoperatively. The FAD has been amended (see Sections 1.2 and 1.3) The committee was aware of the difference in survival in the maximal resection subgroup and the lack of effectiveness in patients in whom 90% resection could not be achieved. Comment noted. No evidence was provided by the manufacturer of the concordance between surgeon estimated and post operative imaging estimated degree of resection. The FAD has been amended (see Sections 1.2 and 1.3)

Comment from	Nature of comment	Response
Society of British Neurological Surgeons (SBNS)	operative MRI Gadolinium enhancement, although used as a surrogate measure of excision is still only a measure of excision of those elements of the tumour that relate to blood brain barrier disruption and are an under-assessment of tumour excision. No specialist surgeon in this area would argue that they can be 100% sure of biological tumour excision as there is no current way to measure this. They would say with some certainty that a 'maximal' macroscopic excision has been achieved where they can show white matter clearance of the tumour. The evidence from the Westphal study (and the Temozolomide study (Stupp)) is that this is associated with a significant improvement in survival by optimising the response to chemotherapy To argue that surgeons cannot provide a convincing enough consensus to support the criteria of tumour excision is naïve and neglects that across the field of surgery surgical clearance by specialists is providing the basis for cure in many cancers, and a highly predictive marker of survival in others. There are compelling reasons why total of excision in the brain remains impossible: additional morbidity being one of them, absolute definition of the tumour mass being another, but a specialist neurosurgeon can determine when the level of surgical excision defined by the RCT is achieved. Even the recent study by Stummer W (et al.Lancet Oncol. 2006 May;7(5):392-401) using 5 Aminolaevulinic acid in an RCT to relate resection to survival ran into a number of problems with morbidity and times where 5ALA staining bore no relation to Gadolinium enhanced postoperative MRI appearances,	

Comment from	Nature of comment	Response
	nonetheless a benefit in survival was shown. A 19.9% improvement in progression free survival (9.1 -30.7 p<.0003)	
Society of British Neurological Surgeons (SBNS)	**There is no doubt that that the tumour decompression associated with maximal tumour removal as a goal, markedly improves a patient's capacity to withstand the debilitating effects of radiotherapy and contributes extensively to their quality of life and the capacity to reduce long term steroid use. These factors have not been considered by NICE but are of massive importance to patients and their carers and doctors**. Indeed the ability to sustain the Temozolomide course is better in those who have had maximal resections. The SBNS maintains that Surgical excision of glioblastoma is a strong predictive marker of tumour response and disease treatment, and to neglect this is to undermine the efforts embodied in the IOG for Brain and CNS tumours and the declared benefits of surgery in many areas. Although there are particular issues in brain tumour surgery, in the current environment with a priori MDT working a decision can be made prospectively using imaging that a patient is suitable for Carmustine wafers based on the likelihood of maximal excision, and confirmed during operation based on macroscopic clearance. The SBNS would thus support the availability of Carmustine wafers for implantation at surgery under these conditions.	The committee was also convinced that the degree of resection per se could improve survival regardless of any other treatment that the patient underwent.
	The cost benefit analysis of the impact of recurrent treatments is incorrect.	

Comment from	Nature of comment	Response
Society of British Neurological Surgeons (SBNS)	The arguments related to cost benefit based on subsequent treatment are incorrectly argued and are more or less the same or favour Carmustine wafers as compared with Temozolomide. I f patients are going to receive Temozolomide at first diagnosis, they are more likely to be offered PCV at recurrence. If they respond to this they should then have access to Carmustine wafers by virtue of this response as they would be unable to continue systemic treatment with PCV. Similarly patients who have Carmustine at first diagnosis would in principle be offered PCV therapy at first recurrence then Temozolomide when the course is finished or they fail this treatment. They might even be offered Temozolomide early, by virtue of their primary therapy. With application of improved follow-up procedures as detailed in the IOG a higher proportion of patients could belong to each of these pathways. Thus patients receiving Carmustine at first diagnosis (£6,000) might be expected to receive Temozolomide at recurrence (ie for 6/12 equivalent to the adjuvant phase of primary Temozolomide therapy £9,000) whereas patient receiving Temozolomide at first diagnosis (£11,000) followed by Carmustine would incur greater expense (£6,000) ie £17,000 vs £15,000.	Use of carmustine implants at recurrence is currently being appraised by NICE. The use of temozolomide at recurrence is also currently being appraised by NICE. These figures need to be considered together with the effectiveness of the use of these interventions in these settings.
Society of British Neurological Surgeons (SBNS)	**The appropriate use of the two treatments neglects current experience** One considered argument has been whether the SBNS would support the Australian approach to these two treatments in which the responses and differences in use have lead to the proposal that patients under their individual circumstance be	The drop out rate and side effect profile are considered in the economic model for temozolomide.

Comment from	Nature of comment	Response
	able to access either Temozolomide **or** Gliadel (Carmustine Wafers) at this stage in their disease. There is additional logic based on the fact that some patients find the seven and half months of chemotherapy with Temozolomide very onerous and clinically difficult to the extent that >16% fail to complete the adjuvant phase. Indeed our current UK experience involving more patients has shown a greater than expected number of patients with significant bone marrow suppression leading to interruptions and suspension of treatment. The SBNS accepts these comments but believes that the 2year survival for Temozolomide patients is impressive and outperforms Carmustine wafers, to the extent that it should be prioritised over this. However after consideration of individual patient related issues and their capacity to cope with the course of treatment etc, it should be left with the MDT to select the best treatment. There will of course be opportunity cost benefits to PCT's as Gliadel is cheaper than Temozolomide.	
Society of British Neurological Surgeons (SBNS)	**A number of patients who would fit within the ICER band spread are excluded** The SBNS welcomes NICE's response to submissions and the revised Weibull model curve fitting that have resulted in broadening of the sensible cost arguments relating to Temozolomide to WHO 0 and 1. It is also clear that a number of patients of level WHO 2 will also benefit from treatment where their MGMT status favours an enhanced response to Temozolomide. (see evaluation document) This test is becoming more widely available and costs around £100 per	The Committee was informed by consultees that MGMT testing is not routine or standardised. If evidence becomes available of the effectiveness of temozolomide in this sub group of patients the guidance will be reappraised.

Comment from	Nature of comment	Response
	patient. The SBNS would propose that patients who fall into the category of WHO 2 who the MDT feel are likely to benefit from treatment and who satisfy a beneficial MGMT test should have access to Temozolomide so that all patients who have been shown to benefit from the RCT and who would also overlap existing ICER bands used in the latest Draft can gain access to this proven treatment in fair manner without anomalous exclusions.	
NHS Quality Improvement Scotland		
Reviewer 1:	This ACD looks pretty good and I am not sure I have much comment now.	Noted
Reviewer 2:	**Whether you consider that all the relevant evidence has been taken into account.** Yes as far as I can tell, this appears to be do. **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.** Yes appears reasonable. The carmustine implants recommendation differs from the SMC but this appears to be due to new modelling by the Assessment Group– the SMC noted its uncertainty around the economic model. **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.**	Noted Noted

Comment from	Nature of comment	Response
	I would defer a view on current and future practice to clinicians in this area but the evidence appears to be sufficiently robust to prepare guidance.	noted
Reviewer 3:	Essentially I was happy with the decision and have no major comments. I am glad that NICE has listened to the experts	Noted
DOH	Page 43, appendix C, fourth bullet - would it be possible to insert 'in a chair or' before 'in bed'.	This has been amended.
WAG	We are content with the technical detail of the evidence supporting the consultation and have no further comments to make at this stage.	Noted
International Brain Tumour Alliance (IBTA)	We note that decision 1.1 will benefit newly diagnosed high grade glioma patients with PS=0 or PS=1. NICE's acknowledgement that people suffering with high grade malignant brain tumours should be allowed access to this treatment on the NHS is welcomed. However, it should be noted that PS=2 patients were also included in the pivotal RCT and some did benefit from the concomitant therapy. Granted that it is very difficult to make a fine distinction between a person with PS=1 and someone with PS=2, decision 1.1 will penalize that small minority of PS=2 patients who may have benefited.	The use of temozolomide in PS 2 patients was not shown to improve survival for these patients.
International Brain Tumour Alliance (IBTA)	We regret decision 1.2 regarding carmustine implants. In a situation where there are few available therapies, the carmustine implants have the unique advantage of acting against the tumour cells in the period between neurosurgery and the commencement of radiation therapy.	This section has been amended.

Comment from	Nature of comment	Response
	Section 2.6 Adjuvant chemotherapy has become part of standard therapy to an even greater degree in non-UK countries. Multi-modalities are now being studied as possibly being more efficacious than single agents in treating malignant glioma. Therefore, it is vital for patients to be given access to clinically effective treatments.	
International Brain Tumour Alliance (IBTA)	Section 4.11.1 In relation to 4.1.11 (MGMT) it is noted that the initial findings of a correlation between MGMT promoter methylation and effectiveness of temozolomide have not yet been validated and that a study has cautioned in interpreting test results (see PA 23 and PA 25, pps 461-462, Neuro-Oncology, Vol 8, Issue 4, October 2006). This development should be noted in paragraph. 4.1.11 of the FAD so that PCTs are not misled into believing that applicants should be subjected to a test for MGMT promoter methylation before being granted access to temozolomide.	Temozolomide is recommended for patients with PS 0 and/or 1 without regard for their MGMT status.
International Brain Tumour Alliance (IBTA)	Section 6.1 Please see comments above in relation to 4.1.11.	
NHS Professional	I don't understand you key dates. The appraisal was issued on 22.12.06. You ask for comments by 22.12.07 and the second appraisal committee meets on 31.1.07?? Please clarify. I agree with the preliminary recommendations and will	Apologies if there has been a typographical error on the website. The Consultation document was issued on 22.12.06. The deadline for comments

Comment from	Nature of comment	Response
	not be making further comments	was 31.01.07. The Appraisal Committee met again on 21.02.07.
Trustee of brain tumour charity – Ali's Dream	I do not agree with 1.2 which would deny patient choice, particularly in relation to grade three patients who would have no other treatment option	Comments noted. Section 1.2 of the FAD has been amended.
Trustee of brain tumour charity – Ali's Dream	If approval is withdrawn a valuable drug will be lost which may be combined with other therapies in the future	If evidence of effectiveness of regimens containing carmustine implants is forthcoming these will be appraised for use in the NHS
Trustee of brain tumour charity – Ali's Dream	Along with radiation therapy - temozolomide and carmustine wafers represent the first breakthrough in brain tumour treatment in thirty years to deny their use would deter future research in this treatment area	The committee issues guidance based on a consideration of the most cost effective use of NHS resources.
Trustee of brain tumour charity – Ali's Dream	If denied access now hundreds of patients (particularly grade 3) would have lost out on an opportunity for quality of life	Carmustine implants are recommended for patients who have undergone maximal resection as they experience a benefit in terms of improved survival.
Trustee of Charlie	I do not agree with 1.2 which would deny patient choice particularly for grade 3 patients who would have no other treatment option	Comments noted. Section 1.2 of the FAD has been amended.
Trustee of Charlie	If approval is withdrawn a valuable drug which may have been combined with other therapies in the future will have been lost	If evidence of effectiveness of regimens containing carmustine implants is forthcoming these will be appraised for

Comment from	Nature of comment	Response
		use in the NHS
Trustee of Charlie	Along with radiation therapy temozolomide and carmustine implants represent the first breakthrough in brain tumour treatment in 30 years to deny access to gliadel would deter future research in this difficult treatment area.	The committee issues guidance based on a consideration of the most cost effective use of NHS resources.
Trustee of Charlie	If denied access now hundreds of patients will be denied the opportunity for quality of life.	Carmustine implants are recommended for patients who have undergone maximal resection as they experience a benefit in terms of improved survival.
Fundraiser for Charity funding brain tumour research	I do not agree with 1.2 which would deny patient choice particularly for patients with Grade 3 glioma, who would have no other treatment option	Comments noted. Section 1.2 of the FAD has been amended.
Fundraiser for Charity funding brain tumour research	If approval for Gliadel is withdrawn a valuable drug which may have been combined with other therapies in the future will have been lost	If evidence of effectiveness of regimens containing carmustine implants is forthcoming these will be appraised for use in the NHS
Fundraiser for Charity funding brain tumour research	Along with radiation therapy, temozolomide and carmustine implants represent the first breakthrough in brain tumour treatment in 30 years; to deny access to gliadel would deter future research in this difficult treatment area.	The committee issues guidance based on a consideration of the most cost effective use of NHS resources.
Fundraiser for Charity funding brain tumour research	If denied access now, hundreds of patients will be denied the opportunity for a better quality of life.	Carmustine implants are recommended for patients who have undergone maximal resection as they experience a benefit in terms of improved survival.