NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final Appraisal Determination

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

1 Guidance

1.1 Temozolomide is recommended for the treatment of newly diagnosed high-grade glioma only in patients with a World Health Organization (WHO) performance status of 0.

1.2 Temozolomide is not recommended for the subsequent treatment of patients with high-grade glioma who have received the drug as part of their first-line treatment.

1.3 Carmustine implants are not recommended for the treatment of newly diagnosed high-grade glioma.

2 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 glioblastoma multiforme (GBM).

2.2 Brain tumours account for less 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 tumours.

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 (see appendix D for details).

2.4 Approximately 30% of adults with high-grade tumours (grades 3 and 4) survive 1 year, and 13% survive 5 years. The median survival of patients with anaplastic astrocytoma is around 2–3 years, and approximately 1 year for patients with GBM. Age, performance status and tumour histology are indicators of pretreatment prognosis. Patients with high-grade tumours 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 computed tomography (CT) scan or magnetic resonance imaging (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.

2.6 In the UK, treatment usually consists of surgical resection where possible, followed by radiotherapy. Surgery may achieve either a 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 5p 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; *BNF* 50th edition, September 2005). Up to eight implants may be used, depending upon 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 Temozolomide is available as 5-mg, 20-mg, 100-mg and 250-mg tablets. It is administered at 75 mg/m^2 daily for 42 days concomitantly with radiotherapy (60 Gy administered in 30 fractions), and then as monotherapy at 150 mg/m^2 daily for 5 days, followed by 23 days without treatment, for a maximum of six cycles. The dose may be increased to 200 mg/m^2 daily in the second and subsequent cycles.

3.8 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* 50th edition, September 2005). Costs may vary in different settings because of negotiated procurement discounts.

3.9 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.

4 Evidence and interpretation

The Appraisal Committee (see appendix A) considered evidence from a number of sources (see 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 to radiotherapy alone. No studies comparing carmustine implants to temozolomide, nor comparing carmustine implants or temozolomide to 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 with a Karnofsky Performance Status (KPS) score of 60 or greater, 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 Drugs Agency (FDA) in the USA expressed several concerns when it evaluated the trial. In particular, it was concerned about an imbalance between the types of tumours in study arms, which could have favoured carmustine implants. The FDA also expressed concern regarding the arrangements for review of histological diagnoses and recommended that a sensitivity analysis be performed using diagnosis from an alternative pathologist. The FDA also expressed concern regarding the analysis of data on the time to decline of neurological symptoms. The Assessment Group noted that three patients withdrew from the RCT and that it was unclear from which arm of the trial the patients withdrew (information regarding these patients was subsequently provided to NICE by the manufacturer). In addition, the manufacturer's analysis of the data included stratification by country, and the FDA reanalysed this data without stratification. The data reported below relate to the unstratified analysis unless otherwise stated.

4.1.4 The median survival was 13.8 months (95% CI: 12.1 to 15.1) in the carmustine implant group, and 11.6 months (95% CI: 10.2 to 12.7) in the

placebo group. The 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, the Kaplan–Meier hazard ratio was 0.73 (log rank statistic: p = 0.02). At 12 months 59.2% of the carmustine implant group and 49.6% of the placebo group were alive, at 24 months survival was 15.8% and 8.3%, and at 36 months survival was 9.2% and 1.7% in each group respectively (all estimates calculated on the basis of survival data censored at the relevant time period).

4.1.5 There was no difference in progression-free survival between treatment groups. The median time to progression was 5.9 months (95% CI: 4.4 to 8.3) in the carmustine implant group and 5.9 months (95% CI: 4.7 to 7.4) in the placebo group (using stratified analysis). The manufacturer's analysis suggested that both the time to decline of KPS and the time to progression on neurological indices were statistically significantly improved (that is, increased) in the carmustine implant group. However, a reanalysis of these data was conducted by the FDA, which treated deaths as censored. This reanalysis found that the differences resulted from variations in survival times between the treatment arms, suggesting that there was no independent effect of treatment on the time to decline of KPS and neurological indices.

4.1.6 In a subgroup of patients with GBM, the median survival was 13.5 months (95% CI: 11.4 to 14.8) in the carmustine implant group and 11.4 months (95% CI: 10.2 to 12.6) 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 Intracranial hypertension was the only adverse event in the largest RCT to have a significantly increased incidence in the carmustine implant group (9.2% compared to 1.7%; p = 0.02).

4.1.8 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 other RCT of temozolomide. 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 to 9.2 months (95% CI: 8.7 to 10.4) in the placebo group. This difference was statistically significant (log rank: 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 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

4.1.9 The inclusion criteria for the largest RCT of temozolomide specified that patients aged 18–70 years with grade 4 glioma and a WHO performance status of 2 or better (lower) should be randomised following 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. A diagnosis of GBM was confirmed by histology in 92–93% of patients; the proportion of grade 3 tumours 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 only a biopsy 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.

4.1.10 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 13.0 months) in the radiotherapy alone group. Absolute 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 absolute 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) in the temozolomide plus radiotherapy group and 5.0 months (95% CI: 4.2 to 5.5 months) in the radiotherapy alone group.

4.1.11 Retrospective subgroup analyses of patients with methylated O^6-methylguanine-DNA methyltransferase (MGMT) promoter and patients with 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 100 (35%) patients in the radiotherapy alone arm, and the MGMT promoter was methylated in 46 of these patients. In the radiotherapy plus temozolomide arm, MGMT promoter methylation status was determined in 106 patients (37%), and the MGMT promoter was methylated in 46 of these patients. Patients whose tumours had MGMT promoter methylation had a median survival gain from radiotherapy plus temozolomide compared to radiotherapy alone of 6.4 months and median progression-free survival gain of 4.4 months. In patients whose tumours did not have MGMT promoter methylation, both the median survival gain and median progression-free survival gain from radiotherapy plus temozolomide compared to radiotherapy alone were less than 1 month, although the gain in progression-free survival was statistically significant ($p = 0.02$).

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

4.1.13 A subgroup analysis of median overall survival by prognostic factors was published for the largest RCT. For patients aged below 50 years (n = 172), median survival was 4.2 months greater in the radiotherapy plus temozolomide group compared to 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 to 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 was 2.9 months greater in the radiotherapy plus temozolomide group compared to the radiotherapy alone group for patients who had undergone resection (n = 480), and 1.5 months greater for patients who had undergone biopsy only (n = 93).

4.1.14 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, as were moderate (grade 2) fatigue, nausea and vomiting, and rash.

4.1.15 The effect of temozolomide upon 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).

4.1.16 Another RCT conducted in Greece randomised patients to receive radiotherapy plus temozolomide (n = 57) or radiotherapy alone (n = 53). Patients 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 only a biopsy 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) in the radiotherapy plus temozolomide group and 7.7 months (95% CI: 5.3 to 9.2) 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 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) in the radiotherapy plus temozolomide group and 5.2 months (95% CI: 3.9 to 7.4) 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 life year gained of carmustine implants plus radiotherapy, compared to placebo plus radiotherapy. The manufacturer of temozolomide submitted a within-trial economic analysis of temozolomide plus radiotherapy, compared to 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 of carmustine implants incorporated the assumption that following 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 wafers per patient). A utility value of 0.8 was assumed for patients without symptoms. Costs and quality-adjusted life years (QALYs) were not discounted.

4.2.3 The Assessment Group expressed concern about the estimation of time to symptoms. When the data were reanalysed by the FDA, no statistically significant differences were found between treatment arms in the time to decline of functional status and time to deterioration of neurological performance scores in 10 of 11 indices.

4.2.4 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 temozolomide plus radiotherapy compared to radiotherapy alone (mean ICER: £53,700 per QALY gained) and for PCV plus radiotherapy compared to radiotherapy alone (mean ICER: £34,200 per QALY gained). The Assessment Group considered the model structure to be sound, but concluded that the main ICER of £28,000 per QALY gained was an underestimate because of the assumptions used to estimate progression-free survival and the omission of treatment costs other than those of the implants.

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 expert advice, the model reflected that 70% of patients would receive treatment with PCV upon disease progression. Aside from perioperative mortality, the risk of death in the model was considered to be time dependent rather than state dependent. For the analysis of carmustine implants, survival was calculated by fitting a Weibull curve to the overall survival curve from the largest RCT. 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 constantly deteriorating 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 In the Assessment Group model the base-case analysis comparing carmustine implants to placebo indicated that the mean incremental costs of carmustine implants were £6100 and mean QALYs gained were 0.107. The additional cost per QALY gained was £57,000. 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. A speculative analysis of patients with a better prognosis found that the mean incremental cost per QALY was just under £37,000.

4.2.7 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. In a subgroup of patients who had undergone maximal resection, defined as removal of 90% or greater of the tumour, the ICER was £47,400 using measures of progression-free survival based on radiological imaging. The ICER for this subgroup was £35,600 when time to neurological performance decline was used to estimate progression-free survival. In a subgroup of patients with GBM who had undergone maximal resection, the ICER was £48,000 using radiological imaging to measure progression-free survival and £36,100 using measures of time to neurological performance decline.

Temozolomide

4.2.8 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 from 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%.

4.2.9 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 employed: 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 £11,000 per life year gained from temozolomide for the full trial cohort and £19,160 per life year gained from temozolomide for the subgroup with resource-use data. For the analysis restricted to 2 years post randomisation, the corresponding ICERs were £19,440 for the full trial cohort and £33,590 for the subgroup with resource-use data.

4.2.10 The Assessment Group's model to estimate the cost effectiveness of temozolomide was the same as that used for carmustine and it is described in section 4.2.5. Survival was calculated by fitting a Weibull curve to the overall survival curve from the largest RCT of temozolomide.

4.2.11 In the Assessment Group's base-case analysis of temozolomide plus radiotherapy compared to radiotherapy alone, the mean incremental cost of temozolomide plus radiotherapy was £8560 and mean QALYs gained were 0.187. The additional cost per QALY gained was £45,800. The one-way sensitivity analyses showed that the model was most sensitive to survival gain and progression-free survival. A speculative analysis of patients with a better prognosis found that the mean incremental cost per QALY was just under £43,000.

4.2.12 The Assessment Group conducted an additional economic analysis to explore the effect of different assumptions about the treatment received by patients upon disease progression. 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 upon 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 incremental cost per QALY gained was £34,200. An alternative analysis was conducted to reflect the existing NICE guidance on temozolomide for the treatment of recurrent glioma. This assumed that chemotherapy upon 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 incremental cost per QALY gained was £45,300.

4.2.13 The Assessment Group also conducted additional analyses based on the overall survival estimates from the subgroup analysis of the largest RCT of temozolomide. The incremental cost per QALY gained was £37,900 for patients aged below 50 years, £52,600 for patients who had undergone resection, £38,900 for patients with WHO performance status 0 and £67,400 for patients with WHO performance status 1. Incorporating the costs associated with chemotherapy upon disease progression based on data from the largest RCT of temozolomide (see section 4.2.10), the ICERs for these subgroups were £29,700 for patients aged below 50 years, £40,200 for patients who had undergone resection, £30,400 for patients with WHO performance status 0 and £50,400 for patients with WHO performance status 1. After incorporating the costs associated with chemotherapy upon disease progression based on existing NICE guidance (see section 4.2.12) the ICERs for these subgroups ranged from £36,800 to £66,600.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed glioma. It considered evidence on the nature of the condition and the value placed on the benefits of carmustine implants and

temozolomide by carers of people with glioma, those who represent people with glioma, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

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

4.3.3 The Committee considered evidence from the experts and carers that glioma has a considerable impact upon the quality of life of patients. In addition, it understood that following an initial response to early treatment, once progression of disease has occurred, most patients experience a fairly rapid decline thereafter. 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 the experts that measurements of progression-free survival using imaging techniques are influenced by the frequency with which the imaging is conducted and may not correlate with neurological or functional status or patients' perception of their health. It also considered that the use of measures of functional status can be problematic due to the variable impact of tumour progression upon physical and cognitive functioning.

4.3.5 The Committee considered testimony from the clinical experts 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

that on the basis of the experts' testimony it was necessary to optimise both the timing and the extent of radiotherapy, with or without prior surgical treatment, to achieve the best results for all glioma patients irrespective of the use of other therapies.

4.3.6 The Committee considered the experts' 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 acknowledged 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 to other chemotherapy regimens such as PCV.

Carmustine implants

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

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 was persuaded

that the evidence suggested a small but statistically significant benefit in overall survival.

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 that the manufacturer's analysis of time to neurological decline showed a statistically significant benefit in favour of carmustine implants. The Committee was mindful that the analysis conducted by the FDA of time to neurological decline failed to show a statistically significant benefit in favour of carmustine implants on most indices.

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 disease. The Committee noted the concern expressed by the FDA that there was a slightly greater proportion of patients with grade 4 tumours 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.

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 described in section 4.3.4 and noted that progression-free survival was measured by the time to decline in neurological symptoms in the largest

RCT of carmustine implants. In addition the Committee noted that the manufacturer's economic model only included the costs associated with the implants themselves and excluded all other costs associated with treating high-grade glioma. The Committee further took into consideration the results of the reanalysis submitted by the manufacturer.

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 patients' disease had progressed. The Committee was aware that the probability of death increases significantly upon 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. The Committee considered that fitting a Weibull curve to the RCT survival data resulted in a slight underestimate of the median survival gain from carmustine implants. The Committee noted that a sensitivity analysis showed that this underestimate would have a marginal effect on the ICERs and concluded that the general approach adopted by the Assessment Group was appropriate. It also concluded that the results of the sensitivity analyses showed the overall survival gain from treatment would have to increase considerably for the incremental cost-effectiveness ratios to decrease substantially.

4.3.13 The Committee 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.

4.3.14 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 and not prespecified. The Committee discussed the results of the Assessment Group's additional analyses, which included alternative measures of disease progression and an assessment of the cost effectiveness of carmustine implants in a subgroup of patients undergoing maximal resection.

4.3.15 Regarding the additional Assessment Group analysis that used alternative measures of assessing progression-free survival, the Committee noted that using time to neurological performance decline as a measure of progression-free survival reduced the ICERs. 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 also mindful, however, of the uncertainty regarding the effect of carmustine implants on progression-free survival and remained concerned over the validity of the trial data to support this (see section 4.3.4). Considering the analysis based on functional measures of progression-free survival, the Committee concluded that the ICERs were high for the subgroup of patients who had undergone maximal resection and would be considerably higher for the full trial cohort.

4.3.16 The Committee considered the subgroup analyses of histological diagnosis and completeness of tumour resection. The Committee noted that this analysis indicated that excluding patients with grade 3 glioma had little effect on estimates of overall survival and accepted that the pragmatic results of the principal RCT were a sufficient basis for making a decision on the clinical effectiveness and cost effectiveness of carmustine implants. The Committee additionally considered that, although tumour resectability per se was an important indicator of prognosis and possibly treatment effect, quantifying the

extent of resection was very difficult and open to considerable bias. The Committee recognised that tumour resection could influence prognosis in the individual patient, even when the extent of resection was limited, but it was not persuaded that it was appropriate to consider subgroups of patients defined according to the extent of primary resection.

4.3.17 In summary, the Committee noted that the largest trial of carmustine implants showed a small but statistically significant benefit in overall survival. It acknowledged that by using some measures of functional status to assess progression-free survival a small average benefit could be shown. The Committee considered that overall there was currently insufficient evidence to support the view that carmustine implants would be more clinically effective or cost effective in any identifiable subgroup of patients. It concluded therefore that the use of carmustine implants for the treatment of newly diagnosed glioma would not be a cost-effective use of NHS resources.

Temozolomide

4.3.18 The Committee considered the evidence on the 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 may have underestimated the delay to functional progression in the patients being treated.

4.3.19 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 disease. 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.

4.3.20 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 upon the quality of life of patients, which may deteriorate rapidly upon disease progression, the Committee concluded that the assessment of cost effectiveness should incorporate the effects of the disease and treatment upon 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 upon 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 from temozolomide. The Committee considered that this reduction in utility was small and that it had only a marginal effect upon 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.

4.3.21 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 was mindful that fitting a Weibull curve to the RCT survival data resulted in a slight overestimate of the survival gain from temozolomide, but concluded that the general approach to the estimation of survival adopted by the Assessment Group was appropriate.

4.3.22 The Committee understood that the choice of treatment for high-grade glioma used after disease progression following initial therapy with temozolomide could affect the results of the cost-effectiveness analysis. The Committee also

considered testimony from the experts that there is considerable uncertainty about the appropriate treatment for patients whose disease progresses following chemotherapy after 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 £34,200 when the analysis included the proportional use of different kinds of chemotherapy after disease progression based on data from the largest RCT of temozolomide. However, the Committee was mindful that the data from this RCT did not reflect existing NICE guidance on temozolomide for the treatment of recurrent glioma, 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 concluded that it was appropriate to consider in the economic analysis the impact of treatments for glioma that might be used after progression of the disease following first-line temozolomide therapy.

4.3.23 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 to that from radiotherapy alone was higher for patients with a WHO performance status of 0 and for patients aged below 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 most appropriate to consider subgroups defined by performance status.

4.3.24 The Committee noted that the Assessment Group's economic analysis showed that the ICER of temozolomide for patients with a WHO performance status of 0 would be between £30,400 and £38,900, depending upon the type

and proportion of chemotherapy received upon disease progression. The Committee also noted that the ICER of temozolomide for patients with a WHO performance status of 1 would be between £50,400 and £67,400. It concluded that temozolomide would not be an appropriate use of NHS resources for the treatment of patients with WHO performance status of 1 or worse.

4.3.25 The Committee further considered whether there might be other subgroups of patients for whom the use of temozolomide might be more clinically effective and cost effective. It acknowledged the results of a retrospective analysis of patients whose tumours had MGMT promoter methylation in the largest RCT of temozolomide. The Committee was aware of continued research in this area. The Committee concluded that although this research was promising, it was premature to use MGMT promoter methylation status to identify patients for whom temozolomide treatment was suitable outside clinical studies and that further research into methods of identifying subgroups of patients for whom temozolomide might be more effective should be pursued.

4.3.26 The Committee was mindful that people with high-grade glioma have a relatively short life span and that previously used chemotherapy regimens have not demonstrated a benefit in survival. The Committee considered that the RCT evidence for temozolomide had demonstrated an improvement in overall survival in high-grade glioma and, most importantly, an increase in progression-free survival, during which patients' quality of life is usually maintained. The Committee concluded that the additional costs of temozolomide for the treatment of newly diagnosed high-grade glioma in patients with a WHO performance status of 0 were acceptable when set against the benefit to these people.

4.3.27 The Committee considered the uncertainty regarding the appropriate treatment for patients whose disease progresses following chemotherapy after initial diagnosis. It noted that there is a lack of evidence on the effectiveness of second-line and subsequent treatment with temozolomide in

patients who have received temozolomide as part of first-line therapy. The Committee concluded that temozolomide should not be recommended for the subsequent treatment of patients who have received temozolomide as part of first-line therapy.

Consideration of carmustine and temozolomide for use in children

4.3.28 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 be likely to apply also to children. It concluded that the issues regarding clinical effectiveness and cost effectiveness outlined above were also relevant to the use of the technologies for the same condition in children.

5 Recommendations for further research

5.1 The Committee noted that a large trial is planned to 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 Implications for the NHS

6.1 The NICE Costing Unit is currently developing this section. A costing template and report will be available at the time of publication of the final guidance.

7 Implementation and audit

7.1 NHS hospitals and clinicians who care for people with newly diagnosed high-grade glioma should review their current practice and policies to take account of the guidance set out in section 1.

7.2 Local guidelines, protocols or care pathways that refer to the care of people with newly diagnosed high-grade glioma should incorporate the guidance.

7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in appendix C.

7.3.1 A person with newly diagnosed high-grade glioma is offered treatment with temozolomide only if the person has a WHO performance status of 0.

7.3.2 A person who has received temozolomide as part of his or her first-line treatment of newly diagnosed high-grade glioma is not given temozolomide for subsequent treatment.

7.3.3 Carmustine implants are not used for the treatment of newly diagnosed high-grade glioma.

8 Related guidance

8.1 Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer). *NICE technology appraisal guidance* no. 23 (2001). Available from: www.nice.org.uk/TA023

8.2 Cancer service guidance for improving outcomes for people with brain and other central nervous system tumours (publication expected June 2006).

9 Proposed date for review of guidance

9.1 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.

9.2 The guidance on these technologies will be considered for review in August 2009.

9.3 Appraisals of temozolomide (review of *Technology appraisal guidance* no. 23) and carmustine implants for the treatment of recurrent high-grade glioma are expected to begin in 2006.

David Barnett
Chair, Appraisal Committee
April 2006

Appendix A. Appraisal Committee members 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 twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice chair and a number of other members attending meetings of both branches. 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 Tom Aslan
General Practitioner, Stockwell, London

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain

Lay Member

Dr Peter Clark

Honorary Chairman, Association of Cancer Physicians

Dr Karl Claxton

Health Economist, 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, Blackpool

Professor Christopher Eccleston

Director Pain Management Unit, University of Bath

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Professor Terry Feest

Professor of Clinical Nephrology, Southmead Hospital

Ms Alison Forbes

Lay Member

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

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

Professor Richard Lilford

Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Judith Paget

Chief Executive, Caerphilly Local Health Board, Wales

Dr Katherine Payne

Health Economist, The North West Genetics Knowledge Park, The University of Manchester

Dr Ann Richardson

Independent Research Consultant

Mrs Kathryn Roberts

Nurse Practitioner, Hattersley Group Practice , Cheshire

Professor Philip Routledge

Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Debbie Stephenson

Head of HTA Strategy, Eli Lilly and Company

Professor Andrew Stevens (Vice Chair)

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

General Practitioner, & Associate Professor, Department of Primary Care & General Practice, University of Birmingham

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Dr Paul Watson

Medical Director, Essex Strategic Health Authority

Dr David Winfield

Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

B. NICE Project Team

Each appraisal of a technology is assigned to a Technical Lead, a Technical Advisor and a Technology Appraisal Project Manager within the Institute.

Louise Longworth

Technical Lead, NICE project team

Janet Robertson

Technical Advisor, NICE project team

Alana Miller

Project Manager, NICE project team

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.

I Garside R, Pitt M, Anderson R et al. The effectiveness and cost effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma: a systematic review and economic evaluation, September 2005.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the appraisal consultation document (ACD). Consultee organisations are provided with the opportunity to appeal against the FAD.

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
- Cancer Research UK
- Cancer Voices

- CancerBACUP
- 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 & 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
- Brain & Central Nervous System Tumours Guideline Development Group
- Bristol-Myers Squibb Pharmaceuticals Ltd
- British National Formulary
- Cambridge Laboratories
- Clonmel Healthcare Ltd
- Institute of Cancer Research
- Mayne Pharma plc
- Medac UK
- MRC Clinical Trials Unit
- National Cancer Research Institute
- National Coordinating Centre for Health Technology Assessment
- National Public Health Service for Wales
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- Peninsula Technology Assessment Group, University of Exeter

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. 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.
- 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. Detail on criteria for audit of the use of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma

Possible objectives for an audit

An audit could be carried out to ensure that carmustine implants and temozolomide are being used appropriately for the treatment of people with newly diagnosed high-grade glioma.

Possible patients to be included in the audit

An audit could be carried out on a reasonable number of people being treated for newly diagnosed high-grade glioma, for audit purposes; for example, patients seen over 1 year.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma are as follows.

Criterion	Standard	Exception	Definition of terms
1. A person with newly diagnosed high-grade glioma is offered treatment with temozolomide only if the person has a WHO performance status of 0	100% of people with newly diagnosed high-grade glioma treated with temozolomide	None	'High-grade gliomas' refers to grade 3 and grade 4 gliomas. Patients with WHO performance status 0 are 'able to carry out all normal activity without restriction'. See appendix D for further details of the WHO performance status classification. Clinicians will need to agree locally on how WHO performance status is documented for audit purposes. See the Summary of Product Characteristics for details of contraindications.
2. A person who has received temozolomide as part of his or her first-line treatment of newly diagnosed high-grade glioma is given temozolomide for subsequent treatment	0% of people who received temozolomide as part of his or her first-line treatment of newly diagnosed high-grade glioma	None	For audit purposes, clinicians will need to agree how to identify first-line and subsequent treatments.
3. Carmustine implants are used for the treatment of newly diagnosed high-grade glioma	0% of people with newly diagnosed high-grade glioma	None	

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the } \textbf{criterion} \textit{ plus } \text{number of patients who meet any } \textbf{exception} \text{ listed}}{\text{Number of patients to whom the } \textbf{measure} \text{ applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.

Appendix D. 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 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.