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

Technology appraisal guidance
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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
1 Guidance

Temozolomide and carmustine implants have been appraised separately for the treatment of newly diagnosed high-grade glioma. On the basis of the evidence presented to the Committee, no recommendation can be made regarding the sequential use of these treatments for newly diagnosed high-grade glioma.

1.1 Temozolomide, within its licensed indications, is recommended as an option for the treatment of newly diagnosed glioblastoma multiforme (GBM) in patients with a World Health Organization (WHO) performance status of 0 or 1.

1.2 Carmustine implants, within their licensed indications, are recommended as an option for the treatment of newly diagnosed high-grade glioma only for patients in whom 90% or more of the tumour has been resected.

1.3 Treatment with carmustine implants should be provided only within specialist centres that in general conform to guidance in 'Improving outcomes for people with brain and other central nervous system tumours' (NICE cancer service guidance 2006), and should be supervised by specialist neurosurgeons who spend at least 50% of their clinical programmed activities in neuro-oncological surgery. The specialists should also have access to:

- multidisciplinary teams to enable preoperative identification of patients in whom maximal resection is likely to be achievable
- magnetic resonance imaging (MRI) to enable preoperative identification of patients in whom maximal resection is likely to be possible, and
- image-directed technology, such as neuronavigation, for use intraoperatively to assist the achievement of maximal resection.

1.4 Carmustine implants are not recommended for the treatment of newly diagnosed high-grade glioma for patients in whom less than 90% of the tumour has been resected.
Clinical need and practice

2.1 Gliomas are the most common type of brain tumour. They develop from the glial cells that support the nerve cells of the brain and spinal cord. There are four main types: astrocytoma, ependymoma, oligodendroglioma and mixed tumours. Gliomas are graded according to their likely rate of growth, from grade 1 (slowest growing) to grade 4 (fastest growing). Grade 3 and 4 gliomas are considered high-grade gliomas. Grade 3 gliomas include anaplastic astrocytoma, anaplastic ependymoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma. Grade 4 gliomas are usually GBM.

2.2 Brain tumours account for fewer than 2% of all primary cancers. Approximately 1860 new cases of malignant glioma are diagnosed in England and Wales each year. High-grade gliomas are more common in men than women, and the incidence increases with age. People diagnosed with GBM are on average older than people diagnosed with grade 3 gliomas.

2.3 Symptoms of high-grade glioma depend on the size, location and degree of infiltration of the tumour. They include headache, nausea, vomiting, seizures, visual disturbance, speech and language problems, and changes in cognitive and/or functional ability. Functional ability of patients can be categorised using scales of performance status, such as the WHO performance status classification (see appendix C for details).

2.4 Approximately 30% of adults with high-grade gliomas survive for at least 1 year, and 13% survive for 5 years. The median survival of patients with anaplastic astrocytoma is around 2–3 years, and that of patients with GBM is approximately 1 year. Age, performance status and tumour histology are indicators of pretreatment prognosis. Patients with high-grade gliomas have a better prognosis if they are younger, have a better performance status, or have a grade 3 tumour.

2.5 Diagnosis of high-grade glioma is provisionally made through a computed tomography (CT) scan or MRI. The diagnosis is then confirmed and the tumour classified histologically, either at the time of surgical resection or by a single-event biopsy if surgery is not possible. There is a growing understanding of the molecular genetics of gliomas, which is allowing a more accurate classification of glioma and may give an indication of prognosis and likely response to treatment.
In the UK, treatment usually consists of surgical resection where possible, followed by radiotherapy. Surgery may achieve either complete resection or partial resection of the tumour. Radiotherapy has been demonstrated to prolong survival and is usually recommended after surgery. Adjuvant chemotherapy is not considered part of standard therapy in the UK, but is used more routinely in the USA. The most frequently used regimens are a combination of procarbazine, lomustine and vincristine (PCV therapy), or single-agent treatment with carmustine or lomustine.
3 The technologies

Carmustine implants

3.1 Carmustine implants (Gliadel, Link Pharmaceuticals) are biodegradable copolymer discs impregnated with an alkylating agent called carmustine. They are about the size of a 5-pence coin, and are implanted into the resection cavity at the time of surgery. Each implant contains 7.7 mg of carmustine, which interacts with DNA, thereby preventing the proliferation of cells.

3.2 Carmustine implants have a UK marketing authorisation for the treatment of newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation, and for the treatment of recurrent GBM as an adjunct to surgery.

3.3 Adverse effects include brain oedema, convulsions, healing abnormalities and intracranial infections. For full details of side effects and contraindications, see the summary of product characteristics.

3.4 The cost of one carmustine implant is £650.38 (excluding VAT; 'British national formulary [BNF]' 52nd edition). Up to eight implants may be used simultaneously, depending on the shape and size of the resection cavity. Costs may vary in different settings because of negotiated procurement discounts.

Temozolomide

3.5 Temozolomide (Temodal, Schering-Plough Ltd) undergoes hydrolysis in the body to produce monomethyl triazenoimidazole carboxamide (MTIC). MTIC is thought to act by methylation of DNA in a way that prevents cell division.

3.6 Temozolomide has a UK marketing authorisation for the treatment of newly diagnosed GBM concomitantly with radiotherapy, and subsequently as monotherapy treatment. It also has a UK marketing authorisation for the treatment of malignant glioma showing recurrence or progression after standard therapy.

3.7 Adverse effects include anorexia, constipation, fatigue, headache, lymphopenia, nausea, neutropenia, thrombocytopenia and vomiting. For full details of side effects and contraindications, see the summary of product characteristics.
3.8 Temozolomide is available as 5 mg, 20 mg, 100 mg and 250 mg tablets. It is administered at 75 mg/m² daily for 42 days concomitantly with radiotherapy (60 Gy administered in 30 fractions), and then as monotherapy at 150 mg/m² daily for 5 days, followed by 23 days without treatment, for a maximum of six cycles. The dose may be increased to 200 mg/m² daily in the second and subsequent cycles.

3.9 The cost of temozolomide is £17.30 for 5 x 5 mg tablets, £69.20 for 5 x 20 mg tablets, £346.00 for 5 x 100 mg tablets and £865.00 for 5 x 250 mg tablets (excluding VAT; BNF 52). Costs may vary in different settings because of negotiated procurement discounts.
4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Group identified two randomised controlled trials (RCTs) that compared the effectiveness of carmustine implants plus radiotherapy with that of placebo plus radiotherapy, and two RCTs of temozolomide plus radiotherapy compared with radiotherapy alone. No studies comparing carmustine implants with temozolomide, or comparing carmustine implants or temozolomide with other antineoplastic agents (for example, the PCV chemotherapy regimen), were identified.

Carmustine implants

4.1.2 The largest RCT of carmustine implants was a multinational trial with a minimum of 12 months' follow-up. Patients with grade 3 and 4 gliomas, aged between 18 and 65 years and with a Karnofsky Performance Status (KPS) score of 60 or higher, were randomised to receive carmustine implants (n = 120) or placebo implants (n = 120). Patients also received radiotherapy at 55–60 Gy administered in 30–33 fractions.

4.1.3 The Assessment Group reported that the Food and Drug Administration (FDA) in the USA expressed several concerns when it evaluated the trial. There was an imbalance between the types of tumours in the study arms, which could have favoured carmustine implants. The FDA requested a review of histological diagnoses and a sensitivity analysis was performed using diagnoses by an alternative pathologist. A further concern was that the manufacturer's analysis treated death as an event when measuring time to progression. A reanalysis was performed of the data on the time to progression as determined by decline of neurological symptoms and performance status, with deaths being censored. In addition, the manufacturer's analysis of the overall survival data included stratification by country, and the data were reanalysed without stratification. The data reported below relate to the unstratified analysis unless otherwise stated.
4.1.4 Median survival was 13.8 months (95% confidence interval [CI] 12.1 to 15.1 months) in the carmustine implant group, and 11.6 months (95% CI 10.2 to 12.7 months) in the placebo group. The Assessment Group reported that the Kaplan–Meier hazard ratio was 0.77 (log-rank statistic: p = 0.08). Based on data from longer-term follow-up (56 months), 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% respectively, and at 36 months survival was 9.2% and 1.7% respectively.

4.1.5 There was no difference in progression-free survival between treatment groups. Median time to progression was 5.9 months (95% CI 4.4 to 8.3 months) in the carmustine implant group and 5.9 months (95% CI 4.7 to 7.4 months) in the placebo group (using stratified analysis). The manufacturer's analysis suggested that both the time to decline of KPS score and the time to progression on neurological indices were statistically significantly improved (that is, increased) in the carmustine implant group. The FDA reanalysis of these data found that there were no statistically significant differences in these measures of progression-free survival and that the differences resulted from variations in survival times between the treatment arms.

4.1.6 In a subgroup of patients with GBM, median survival was 13.5 months (95% CI 11.4 to 14.8 months) in the carmustine implant group and 11.4 months (95% CI 10.2 to 12.6 months) in the placebo group. The Kaplan–Meier hazard ratio was 0.82 (log-rank statistic: p = 0.20). There was no statistically significant difference between treatment groups in progression-free survival for patients with GBM (stratified log-rank test: p = 0.62).

4.1.7 The manufacturer identified a further subgroup of patients, which was not prespecified, with high-grade glioma who had undergone maximal resection, defined as resection of 90% or more of the tumour. This subgroup (n = 111) showed a mean overall survival gain of 4.2 months and a median survival gain of 2.15 months in the carmustine implant group compared with the placebo group (unstratified log-rank analysis: p = 0.0061). The mean gain in progression-free survival was 0.3 months if determined by radiological imaging, 2.6 months measured by time to KPS decline and 3.06 months by time to decline in neurological performance. No statistically significant difference in survival
between the treatment arms was shown for the subgroup of patients in whom maximal resection was not achieved.

4.1.8 In the largest RCT, intracranial hypertension was the only adverse event that had a statistically significantly increased incidence in the carmustine implant group compared with the placebo group (9.2% compared with 1.7%; \( p = 0.02 \)).

4.1.9 The second RCT was based in Scandinavia and had a minimum follow-up of 24 months. The design and inclusion criteria were similar to those for the main RCT of carmustine implants. However, the sample size was smaller (\( n = 32 \)) and recruitment to the study was terminated early, as the investigators were unable to source additional carmustine implants. In this RCT, fewer patients had a diagnosis of GBM in the carmustine implant group (69%) than in the placebo group (100%). Median survival in the carmustine implant group was 13.4 months (full CI not reported), compared with 9.2 months (95% CI 8.7 to 10.4 months) in the placebo group. This difference was statistically significant (log-rank statistic: \( p = 0.01 \)). Survival at 12 months was 62.5% in the carmustine implant group and 18.8% in the placebo group, and at 24 months it was 31.3% and 6.3% respectively (estimates based on censored data). There was no statistically significant difference in progression-free survival between treatment groups.

**Temozolomide**

4.1.10 The inclusion criteria for the largest RCT of temozolomide specified that patients aged 18–70 years with GBM and a WHO performance status of 2 or better (lower) should be randomised after surgery to receive radiotherapy plus temozolomide (\( n = 287 \)) or radiotherapy alone (\( n = 286 \)). Temozolomide was administered in accordance with its UK marketing authorisation. The median age of patients was 56 years (range 19–70 years) in the radiotherapy plus temozolomide group, and 57 years (range 23–71 years) in the radiotherapy alone group. Histological slides from the treatment centres were submitted for central review for a final and definitive diagnosis. The diagnosis of GBM was confirmed at central review in 93% of patients. The proportion of tumours reclassified as grade 3 was similar in both treatment groups. In the radiotherapy plus temozolomide group, tumour removal was complete in 39% of patients and partial in 44%, and biopsy only was possible in 17% of patients. The extent of surgery was similar in the radiotherapy alone group (40% complete, 45% partial...
and 16% biopsy only). Median follow-up time was 28 months. The manufacturer also submitted to NICE 5-year follow-up data from the trial, marked as confidential.

4.1.11 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 alone group. Survival rates at 12 months, based on censored data, were 61.1% for the radiotherapy plus temozolomide group and 50.6% for the radiotherapy alone group. At 24 months, corresponding survival rates were 26.5% and 10.4% respectively. Median time to disease progression was 6.9 months (95% CI 5.8 to 8.2 months) in the radiotherapy plus temozolomide group and 5 months (95% CI 4.2 to 5.5 months) in the radiotherapy alone group.

4.1.12 Retrospective subgroup analyses of patients found to have a methylated O\textsuperscript{6}-methylguanine-DNA methyltransferase (MGMT) promoter and patients with an unmethylated MGMT promoter were conducted. MGMT is an enzyme that repairs DNA damage at a site commonly targeted by cytotoxic drugs, thereby inhibiting the effect of chemotherapy on tumours. MGMT promoter methylation has been associated with extended overall survival and progression-free survival. The methylation status of the MGMT promoter was determined in 106 patients (37%) in the radiotherapy plus temozolomide arm and the MGMT promoter was methylated in 46 of these patients. In the radiotherapy alone arm, MGMT promoter methylation status was determined in 100 (35%) patients and the MGMT promoter was methylated in 46 of these patients. In patients whose tumours had MGMT promoter methylation there was a median survival gain of 6.4 months in the radiotherapy plus temozolomide group compared with radiotherapy alone, and a median progression-free survival gain of 4.4 months. In patients whose tumours did not have MGMT promoter methylation, both median survival gain and median progression-free survival gain were less than 1 month in the radiotherapy plus temozolomide group compared with the radiotherapy alone group, although the gain in progression-free survival was statistically significant in the radiotherapy plus temozolomide group (p = 0.02).

4.1.13 The manufacturer reported the results of a subgroup analysis by extent of tumour resection. For patients who underwent a complete resection, median survival was 18.3 months (95% CI 15.7 to 22.5 months) in the radiotherapy plus...
temozolomide group and 14.2 months (95% CI 12.7 to 16.2 months) in the radiotherapy alone group. For patients who underwent a partial resection, median survival was 13.5 months (95% CI 11.9 to 16.3 months) and 11.7 months (95% CI 9.7 to 13.1 months) respectively.

4.1.14 A subgroup analysis of median overall survival by prognostic factors was published for the largest RCT. For patients under the age of 50 years (n = 172), median survival was 4.2 months greater in the radiotherapy plus temozolomide group compared with the radiotherapy alone group; for patients aged 50 years and over (n = 401) the difference was 1.7 months. The median survival gain from radiotherapy plus temozolomide compared with radiotherapy alone was 4.1 months for patients with a WHO performance status of 0 (n = 223) and 2.1 months for patients with a WHO performance status of 1 (n = 277). For patients with a WHO performance status of 2 (n = 73), median survival was 0.6 months less in the radiotherapy plus temozolomide group than in the radiotherapy alone group. Median overall survival in the radiotherapy plus temozolomide group compared with the radiotherapy alone group was 2.9 months greater for patients who had undergone resection (n = 480) and 1.5 months greater for patients who had undergone biopsy only (n = 93).

4.1.15 Severe myelosuppression (a reduction in the ability of bone marrow to produce blood cells) was reported in 16% of patients in the radiotherapy plus temozolomide group. No cases of severe myelosuppression were reported in the radiotherapy alone group. Of the reported serious (grades 3 and 4) adverse events, fatigue, unspecified constitutional symptoms and infection were statistically significantly more frequent in the radiotherapy plus temozolomide group than in the radiotherapy alone group, as were moderate (grade 2) fatigue, nausea and vomiting, and rash.

4.1.16 The effect of temozolomide on the quality of life of patients was investigated in the largest RCT using a cancer-specific quality-of-life questionnaire. Of seven preselected scales, the only statistically significant difference between treatment groups was in social functioning at the first follow-up during adjuvant treatment with temozolomide (in favour of the radiotherapy alone group).

4.1.17 Another RCT, conducted in Greece, randomised patients to receive radiotherapy plus temozolomide (n = 57) or radiotherapy alone (n = 53). Patients in this RCT generally had a worse prognosis than those in the larger trial. In the
radiotherapy plus temozolomide group, tumour removal was complete in 18% of patients and partial in 40%, and biopsy only was possible in 42% of patients. The extent of surgery in the radiotherapy alone group was 15% complete, 43% partial and 42% biopsy only. Median survival was 13.4 months (95% CI 9.5 to 17.1 months) in the radiotherapy plus temozolomide group and 7.7 months (95% CI 5.3 to 9.2 months) in the radiotherapy alone group. At 12 months, survival was 56.3% in the radiotherapy plus temozolomide group and 15.7% in the radiotherapy alone group, and at 18 months survival was 24.9% and 5.4% respectively (all estimates were calculated on the basis of survival data censored at the relevant time period). Median time to progression was 10.8 months (95% CI 8.1 to 14.7 months) in the radiotherapy plus temozolomide group and 5.2 months (95% CI 3.9 to 7.4 months) in the radiotherapy alone group.

4.2 Cost effectiveness

4.2.1 The manufacturer of carmustine implants submitted an economic model that estimated the cost per quality-adjusted life year (QALY) of carmustine implants plus radiotherapy, compared with placebo plus radiotherapy. The manufacturer of temozolomide submitted a within-trial economic analysis of radiotherapy plus temozolomide compared with radiotherapy alone. The Assessment Group reviewed both manufacturers' analyses. The Assessment Group also constructed their own economic model, which was designed to estimate the cost effectiveness of carmustine implants and the cost effectiveness of temozolomide.

Carmustine implants

4.2.2 The structure of the economic model submitted by the manufacturer for carmustine implants incorporated the assumption that, after surgery, patients experience a constant level of quality of life. This continues until the onset of symptoms, after which time patients experience a constant deterioration in quality of life until death. Data from the largest RCT of carmustine implants were used to estimate survival and time to symptoms (which was estimated from the median time to deterioration in neurological performance scores). It was assumed that the only difference in costs between the two treatment groups was the cost of the implants themselves (mean: 6.54 implants per
A utility value of 0.8 was assumed for patients without symptoms. Costs and QALYs were not discounted.

4.2.3 In the manufacturer's model 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 is £30,000 per additional QALY. The manufacturer of carmustine implants also included cost-effectiveness estimates for radiotherapy plus temozolomide compared with radiotherapy alone (mean ICER: £53,700 per QALY gained) and for the PCV chemotherapy regimen plus radiotherapy compared with radiotherapy alone (mean ICER: £34,200 per QALY gained).

4.2.4 During consultation, the manufacturer provided an illustrative analysis that included costs of chemotherapy at disease recurrence. This was based on the difference between the proportion of patients receiving any active chemotherapy, as well as the difference in the proportion of patients receiving chemotherapy who received temozolomide, between the two arms in the main RCT of temozolomide. The analysis suggested that the ICER for carmustine implants, using these assumptions, would be between £25,500 and £35,500 per QALY gained, depending on the assumptions made about progression-free survival. The manufacturer also provided data on a subgroup of patients who had undergone maximal resection (defined as 90% or more tumour removal). An illustrative analysis for this group of patients suggested that the ICER for carmustine implants would be between £13,000 and £43,300 per QALY gained depending on the assumptions made about progression-free survival and the proportions of patients receiving active chemotherapy on disease recurrence.

4.2.5 The Assessment Group constructed a Markov model to estimate the cost effectiveness of carmustine implants for patients with operable grade 3 and 4 gliomas and a mean age of 55 years. The time horizon for the model was 5 years, and each cycle of the model represented 1 week. Six health states were included in the model: surgery; postoperative recovery; radiotherapy; stable disease; progression; and death. Patients surviving the postoperative recovery period were assumed to undergo a course of radiotherapy at 60 Gy fractions (five
fractions per week) for a maximum of 6 weeks. Based on clinical specialist advice, the model reflected that 70% of patients would receive treatment with PCV on disease progression. Aside from perioperative mortality, the risk of death in the model was considered to be time dependent rather than state dependent. Health-related utility values were elicited from 93 members of the general population, and were based on scenarios developed by the Assessment Group describing various states of health of people with glioma. Patients in the progressive disease state were assumed to experience constant deterioration in quality of life (modelled as a reduction of health-related utility of 0.5% per week). Resource-use and cost data were taken from the published literature, manufacturer submissions and expert opinion. Costs were discounted at 6% and benefits at 1.5%. A range of one-way sensitivity analyses were conducted, as well as a probabilistic simulation.

4.2.6 The manufacturer provided patient-level data to the Assessment Group from the main RCT of carmustine implants. The curve fitted to the data was extrapolated in a straight line beyond 2 years. In the Assessment Group model, the base-case analysis comparing carmustine implants with placebo indicated that the mean incremental costs of carmustine implants were £6632 and mean QALYs gained were 0.122. The incremental cost per QALY gained was £54,500, with a probability of 0.11 of carmustine implants being cost effective at a threshold of £30,000 per additional QALY gained, and a probability of 0 of being cost effective at a threshold of £20,000 per additional QALY gained. The one-way sensitivity analyses suggested that the model was most sensitive to changes in overall survival gain, progression-free survival, the risk of death due to surgery and the cost of carmustine implants. The results of a sensitivity analysis using alternative assumptions to reflect the decline in quality of life after disease progression found that the ICERS varied between £39,000 (no decline) and £79,900 per QALY gained. The sensitivity analysis that assumed a slow initial deterioration followed by a more rapid decline showed that the ICER was £59,600 per QALY gained.

4.2.7 During the course of the appraisal, the price of carmustine implants decreased by about 5% (from £687.50 per implant to £650.38). Using the new price in the Assessment Group's model resulted in a decrease in the base-case ICER to £52,500 per QALY gained (from £54,500).
4.2.8 The Assessment Group conducted additional analyses of the cost effectiveness of carmustine implants in subgroups of patients using different measures of disease progression based on data from the largest RCT. The ICER was £36,100 per QALY gained when time to decline in functional status was used to estimate progression-free survival, and £29,700 per QALY gained when time to decline in neurological performance was used to define disease progression. In a subgroup of patients who had undergone maximal resection, defined as removal of 90% or more of the tumour, the ICER was £45,100 per QALY gained when the base-case assumptions were used in the analysis. The ICER for this subgroup was £20,600 per QALY gained when time to decline in neurological performance was used to estimate progression-free survival and £23,100 per QALY gained when time to decline in functional status was used. In the subgroup of patients with GBM who had undergone maximal resection, the ICER was £51,900 per QALY gained when the base-case assumptions were used in the analysis. A threshold analysis revealed that for the ICER to drop below £30,000 per additional QALY gained, the median gain in progression-free survival, regardless of how it is defined, would have to be about 8 weeks.

Temozolomide

4.2.9 The economic evaluation submitted by the manufacturer of temozolomide was based on the largest RCT of temozolomide. Resource-use data were collected for a subgroup of 224 patients during the original trial. Data included the number of radiotherapy sessions, details of temozolomide cycles and dosages, concomitant medications, laboratory tests, hospitalisations due to serious adverse events, and the frequency of serious toxicity-related events. Health benefits were expressed in terms of life years gained based on data from the largest RCT. Costs and life years gained were discounted at 3.5%.

4.2.10 The manufacturer of temozolomide presented two analyses, one based on the subgroup for which resource-use data had been collected, and the other based on extrapolating these data to the full trial cohort. In addition, two methods of estimating survival were used: one included survival to 2 years post randomisation only, and the other extrapolated from time of randomisation until death. Base-case results with extrapolated survival were ICERs of £11,000 per life year gained with temozolomide for the full trial cohort and £19,200 per life year gained with temozolomide for the subgroup with resource-use data. For the analysis restricted to 2 years post randomisation, the corresponding ICERs
were £19,400 per life year gained for the full trial cohort and £33,600 per life year gained for the subgroup with resource-use data.

4.2.11 The Assessment Group's model to estimate the cost effectiveness of temozolomide was the same as that used for carmustine implants (as described in section 4.2.6). Survival was calculated by fitting a Weibull curve to the overall survival curve from the largest RCT of temozolomide. The fitting of the curve to the trial progression-free survival data was improved by fitting two curves to the trial data: one up to 12 months and one 12 months and beyond.

4.2.12 In the Assessment Group's base-case analysis of radiotherapy plus temozolomide compared with radiotherapy alone, the mean incremental cost of temozolomide plus radiotherapy was £7788 and mean QALYs gained were 0.217. The additional cost per QALY gained for temozolomide was £35,800. There was a probability of 0.23 of temozolomide being cost effective at a threshold of £30,000 per additional QALY gained, and a probability of 0 at a threshold of £20,000 per additional QALY gained. The one-way sensitivity analyses showed that the model was most sensitive to survival gain and progression-free survival.

4.2.13 The Assessment Group conducted an additional economic analysis to explore the effects on disease progression of different assumptions about the treatment received by patients. Based on data from the largest RCT, 58% of patients previously receiving radiotherapy plus temozolomide and 72% of patients receiving radiotherapy alone were assumed to receive chemotherapy on disease progression. Of these patients, 25% who had received temozolomide as part of their first-line therapy and 60% who had received radiotherapy alone were assumed to receive temozolomide as part of second-line treatment; the remainder were assumed to receive PCV. Based on these data, the ICER per QALY gained was £25,300. An alternative analysis was conducted to reflect NICE guidance in 'Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer)' (NICE technology appraisal guidance 23). This analysis assumed that chemotherapy on disease recurrence would be with PCV, and that subsequent chemotherapy would be with temozolomide for patients who had not received it as part of first-line treatment and with PCV for those who had. Based on these data, the ICER per QALY gained was £35,700.
4.2.14 The Assessment Group also conducted additional analyses based on the overall survival estimates from the subgroup analysis of the largest RCT of temozolomide. The ICER per QALY gained was £24,700 for patients aged below 50 years, £38,500 for patients who had undergone resection, £26,400 for patients with a WHO performance status of 0, and £64,700 for patients with a WHO performance status of 1. Incorporating the costs associated with chemotherapy on disease progression, based on data from the largest RCT of temozolomide (see section 4.2.13), the ICERs for these subgroups were £17,300 per QALY gained for patients aged below 50 years, £27,500 per QALY gained for patients who had undergone resection, £19,000 per QALY gained for patients with a WHO performance status of 0, and £47,200 per QALY gained for patients with a WHO performance status of 1. After incorporating the costs associated with chemotherapy on disease progression, based on NICE guidance on the use of temozolomide for the treatment of recurrent glioma (NICE technology appraisal guidance 23; also see section 4.2.13 of this document), the ICERs for these subgroups ranged from £24,700 to £63,100 per QALY gained.

4.2.15 The Assessment Group reported an assessment of the 5-year follow-up data from the RCT of temozolomide supplied by the manufacturer. It noted that there had been few additional events since the last reported follow-up. The Assessment Group also noted that the updated hazard ratio was similar to that reported previously. The Assessment Group commented that it was considered inappropriate to fit curves to the 5-year survival curves because the tails of the curves were flat. The Assessment Group also reported that the 5-year data would not substantially change the cost effectiveness of temozolomide.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma, having considered evidence on the nature of the condition and the value placed on the benefits of carmustine implants and temozolomide by people with high-grade glioma and their carers, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee was mindful when considering the use of carmustine implants and temozolomide as initial therapy for newly diagnosed high-grade glioma that
this disease has a very poor prognosis despite various treatments being available.

4.3.3 The Committee considered evidence from clinical specialists and carers that glioma has a considerable impact on patients' quality of life. It understood that although the disease may respond to early treatment, most patients experience a rapid decline once progression of disease has occurred. However, the Committee was also aware that the rate of deterioration in quality of life will vary between patients and will depend on the location of the tumour and the rate of progression. The Committee was persuaded that the quality of life of patients is paramount, especially during the period after initial diagnosis and treatment, before further progression occurs.

4.3.4 The Committee acknowledged the difficulty in measuring disease progression in patients with glioma. It considered evidence from clinical specialists that the estimation of progression-free survival using imaging techniques is influenced by the frequency with which the imaging is conducted, and may not correlate with neurological or functional status or with the patient's perception of their quality of life. It also considered that the use of measures of functional status can be problematic due to the variable impact of tumour progression on physical and cognitive functioning.

4.3.5 The Committee considered testimony from clinical specialists that, on average, patients in the control arms of the largest RCT for carmustine implants and the largest RCT for temozolomide survived longer than is currently the norm in UK clinical practice. It was also mindful that carmustine implants and temozolomide are part of mixed treatment regimens given as adjunct specifically to surgery and radiotherapy. The Committee concluded, on the basis of the clinical specialists' testimony, that it is necessary to optimise both the timing and the duration of radiotherapy, with or without prior surgical treatment, to achieve the best results for all patients with glioma irrespective of the use of other therapies.

4.3.6 The Committee considered the clinical specialists' testimony that there was evidence from a meta-analysis of RCTs suggesting a small benefit from chemotherapy with the PCV regimen. However, it acknowledged that the magnitude of this benefit was small and that there are significant toxicities associated with the PCV regimen. It was aware that a trial comparing the
efficacy and toxicity of temozolomide and PCV in patients with recurrent glioma was ongoing, and that there were no trials comparing carmustine implants with other chemotherapy regimens such as PCV.

Carmustine implants

4.3.7 The Committee considered the evidence on the clinical effectiveness of carmustine implants. It acknowledged that the RCTs showed a gain in mean overall survival with carmustine implants. The Committee also carefully considered the concerns expressed by the FDA and the Assessment Group about the analysis of the largest RCT of the use of carmustine implants, specifically the different approaches to stratification of the data. The Committee discussed in detail the major issues raised by the FDA in their critique, namely the stratification of results by country, the alternative approaches to censoring of the data on progression-free survival, and the degree of overlap between grade 3 and grade 4 gliomas in the trial population.

4.3.8 The Committee acknowledged that stratification by country was included in the original statistical analysis plan for the RCT and that the unstratified analysis of long-term survival demonstrated a statistically significant difference in favour of carmustine implants. The Committee concluded that the analysis including stratification by country was appropriate. It was persuaded that the evidence suggested a small but statistically significant benefit in overall survival with carmustine implants.

4.3.9 The Committee was mindful that although the largest RCT of carmustine implants did not show any gain in progression-free survival when this was measured using imaging techniques, there was evidence that time to functional decline was increased, and the manufacturer's analysis of time to neurological decline showed a statistically significant benefit in favour of carmustine implants. The Committee was aware that the analysis conducted by the FDA of time to neurological or functional decline failed to show a statistically significant benefit of carmustine implants, but accepted that the manufacturer's approach of including deaths as events was appropriate.

4.3.10 The Committee discussed the reported difficulties of making a definitive pathological diagnosis of high-grade glioma, in particular in distinguishing between grade 3 and grade 4 tumours. The Committee noted the concern
expressed by the FDA that there was a slightly higher proportion of patients with grade 4 gliomas in the placebo group than in the carmustine implant group. It also noted that this imbalance was increased when the histological data were reviewed by an alternative pathologist at the request of the FDA. However, the Committee was persuaded that it was appropriate to consider the pragmatic evidence on pathological diagnosis 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. The Committee was also aware of the wording of the marketing authorisation for carmustine implants, which refers to 'high-grade' glioma, and concluded that guidance on the use of this technology should relate to this category of tumour alone.

4.3.11 The Committee considered the evidence on the cost effectiveness of carmustine implants. The Committee was aware that the main drivers of the economic model submitted by the manufacturer of carmustine implants were the difference in progression-free survival and the incremental costs of treatment. It was mindful of the difficulty of measuring progression-free survival, as described in section 4.3.4, and noted that progression-free survival in the manufacturer's model was based on the time to decline in neurological symptoms using data from the largest RCT of carmustine implants. In addition, the Committee noted that the manufacturer's economic model included in their initial submission considered only the costs associated with the implants themselves and did not include all other costs associated with treating high-grade glioma.

4.3.12 The Committee considered the assumptions adopted in the Assessment Group's economic model. It noted that the model included an assumption that the probability of death was based on the length of survival, and not on whether the patient's disease had progressed. The Committee was aware that the probability of death increases significantly on tumour progression and that death may occur very soon after disease progression. It accepted that the Assessment Group's assumption enabled the model to use data on overall survival from the RCT. It was also aware that a sensitivity analysis demonstrated that the model was not sensitive to this time-dependency assumption. It also concluded that the results of the sensitivity analyses showed that the overall survival gain from treatment would have to increase considerably for the ICERs to decrease substantially. The Committee considered all the analyses submitted by the manufacturer of carmustine implants and the Assessment Group. It
concluded that the economic analysis of carmustine implants submitted by the Assessment Group was the most appropriate. This was because estimates of survival were based on measures of overall survival from the largest RCT and included all the relevant costs of treating patients with high-grade glioma.

4.3.13 The Committee discussed how the costs of treatment on disease progression should be included in the economic evaluation of carmustine implants. The manufacturer’s initial approach of not including additional healthcare costs during any survival gain and the omission of all costs other than the acquisition cost of the technology under appraisal was considered inappropriate. The Committee considered whether patients who receive carmustine implants at initial resection would receive less active chemotherapy on disease recurrence. It noted that there was no evidence to support this. It also considered the testimonies from clinical specialists that a potential benefit of carmustine implants is that temozolomide could be used to treat disease recurrence. It therefore rejected the manufacturer’s suggestion that the costs of treating disease progression should be based on data from the RCT of temozolomide. It concluded that the Assessment Group's approach to the inclusion of costs was the most appropriate.

4.3.14 The Committee discussed the results of the Assessment Group's additional analyses that included alternative measures of disease progression. The Committee carefully considered which measure of progression-free survival was most appropriate for inclusion in the economic analysis. It noted that progression-free survival in the Assessment Group's model was based on the composite measure of imaging and clinical assessment from the main RCT. It considered the suggestion from the manufacturer that alternative measures of functional status and neurological performance should be used to represent progression-free survival in the model. It was aware that the largest RCT of carmustine implants had demonstrated a benefit in progression-free survival using measures of functional status, but no benefit when using measures based on neurological imaging. The Committee was mindful that the measure of neurological performance decline was not based on a validated instrument. However, it was satisfied that the KPS measure of functional status is widely accepted and used. It was also aware that the confidence intervals around the mean time to decline of functional status in the RCT demonstrated considerable uncertainty around the benefit from carmustine implants. The Committee was mindful that patients could have experienced a period of clinical decline before
reaching the endpoint of functional status decline as defined in the trial. The Committee concluded that the ICERs remained high for the whole study population when these alternative measures of progression-free survival were used in the analysis and were also subject to considerable uncertainty.

4.3.15 The Committee considered whether there might be subgroups of patients for whom the use of carmustine implants would be more clinically effective and cost effective. This included consideration of the subgroup analyses that were suggested by the manufacturer. Of these subgroup analyses, the analysis based on the completeness of surgical resection of the tumour was not pre-specified.

4.3.16 The Committee considered the potential imbalance in tumour types between treatment arms in the main RCT. It noted that the analysis of the study population when patients with a histological diagnosis of grade 3 glioma were excluded (that is, relating to grade 4 tumours only) had little effect on estimates of overall survival. It accepted that the pragmatic results of the principal RCT were a sufficient basis for making a decision on the overall clinical and cost effectiveness of the use of carmustine implants within the licensed indication for newly diagnosed high-grade glioma.

4.3.17 The Committee considered data from an analysis of overall survival submitted by the manufacturer for subgroups defined by the extent of tumour resection. The Committee was persuaded that tumour resectability per se could be an important indicator of prognosis and possibly treatment effect, and that achieving maximal resection produced the best survival results regardless of any other concurrent or adjuvant treatment. It accepted that there was a gain in mean overall survival for patients who had undergone maximal resection (defined as removal of 90% or more of the tumour). The Committee was aware that the subgroup analysis had not been prespecified in the analysis plan for the trial, but was persuaded by the testimony from clinical specialists that the survival gain in this subgroup had biological plausibility. The Committee also noted that the subgroup analysis provided by the manufacturer showed that carmustine implants provided no benefit in either overall survival or progression-free survival for patients in whom 90% or more tumour resection had not been possible. The Committee concluded, therefore, that accurate intraoperative assessment of maximal resection of the tumour was essential in order to achieve clinical effectiveness from the use of carmustine implants.
4.3.18 The Committee was aware of NICE guidance on 'Improving outcomes for people with brain and other central nervous system tumours' (NICE cancer service guidance 2006). This guideline recommends that the care of patients with brain tumours should be coordinated through a specific model of multidisciplinary assessment and care, and should include a specialist neurosurgeon who spends at least 50% of their clinical programmed activities in neuro-oncological surgery. The Committee heard from the clinical specialists that the health outcomes of patients treated with carmustine implants would be improved if care was provided in accordance with this cancer service guideline. It concluded that carmustine implants should be provided only by neurosurgeons experienced in this type of neuro-oncological surgery at specialist centres.

4.3.19 The Committee considered that quantifying the extent of resection is very difficult and open to considerable uncertainty. However, it was persuaded by the clinical specialists and consultees representing neurosurgeons that maximal resection can be routinely achieved in patients carefully selected on the basis of preoperative imaging, and that resection can be confirmed intraoperatively on a clinical basis, supported by the use of technology that is routinely available in the UK. The Committee was aware that intraoperative MRI is accurate in defining the extent of resection and is considered the gold standard for this purpose, but that this is not routinely available. The Committee heard that other procedures, including neuronavigation and cortical mapping, can assist in ensuring that maximal resection has been achieved when used intraoperatively by experienced neurosurgeons. The Committee was persuaded that, in order to ensure that maximal resection is achieved intraoperatively, as predicted by preoperative assessment, the care of patients with high-grade glioma would need to take place in specialist units with appropriate expertise. The Committee considered that specialist centres could establish audit criteria to confirm that maximal resection had been achieved using comparisons of preoperative and postoperative MRI.

4.3.20 The Committee noted that the ICER from the Assessment Group's economic analysis based on measures of functional status was £23,100 per QALY gained in the subgroup of patients in whom 90% or more tumour resection had been achieved. It concluded that carmustine implants would be cost effective for this subgroup of patients. The Committee noted that the extent of tumour resection as defined in the RCT was judged retrospectively on postoperative imaging. Additionally, it noted that surgeons also made an estimate of the extent of
resection at the end of the surgical procedure, but this was not reported in the published effectiveness analysis of the trial. The subgroup analysis based on the neurosurgeons' estimates of resection suggested that there was a significant increase in progression-free survival in those patients in whom 90% or more of the tumour had been resected. The Committee noted the evidence that there was no benefit in overall survival from carmustine implants unless maximal resection had been achieved, and therefore concluded that carmustine implants should not be recommended for patients in whom less than 90% resection of the tumour had been achieved.

4.3.21 In summary, the Committee noted that the largest RCT of carmustine implants showed a statistically significant benefit in overall survival. It also acknowledged that by using some measures of functional status, progression-free survival was significantly prolonged. The Committee accepted that the subgroup of patients who had undergone maximal resection of the tumour, defined as 90% or more resection, experienced a significantly improved survival compared with the subgroup whose tumours were resected by less than 90%, in whom no survival benefit was demonstrable. The Committee concluded that, in order to be confident that this degree of resection is achievable on a routine basis, patients should undergo surgery only at specialist centres that have staff with the appropriate skills and experience. This includes access to intraoperative measurement techniques that aid the neurosurgeon in judging the extent of resection. In this maximal resection subgroup of patients, the Committee concluded that carmustine implants represent a cost-effective use of NHS resources.

Temozolomide

4.3.22 The Committee considered the evidence on the clinical effectiveness of temozolomide. It noted that the RCTs demonstrated a gain in progression-free survival and overall survival. Acknowledging the difficulties in measuring disease progression using either imaging or measures of functional status (noted in section 4.3.4), the Committee was persuaded that the measures of progression using imaging in the principal temozolomide trial were appropriate, and that it was likely that these would have underestimated the delay to functional progression in the patients being treated.
As noted in section 4.3.10, the Committee was aware of the reported difficulties in making a definitive pathological diagnosis of high-grade glioma, in particular in distinguishing between grade 3 and grade 4 tumours. It was, however, persuaded that it was appropriate to consider the pragmatic evidence on pathological diagnosis from the temozolomide RCTs as a reflection of the realities of current clinical practice. The Committee was also aware of the wording of the marketing authorisation for temozolomide, which refers specifically to the GBM type of newly diagnosed high-grade glioma, and concluded that guidance on the use of this technology should relate to this category of tumour alone.

The Committee considered the evidence on the cost effectiveness of temozolomide. It noted that the economic evaluation submitted by the manufacturer of temozolomide expressed health outcomes in life years gained. Noting that glioma can have a considerable impact on patients' quality of life, which may deteriorate rapidly on disease progression, the Committee concluded that the assessment of cost effectiveness should incorporate the effects of the disease and treatment on quality of life in addition to survival. The Committee noted the results of the study that demonstrated that the side effects of temozolomide had little impact on patients' health-related quality of life. It also noted that the Assessment Group's model included a reduction in health-related utility due to side effects of temozolomide. The Committee considered that this reduction in utility was small and that it had only a marginal effect on the cost effectiveness of temozolomide as expressed in the Assessment Group's analysis. The Committee therefore concluded that the economic analysis of temozolomide submitted by the Assessment Group was the most appropriate because it incorporated an estimate of the effect of the disease on health-related quality of life.

The Committee noted that its considerations of the assumptions adopted in the Assessment Group's economic model reported in section 4.3.12 would also apply to temozolomide. The Committee considered the Assessment Group's approach to the inclusion of survival data from the RCT into the model and concluded that the general approach was appropriate.

The Committee understood that the choice of treatment for high-grade glioma used on disease progression after initial therapy with temozolomide could affect the results of the cost-effectiveness analysis. The Committee also
considered testimony from clinical specialists that there is considerable uncertainty about the appropriate treatment for patients whose disease progresses after chemotherapy following initial diagnosis. It therefore considered carefully the additional analyses conducted by the Assessment Group and the statements from consultees on this issue. The Committee noted that the ICER was £25,300 per QALY gained for the whole RCT cohort when the analysis included the proportional use of different kinds of chemotherapy after disease progression based on data from the largest RCT of temozolomide. It acknowledged that this pattern of treatment informed the estimates of treatment effect included in the model. The Committee was mindful that the data from this RCT did not reflect NICE guidance on the use of temozolomide for the treatment of recurrent glioma (NICE technology appraisal guidance 23), which recommends treatment with temozolomide only after failure of first-line chemotherapy. It also noted the lack of evidence on the effectiveness of temozolomide for treatment of high-grade glioma after disease progression in patients who have received temozolomide as part of first-line therapy. The Committee considered that the use of temozolomide as part of initial treatment may lead to a reduction in the use of active chemotherapy, particularly with temozolomide, on disease progression. It concluded that taking this into account in the analysis would improve the estimates of the cost effectiveness of temozolomide.

4.3.27 The Committee considered the long-term follow-up data (up to 5 years) from the main RCT of temozolomide. The Committee discussed how the long-term data should be incorporated into the analysis. It noted that the estimate of treatment effect measured by the hazard ratio took into account all the data reported in the long-term follow up. The Committee noted that the estimate of treatment effect was similar to that demonstrated in the original trial report. The Committee noted that the Assessment Group’s economic analysis was truncated at 5 years, but the long-term results of the trial showed that a small proportion of patients in both treatment arms were alive at 5 years of follow-up. It considered that this may have resulted in an underestimation of the survival gain from temozolomide, and concluded that temozolomide may be more cost effective than indicated in the Assessment Group’s base-case analysis.

4.3.28 The Committee considered the evidence relating to the use of temozolomide in specific subgroups. It noted that the evidence from the largest RCT suggested that the survival gain from radiotherapy plus temozolomide compared with that
from radiotherapy alone was higher for patients with a WHO performance status of 0 and for patients under the age of 50 years. The Committee noted that it was not possible to assess the extent to which age and performance status were related as predictors of response to temozolomide. The Committee concluded that it was appropriate only to consider subgroups defined by performance status.

4.3.29 The Committee noted that the Assessment Group’s economic analysis showed a substantial difference in the estimates of cost effectiveness of temozolomide for patients with a WHO performance status of 0 and patients with a WHO performance status of 1. It considered the comments from consultees about the difficulty of distinguishing between performance status levels 0 and 1. The Committee was mindful that the main RCT of temozolomide had stratified patients by performance status and had presented results for these groups separately. The Committee considered the uncertainty around the treatment effects for these two subgroups and noted that the confidence intervals overlapped. It heard from the Assessment Group that if this uncertainty was taken into account in the economic analysis, confidence intervals around the ICERs were likely to overlap. The Committee concluded that it was not appropriate to distinguish between these two subgroups, and that the use of temozolomide for the treatment of patients with a WHO performance status of 0 or 1 represents an appropriate use of NHS resources.

4.3.30 The Committee considered the use of temozolomide in patients with a WHO performance status of 2. It heard from clinical specialists that patients with a performance status of 2 would not be routinely treated with temozolomide. It noted that patients with a performance status of 2 who had received temozolomide in the main RCT survived for a shorter time than those who did not receive temozolomide. The Committee concluded that temozolomide should not be recommended for the treatment of patients with a WHO performance status of 2.

4.3.31 The Committee was mindful that people with high-grade glioma have a relatively short life span, and that chemotherapy regimens used previously have not conclusively demonstrated a benefit in quality of life and survival. The Committee considered that the RCT evidence for temozolomide had demonstrated an improvement in overall survival in patients with high-grade glioma and, most importantly, an increase in progression-free survival, during
which patients' quality of life was usually maintained. The Committee concluded that temozolomide, for the treatment of newly diagnosed high-grade glioma in patients with a WHO performance status of 0 or 1, represents a cost-effective use of NHS resources.

Consideration of carmustine implants and temozolomide for use in children

4.3.32 The Committee was mindful that glioma affects people of all ages, including children, but that the RCT and economic evidence related to the use of the technologies in adults. The Committee accepted that this evidence would also be likely to apply to children. It concluded that the issues about clinical effectiveness and cost effectiveness outlined above are also relevant to the use of the technologies, in accordance with their marketing authorisations, for the treatment of high-grade glioma in children.
5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in ‘Standards for better health’ issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 ‘Healthcare Standards for Wales’ was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has newly diagnosed high-grade glioma and the doctor responsible for their care thinks that carmustine implants and temozolomide are the right treatments, they should be available for use, in line with NICE’s recommendations.

5.4 NICE has developed tools to help organisations implement this guidance (listed below).

- Local costing template incorporating a costing report to estimate the savings and costs associated with implementation.
- Audit criteria to monitor local practice.
6 Recommendations for further research

6.1 The Committee noted that a large trial is planned that will compare low-dose temozolomide with dose-intense temozolomide, and that this trial is expected to include stratification of patients by MGMT promoter methylation status.

6.2 The Committee noted that there was an ongoing trial comparing PCV therapy with temozolomide in the treatment of recurrent high-grade glioma.

6.3 The Committee recommended that specialist centres should establish audit criteria to confirm that maximal resection of 90% or more has been achieved using comparisons of preoperative and postoperative MRI.
7 Related NICE guidance

Improving outcomes for people with brain and other central nervous system tumours. NICE cancer service guidance (2006).

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technologies should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on these technologies will be considered for review in 2015.

Andrew Dillon
Chief Executive
June 2007
Appendix A. Appraisal Committee members, guideline representative and NICE project team

A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam
Radiologist, St George's Hospital, London

Professor A E Ades
MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Amanda Adler
Consultant Physician, Addenbrooke's Hospital, Cambridge

Dr Tom Aslan
General Practitioner, Stockwell, London

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain
Lay member
Professor Karl Claxton
Professor of Health Economics, University of York

Dr Richard Cookson
Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice, University of East Anglia

Mrs Fiona Duncan
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital

Professor Christopher Eccleston
Director, Pain Management Unit, University of Bath

Dr Paul Ewings
Statistician, Taunton and Somerset NHS Trust

Professor John Geddes
Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston
Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin
Health Outcomes Manager, Johnson & Johnson Medical Ltd

Ms Linda Hands
Consultant Surgeon, John Radcliffe Hospital, Oxford

Dr Elizabeth Haxby
Lead Clinician in Clinical Risk Management, Royal Brompton Hospital

Dr Rowan Hillson
Consultant Physician, Diabeticare, The Hillingdon Hospital

Dr Catherine Jackson
Clinical Senior Lecturer in Primary Care Medicine, University of Dundee
The following individual, representing the National Collaborating Centre responsible for developing NICE’s cancer service guidelines, was invited to attend all Appraisal Committee meetings to observe and to contribute as an adviser to the Committee.

- Dr Fergus Macbeth, Director, National Collaborating Centre for Cancer

**C NICE project team**

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Elangovan Gajraj**
Technical Lead

**Louise Longworth**
Technical Adviser

**Alana Miller**
Project Manager
Appendix B. Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by Peninsula Technology Assessment Group (PenTAG), Peninsula Medical School, Wessex Institute for Health Research and Development, University of Southampton.


B. The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope. Organisations listed in I and II were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I) Manufacturers/sponsors:

- Link Pharmaceuticals Ltd
- Schering-Plough Ltd

II) Professional/specialist and patient/carer groups:

- Association of British Neurologists
- Brain and Spine Foundation
- British Brain Tumour Association
- British Oncological Association
- British Oncology Pharmacy Association
- British Psychosocial Oncology Society
- Cancerbackup
- Cancer Research UK
- Cancer Voices
- Denbighshire Local Health Board
- Department of Health
• Gedling PCT
• Long-Term Medical Conditions Alliance
• Macmillan Cancer Relief
• Marie Curie Cancer Care
• National Cancer Alliance
• National Council for Hospice and Specialist Palliative Care Services
• National Hospital for Neurology and Neurosurgery
• Neurological Alliance
• Royal College of General Practitioners
• Royal College of Nursing
• Royal College of Physicians’ Medical Oncology Joint Special Committee
• Royal College of Radiologists
• Royal College of Surgeons
• Royal Pharmaceutical Society
• Samantha Dickson Research Trust
• Society of British Neurological Surgeons
• Tenovus Cancer Information Centre
• UK Brain Tumour Society
• Welsh Assembly Government

III) Commentator organisations (without the right of appeal):

• Board of Community Health Councils in Wales
• Bristol-Myers Squibb Pharmaceuticals Ltd
• British National Formulary
C. The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Michael Brada, Professor of Clinical Oncology Institute of Cancer Research, nominated by the Institute of Cancer Research – clinical specialist
- Professor Garth Cruickshank, Consultant Neurosurgeon, Society of British Neurological Surgeons, nominated by the Society of British Neurological Surgeons – clinical specialist
- Dr Jeremy Rees, Consultant Neurologist, Institute of Neurology, nominated by the Association of British Neurologists – clinical specialist
• Professor David Walker, Professor of Paediatric Oncology, Queen's Medical Centre, nominated by UK Brain Tumour Society – clinical specialist

• Mr. Colin Watts, Clinical Scientist and Consultant Neurosurgeon, Cambridge University, nominated by the Society of British Neurological Surgeons – clinical specialist

• Mrs Tina Mitchell, Chairman, Hammer Out (Brain Tumours), nominated by Brain and Spine Foundation – patient expert

• Ms Jane Redman, nominated by the Samantha Dickson Research Trust – patient expert
Appendix C. WHO performance status classification

The WHO performance status classification categorises patients as:

- 0: able to carry out all normal activity without restriction
- 1: restricted in strenuous activity but ambulatory and able to carry out light work
- 2: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
- 3: symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden
- 4: completely disabled; cannot carry out any self-care; totally confined to bed or chair.
Changes after publication

March 2014: implementation section updated to clarify that carmustine implants and temozolomide are recommended options for treating newly diagnosed high-grade glioma. Additional minor maintenance update also carried out.

March 2012: minor maintenance
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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