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R Garside, M Pitt, R Anderson, G Rogers, M Dyer, S Mealing, M Somerville, A Price and K Stein

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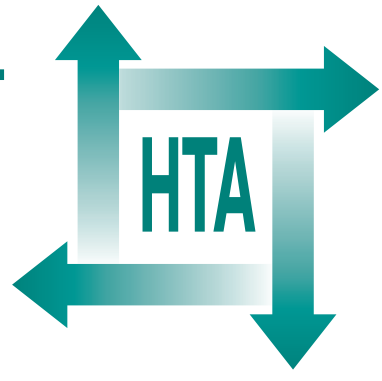

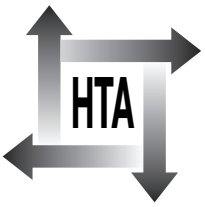

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The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation

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The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 04/20/01. The protocol was agreed in April 2005. The assessment report began editorial review in December 2005 and was accepted for publication in February 2006. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

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

R Garside,[1*] M Pitt,[1] R Anderson,[1] G Rogers,[1] M Dyer,[1] S Mealing,[1] M Somerville,[2] A Price[3] and K Stein[1]

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Objectives: To assess the clinical and cost-effectiveness of adjuvant carmustine wafers (BCNU-W) and also of adjuvant and concomitant temozolomide (TMZ), compared with surgery with radiotherapy.

Data sources: Electronic databases were searched up to August 2005.

Review methods: Included trials were critically appraised for key elements of internal and external validity. Relevant data were extracted and a narrative synthesis of the evidence produced. Where possible, data on absolute survival at a fixed time point were meta-analysed using a random effects model. A Markov (state transition) model was developed to assess the cost–utility of the two interventions. The model compared BCNU-W or TMZ separately with current standard treatment with surgery and radiotherapy. The simulated cohort had a mean age of 55 years and was modelled over 5 years.

Results: Two randomised controlled trials (RCTs) ($n = 32$, $n = 240$) and two observational studies of BCNU-W compared with placebo wafers as adjuvant therapy to surgery and radiotherapy for newly diagnosed high-grade glioma were identified. All the studies were in adults and provided data on 193 patients who had received BCNU-W. The RCT findings excluded under 65-year-olds and those with a Karnofsky Performance Status of less than 60. The largest multi-centre RCT suggested a possible survival advantage with BCNU-W among a cohort of patients with grade III and IV tumours, adding a median of 2.3 months [95% confidence interval (CI) –0.5 to 5.1]. However, analysis using per-protocol, unstratified methods shows this difference to be not statistically significant (HR 0.77, 95% CI 0.57 to 1.03, $p = 0.08$). Long-term follow-up suggests a significant survival advantage using unstratified analysis. No difference in progression-free survival (PFS) was demonstrated. Subgroup analysis of those with grade IV tumours also showed no significant survival advantage with BCNU-W [hazard ratio (HR) 0.82, 95% CI 0.55 to 1.11, $p = 0.20$, unstratified analysis]. It is estimated that the cost of surgery and radiotherapy, with follow-up, treatment of adverse effects and end of life care is around £17,000 per patient. Treatment with BCNU-W adds an additional £6600. Across the modelled cohort of 1000 patients, use of BCNU-W costs an additional £6.6 million and confers an additional 122 quality-adjusted life-years (QALYs). On average, that is £6600 per patient for 0.122 QALYs (6.3 quality-adjusted life-weeks). The base-case incremental cost-effectiveness ratio (ICER) is £54,500/QALY. In probabilistic sensitivity analyses, BCNU-W was not cost-effective in 89% of the simulations assuming a willingness to pay threshold of £30,000/QALY. In 15% of simulations, BCNU-W was dominated (i.e. did more harm than good, conferring fewer QALYs at greater cost). The cost-effectiveness acceptability curve (CEAC) suggests that it is very unlikely to be the most cost-effective option at normal levels of willingness to pay (11% probability at £30,000/QALY), only becoming likely to be the most cost-effective option at much higher levels of willingness to pay (50% probability at £55,000/QALY). Two RCTs ($n = 130$, $n = 573$) and two observational studies were included, giving evidence for 429 adult patients receiving TMZ. Currently, TMZ is licensed for use in those with newly diagnosed grade IV gliomas only. The RCTs excluded those with lower performance status and, in the larger RCT, those older than 70 years.

TMZ provides a small but statistically significant median survival benefit of 2.5 months (95% CI 2.0 to 3.8), giving an HR of 0.63 (95% CI 0.52 to 0.75, $p < 0.001$). At 2 years, 26.5% of patients treated with TMZ were alive compared with 10.4% of those in the control arm. Median PFS is also enhanced with TMZ, giving a median 1.9 months' advantage (95% CI 1.4 to 2.7, $p < 0.001$). No analysis of the subgroup of patients with confirmed grade IV tumours was undertaken. Subgroup analysis of patients by O^6-methylguanine-DNA methyltransferase (MGMT) activity showed a significant treatment advantage for those with reduced MGMT activity but not for those with normal activity, although this analysis was based on a selected sample of patients and the test used has proved difficult to replicate. A median gain of 6.4 (95% CI 4.4 to 9.5) more life-months is seen with TMZ among those with reduced MGMT, giving an HR of 0.51 ($p < 0.007$). PFS is increased by a median of 4.4 months (95% CI 1.2 to 6.3), giving an HR of 0.48 ($p = 0.001$). The model shows a cost per patient for being treated with surgery, radiotherapy and including adverse effects of treatment and end of life care of around £17,000 per patient. TMZ in the adjuvant and concomitant phase adds an additional cost of around £7800. Across the modelled cohort of 1000 patients, use of TMZ costs an additional £7.8 million and confers an additional 217 QALYs. For the average patient this is £7800 for an additional 0.217 QALYs (11 quality-adjusted life-weeks). The base-case ICER is £36,000/QALY. Probabilistic sensitivity analyses shows that TMZ was not cost-effective in 77% of the simulations. The CEAC suggests that there is a 23% chance that TMZ is the most cost-effective option at a willingness to pay level of £30,000/QALY, rising to be more cost-effective than no TMZ at slightly higher levels (50% probability at £35,000/QALY).

Conclusions: BCNU-W has not been proven to confer a significant advantage in survival for patients with grade III tumours when treated with the drug, compared with placebo. There does not appear to be a survival advantage for patients with grade IV tumours. No increase in PFS has been shown. Limited evidence suggests a small but significant advantage in both overall survival and PFS with TMZ among a mixed population with grade IV and grade III (7–8%) tumours. However, it remains unclear whether this is true in grade IV tumours alone. On the basis of best available evidence, the authors consider that neither BCNU-W nor TMZ is likely to be considered cost-effective by NHS decision-makers. However, data for the model were drawn from limited evidence of variable quality. Tumour type is clearly important in assessing patient prognosis with different treatments. Grade IV tumours are commonest and appear to have least chance of response. There were too few grade III tumours included to carry out a formal assessment, but they appear to respond better and drive results for both drugs. Future use of genetic and biomarkers may help identify subtypes which will respond, but current licensing indications do not specify these. Further research is suggested into the effectiveness of these drugs, and also into areas such as genetic markers, chemotherapy regimens, patient and carer quality of life, and patient views on survival advantages vs treatment disadvantages.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Adjuvant treatment Treatment with chemotherapy after surgery and radiotherapy.

Anaemia Reduced level of circulating red cells, resulting in low levels of haemoglobin and hence a reduced oxygen-carrying capacity of the blood.

Aphasia Loss of the ability to speak or write or of ability to understand spoken or written language.

Ataxia Loss of muscle coordination.

Concomitant treatment Treatment with chemotherapy alongside radiotherapy.

Encephalopathy Diffuse disease of the brain that alters brain function or structure. There are many causes, including infectious agents (bacteria, virus or prion), metabolic or mitochondrial dysfunction, brain tumour or increased pressure in the skull, prolonged exposure to toxic elements (including solvents, drugs, radiation, paints, industrial chemicals and certain metals), chronic progressive trauma, poor nutrition or lack of oxygen or blood flow to the brain.

Hemiparesis Paralysis of one side of the body.

Intercranial hypertension Raised intercranial pressure that may cause vomiting and headaches.

Leukopenia Abnormal decrease in the number of white blood cells generally.

Lymphocytopenia Abnormal decrease in the number of lymphocytes (a type of white blood cell that fights infection).

Metastasis Transfer of cancer cells from one part of the body to another.

Methylation The addition of methyl groups to DNA components. Methyl group tags in the DNA of humans and other mammals play an important role in determining whether some genes are or are not expressed. Very frequent abnormal increases or decreases in DNA methylation tags are found in most human cancers and contribute to their development.

MGMT A DNA repair protein that interferes with the effect of alkylating chemotherapies. MGMT concentration in tumours appears to be inversely correlated with sensitivity to chemotherapy.

Myelosuppression Reduced bone marrow activity, causing a reduction in the number of circulating platelets, red blood cells and white blood cells. Myelosuppression is a side-effect of some forms of chemotherapy.

Neutropenia Abnormal decrease in neutrophils (a type of white blood cell that fights bacterial infection).

Nystagmus Involuntary, rapid eyeball movement.

Papilloedema Swelling of the optic disc caused by raised intercranial pressure.

Thrombocytopenia Abnormal decrease in the number of blood platelets, resulting in potential for increased bleeding and decreased clotting.

List of abbreviations

AA	anaplastic astrocytoma
AE	adverse effect
AO	anaplastic oligodendroglioma
AOA	anaplastic oligoastrocytoma
BCNU	1,3-bis(2-chloroethyl)-1-nitrosourea (carmustine)
BCNU-W	carmustine wafer
BNF	British National Formulary
CCNU	1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CSF	cerebrospinal fluid
CT	computed tomography
EORTC	European Organisation for Research and Treatment of Cancer
FACT	Functional Assessment of Cancer Therapy
FDA	US Food and Drug Administration
GBM	glioblastoma multiforme (grade IV glioma)
HR	hazard ratio
HRG	Healthcare Resource Group
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
KPS	Karnofsky Performance Status
MGMT	O^6-methylguanine-DNA methyltransferase
MRI	magnetic resonance imaging
MTIC	monomethyltriazenoimidazole-carboxamide
NCIC	National Cancer Institute of Canada
NCI CTC	US National Cancer Institute Common Toxicity Criteria
NICE	National Institute for Health and Clinical Excellence
PCV	procarbazine, lomustine and vincristine
PenTAG	Peninsula Technology Assessment Group
PFS	progression-free survival
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QLQ	Quality of Life Questionnaire
QoL	quality of life
Q-TWiST	quality-adjusted time without symptoms of disease or toxicity of treatment
RCT	randomised controlled trial
RT	radiotherapy
TMZ	temozolomide
VoHP	Value of Health Panel

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

High-grade (grade III and IV) gliomas are rare but very aggressive brain tumours. There are about 1700 new cases of high-grade glioma diagnosed annually in England (3.6/100,000). Incidence is highest among those in their early 70s and gliomas are slightly more common in men than women. High-grade gliomas are incurable and treatment aims to increase survival while maintaining quality of life. Median survival is around 1 year for those with grade IV tumours and 2–3 years for those with grade III tumours.

Current treatments include surgery, which may relieve symptoms through debulking and provides material for histological diagnosis. Radiotherapy in addition to surgery has been shown to improve survival over surgery alone. Hitherto, existing approaches to chemotherapy have not conclusively demonstrated a significant survival benefit and may be associated with considerable adverse effects.

Carmustine-impregnated wafers (BCNU-W) are used in newly diagnosed grade III and IV gliomas as adjuvant therapy to surgery and radiotherapy. BCNU-W are inserted into the tumour cavity at the time of operation.

Temozolomide (TMZ) is an oral preparation used in newly diagnosed grade IV gliomas as adjuvant and concomitant therapy to surgery and radiotherapy.

Objectives

This report assesses the clinical and cost-effectiveness of:

- adjuvant BCNU-W with surgery and radiotherapy, compared with surgery and radiotherapy alone
- adjuvant and concomitant TMZ with surgery and radiotherapy, compared with surgery and radiotherapy alone.

Methods

Electronic databases were searched for relevant published research on effectiveness and cost-effectiveness of BCNU-W or TMZ as treatments for newly diagnosed high-grade glioma. Updated searches were undertaken on 25 August 2005. Included trials were critically appraised for key elements of internal and external validity. Relevant data were extracted and a narrative synthesis of the evidence was produced. Where possible, data on absolute survival at a fixed time point were meta-analysed using a random effects model.

A Markov (state transition) model was developed in Excel to assess the cost–utility of the two interventions. The model compared BCNU-W or TMZ separately with the current standard treatment of surgery and radiotherapy. The simulated cohort had a mean age of 55 years and was modelled over 5 years.

Results: carmustine wafers

Number and quality of studies

Two previous systematic reviews of BCNU-W were identified. One used patient-level data from two randomised controlled trials (RCTs) to assess the effectiveness of BCNU-W. However, few details of methods used to identify studies were given and there was no assessment of study quality. The other was not peer reviewed and gave few details about study quality. We therefore undertook our own systematic review.

Two randomised trials ($n = 32$, $n = 240$) and two observational studies of BCNU-W compared with placebo wafers as adjuvant therapy to surgery and radiotherapy for newly diagnosed high-grade glioma were identified. All the studies were in adults and provided data on 193 patients who had received BCNU-W.

The RCTs appear to use adequate randomisation and allocation concealment methods, although blinding was challenged by differences between the active and placebo wafers. Given the primary end-point of survival, this is unlikely to have an impact; however, it may have influenced identification of the point at which disease progressed, which allowed investigators discretion as to salvage therapy to be instigated. Choice of salvage therapy may also have been influenced by knowledge of first-line treatment.

Intention-to-treat analyses were used. However, the statistical analysis reported in the published paper for the main trial was not per protocol and enhances the apparent treatment effect.

There was a slight imbalance in tumour type between the two arms, with more chemosensitive types being seen in the group receiving BCNU-W. Further, although these were defined by a central pathologist, a different central pathologist's assessment suggested that there might be greater imbalance in grade III tumours between the arms.

The RCT findings may not be widely generalisible owing to the exclusion of under 65-year-olds and those with a Karnofsky Performance Status of less than 60.

Summary of risks and benefits

The previous meta-analysis used patient-level data from two RCTs and found a 32% reduction in the risk of death with BCNU-W compared with placebo wafer [unadjusted hazard ratio (HR) 0.68; 95% confidence interval (CI) 0.57 to 0.87: $p = 0.006$].

The largest multi-centre RCT suggested a possible survival advantage with BCNU-W among a cohort of patients with grade III and IV tumours, adding a median of 2.3 months (95% CI –0.5 to 5.1). However, analysis using per-protocol, unstratified methods shows this difference to be not statistically significant (HR 0.77, 95% CI 0.57 to 1.03, $p = 0.08$). Long-term follow-up suggests a significant survival advantage using unstratified analysis. However, this is based on a small number of the original cohort and may be influenced by tail effects. Furthermore, there is overlap in the CIs for median survival time reported for BCNU-W and placebo wafer.

No difference in progression-free survival (PFS) was demonstrated.

Subgroup analysis of those with grade IV tumours also showed no significant survival advantage with BCNU-W (HR 0.82, 95% CI 0.55 to 1.11, $p = 0.20$, unstratified analysis).

The only adverse effect reported in significantly more of those in the treatment arm was intracranial hypertension. However, the control arm used a placebo wafer implant and it is not clear if this wafer itself may lead to increased adverse effects.

Summary of costs

It is estimated that the cost of surgery and radiotherapy, with follow-up, treatment of adverse effects and end of life care is around £17,000 per patient. Treatment with BCNU-W adds an additional £6600.

Summary of cost-effectiveness

Across the modelled cohort of 1000 patients, use of BCNU-W costs an additional £6.6 million and confers an additional 122 quality-adjusted life-years (QALYs). On average, that is £6600 per patient for 0.122 QALYs (6.3 quality-adjusted life-weeks). The base-case incremental cost-effectiveness ratio (ICER) is £54,500/QALY.

Sensitivity analyses

One-way sensitivity analysis showed that the model is particularly sensitive to:

- median overall survival benefit with treatment
- median PFS benefit with treatment
- quality of life (utility) for 'stable' disease
- quality of life (utility) for 'progressive' disease
- cost of BCNU-W.

These were investigated through one-way threshold analyses. In order for the ICER for BCNU-W to become £30,000/QALY, median survival benefit would need to increase to 18 weeks (from the 10 weeks modelled from trial data), or PFS to 8 weeks (from none in the modelled trial data). As utility values have an upper limit of one, it was not possible for the ICER to be estimated below £30,000. However, if utility values are lowered, which seems possible as the estimates obtained for the model are high, then the ICER rises, slightly for lower utility values in stable disease and dramatically for lower utility values in the progressive disease state.

In probabilistic sensitivity analyses, BCNU-W was not cost-effective in 89% of the simulations assuming a willingness to pay threshold of £30,000/QALY. In 15% of simulations, BCNU-W was dominated (i.e. did more harm than good, conferring fewer QALYs at greater cost). The cost-effectiveness acceptability curve (CEAC) suggests that it is unlikely to be the most cost-effective option at normal levels of willingness to pay (11% probability at £30,000/QALY), only becoming likely to be the most cost-effective option at much higher levels of willingness to pay (50% probability at £55,000/QALY).

Results: temozolomide

Number and quality of studies

No previous systematic reviews of TMZ in newly diagnosed high-grade glioma were identified.

Two RCTs (n = 130, n = 573) and two observational studies were included, giving evidence for 429 adult patients receiving TMZ. Patients in the RCTs were randomised up to 6 weeks post-surgery, which will have excluded patients with surgical complications and those who died soon after surgery. The trials were open label but the main outcome, survival, is unlikely to be affected by this. Detection bias in measuring PFS, however, is possible. Methods of randomisation were not detailed in either trial.

The trials were limited to those with grade IV tumours. However, 7–8% were re-categorised as having grade III tumours. No analysis restricted to confirmed grade IV tumours was undertaken. It is possible that small numbers of more chemosensitive tumours may have impacted on findings. Currently, TMZ is licensed for use in those with newly diagnosed grade IV gliomas only.

The RCTs may not be widely generalisible owing to the exclusion of those with lower performance status and, in the larger RCT, those older than 70 years.

Summary of risks and benefits

TMZ provides a small but statistically significant median survival benefit of 2.5 months (95% CI 2.0 to 3.8), giving an HR of 0.63 (95% CI 0.52 to 0.75, $p < 0.001$).

At 2 years, 26.5% of patients treated with TMZ were alive compared with 10.4% of those in the control arm.

Median PFS is also enhanced with TMZ, giving a median 1.9 months' advantage (95% CI 1.4 to 2.7, $p < 0.001$).

No analysis of the subgroup of patients with confirmed grade IV tumours was undertaken.

Subgroup analysis of patients by O^6-methylguanine-DNA methyltransferase (MGMT) activity showed a significant treatment advantage for those with reduced MGMT activity but not for those with normal activity. However, it should be noted that this analysis was based on a selected sample of patients and that the test used has proved difficult to replicate. A median gain of 6.4 (95% CI 4.4 to 9.5) more life-months is seen with TMZ among those with reduced MGMT, giving an HR of 0.51 ($p < 0.007$). PFS is increased by a median of 4.4 months (95% CI 1.2 to 6.3), giving an HR of 0.48 ($p = 0.001$).

It is possible that the overall trial results are being driven by the chemosensitive tumours, as indicated either by grade III tumour types or possibly those with reduced MGMT activity described above.

Summary of costs

The model shows a cost per patient for being treated with surgery, radiotherapy and including adverse effects of treatment and end of life care of around £17,000 per patient. TMZ in the adjuvant and concomitant phase adds an additional cost of around £7800.

Summary of cost-effectiveness

Across the modelled cohort of 1000 patients, use of TMZ costs an additional £7.8 million and confers an additional 217 QALYs. For the average patient this is £7800 for an additional 0.217 QALYs (11 quality-adjusted life-weeks). The base-case ICER is £36,000/QALY.

Sensitivity analyses

The model is particularly sensitive to:

- median overall survival benefit
- median PFS benefit
- quality of life (utility) with 'stable' disease
- quality of life (utility) with 'progressive' disease
- cost of TMZ.

These were investigated through one-way threshold analyses. In order for the ICER for TMZ to be £30,000/QALY, median survival benefit would need to increase to 22 weeks (from the 10.8 weeks modelled from trial data), or PFS to 14 weeks (from 8.2 weeks in the modelled trial data). As utility values have an upper limit of one, it was not possible to estimate an ICER of below £30,000/QALY. However, if utility values are lowered, which is possible as the estimates obtained for the model seem high, then the ICER rises slightly for utility in progressive disease and dramatically in the stable disease state.

Probabilistic sensitivity analyses shows that TMZ was not cost-effective in more than 77% of the simulations. The CEAC suggests that there is a small chance (23%) that TMZ is the most cost-effective option at a willingness to pay level of £30,000/QALY, only rising to be more cost-effective than no TMZ at higher levels (50% probability at £35,000/QALY).

Discussion

Strengths and weaknesses of analyses and uncertainties

The systematic review is based on few trials, which are variable in quality.

No studies in children were identified.

No previous cost–utility assessment relevant to the UK exists for either drug. Extensive sensitivity analyses were undertaken in the PenTAG model.

Utility values obtained using the Value of Health Panel are high. Sensitivity analysis showed that lower utilities increased the ICER.

The impact of specific tumour type needs to be further explored to identify which, if any, patients are likely to benefit from chemotherapy.

Generalisibility of findings

The exclusion criteria of the included trials means that a younger, fitter population is studied than that found in normal clinical practice.

For both drugs, results may be driven by a small number of patients with chemosensitive tumours. The BCNU-W analysis shows no survival advantage for patients with grade IV tumours, and the TMZ trial does not provide subgroup analysis in patients with confirmed grade IV tumours.

It is not known how delays in receiving radiotherapy in the NHS impact on patient survival and what impact this has on the generalisibility of these results.

Conclusions

BCNU-W has not been proven to confer a significant advantage in survival for patients with grade III tumours when treated with the drug, compared with placebo. There does not appear to be a survival advantage for patients with grade IV tumours. No increase in PFS has been shown.

Limited evidence suggests a small but significant advantage in both overall survival and PFS with TMZ among a mixed population with grade IV and grade III (7–8%) tumours. However, it remains unclear whether this is true in grade IV tumours alone.

On the basis of best available evidence, we consider that neither BCNU-W nor TMZ is likely to be considered cost-effective by NHS decision-makers. However, data for the model were drawn from limited evidence of variable quality.

Tumour type is clearly important in assessing patient prognosis with different treatments. Grade IV tumours are commonest and appear to have least chance of response. There were too few grade III tumours included to carry out a formal assessment, but they appear to respond better and drive results for both drugs. Future use of genetic and biomarkers may help identify subtypes which will respond, but current licensing indications do not specify these.

Further research

Further research is suggested into the following areas:

- The effectiveness and cost-effectiveness of BCNU-W have not been proven. Further research is needed to investigate these in specific populations.
- Evidence for effectiveness of TMZ is limited. In particular, it is not known whether patients with confirmed grade IV tumours (the licensed indication) benefit from TMZ. Further research should investigate this.
- The emerging work on genetic markers suggests that grade III and IV tumours can also be classified according to genetic subtype with strong implications for their responsiveness to chemotherapy. Further research on refining these categories/subtypes, and their identification, is required, followed by studies that explore the feasibility of using these markers to inform treatment decisions for individual patients in standard clinical settings.
- Future trials should seek to compare different chemotherapy regimens directly rather than against placebo, and also seek to specify and evaluate sequences of treatment, including second- and third-line treatments, more closely.
- Future trials should also seek to clarify aspects of quality of life that matter most to patients and to characterise the changes in quality of life that occur during stable and progressive disease. More explicit consideration of carer views should also be sought.
- It is important to explore the value that patients put on small absolute survival advantages compared with the disadvantages of treatment requirements; these advantages may be valued differently by those with terminal illness than others in the population.

Chapter 1

Aims

The aim of this report was twofold:

- Carmustine wafers (BCNU-W) are used in newly diagnosed grade III and grade IV gliomas as adjuvant therapy to surgery and radiotherapy. This report assesses the clinical and cost-effectiveness of this regimen compared with surgery with radiotherapy.
- Temozolomide (TMZ) is used in newly diagnosed grade IV gliomas as adjuvant and concomitant therapy to surgery and radiotherapy. This report assesses the clinical and cost-effectiveness of this regimen compared with surgery with radiotherapy.

Chapter 2
Background

Description of underlying health problem

Definition and classification

Gliomas are a type of brain tumour which develop from the glial cells that support the nerve cells in the brain and spinal cord. There are four main types:

- Astrocytoma – the most common, which develop from the astrocytes (star-shaped cells which are the largest and most numerous of the glial cells).
- Oligodendroglioma – which develop from the oligodendrocytes that form the myelin sheaths which insulate axons.
- Mixed tumours – so-called when tumour cell morphology resembles both astrocytes and oligodendrocytes.
- Ependymoma – very rare tumours which develop from ependymal cells that line the ventricles of the brain

Gliomas are graded (based on the WHO classification) from I to IV based on histological morphology of the tumour (*Box 1*). Grade I and II tumours are 'low grade'. They are slow growing, unlikely to metastasise and have a better prognosis. They can still be life threatening if they occur in areas of the brain such as the brainstem and they can also progress to become more aggressive.

Grades III and IV are 'high-grade' tumours and are the most common form of primary brain tumour. Of these, grade IV glioblastoma multiforme (GBM) is the most common (40–45%), followed by anaplastic astrocytoma (AA) (30–35%) and anaplastic oligodendroglioma (AO) (5–15%),[2] both of which are grade III tumours. About 40% of GBM evolve through a multi-step mutation from well-differentiated benign glioma through AA to GBM, whereas 60% of GBM seem to evolve *de novo*.[3]

Diagnosis is provisionally made using computed tomography (CT) scan or magnetic resonance imaging (MRI), with or without contrast, but is nearly always confirmed and classified histologically by brain biopsy. The latter takes place at the time of surgical treatment or as a single event if surgery is not possible (or not indicated as part of the treatment plan). Biopsy is important since radiological diagnosis is not always accurate[4] and histology is an important factor in determining both treatment and prognosis. However, there is evidence of significant inter-observer variability among neuropathologists with regard to both type and grade of tumour.[5–8]

Epidemiology of high-grade glioma

Primary brain tumours are rare, accounting for only 2% of all primary cancers.[1] However, owing to their often aggressive nature and the central role of the brain and the functional consequences of damage to the central nervous system, they are responsible for 7% of the years of life lost from cancer before the age of 70.[9] Primary brain tumours are the 13th most common primary

BOX 1 *Classification of high-grade gliomas (modified from Souhami* et al.*, 2001[1])*

Glioma	Grade III	Grade IV
Astrocytoma	Anaplastic astrocytoma (AA)	Glioblastoma multiforme (GBM) Giant cell glioblastoma (rare) Gliosarcoma (rare)
Oligodendroglioma	Anaplastic oligodendroglioma (AO)	
Mixed	Anaplastic oligoastrocytoma (AOA)	
Ependymoma	Anaplastic ependymoma	

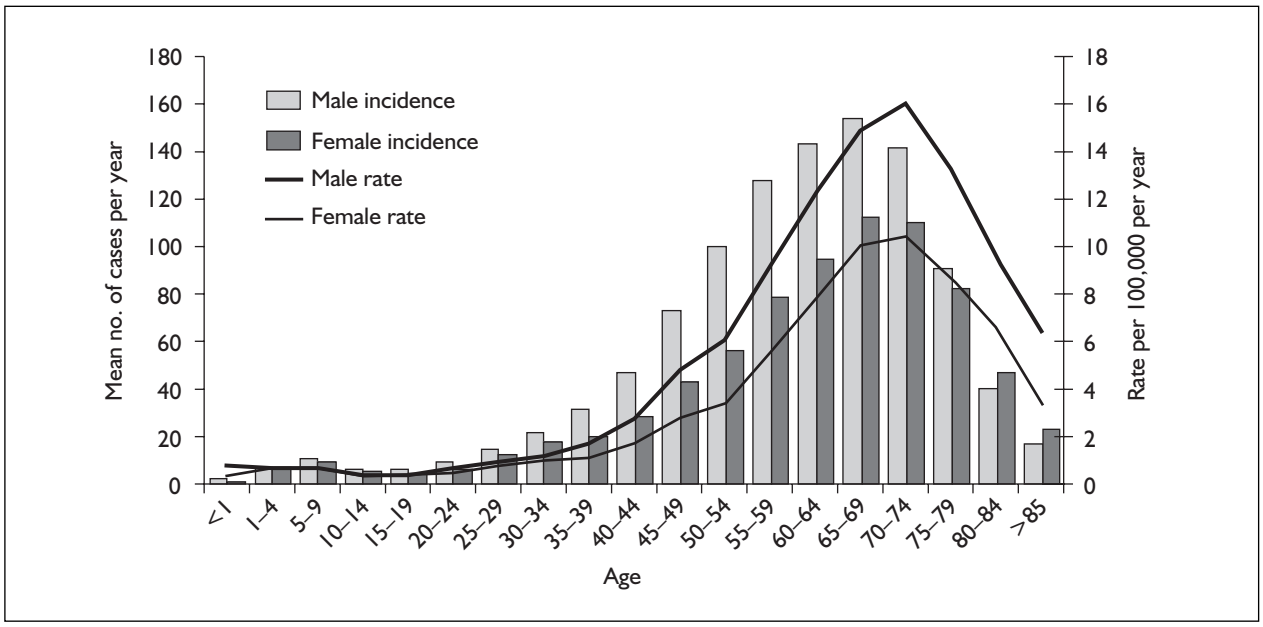

FIGURE 1 *Incidence of high-grade gliomas in England (1990–2001): distribution by age group. Data from ONS Cancer Registry.*[13]

cancers in men, the 15th most common in women[10] and one of the most frequently occurring in children (second only to the leukaemias).[11] Malignant gliomas are regarded as incurable, with very poor prognosis and a potentially devastating impact on the quality of life of the patient. More than 80% recur within 2–3 cm of the margin of the original tumour.[12]

Registry data (*Figure 1*) show that, in England from 1990 to 2001, an average of 1758 new cases of malignant glioma were diagnosed each year, equating to a mean incidence rate of 3.56 cases per 100,000 per year. We have not obtained detailed data for Wales. However, applying the English incidence rate to the Welsh population would amount to a further 103 new cases per year, to give a total of 1861 cases per year in England and Wales.

Age-related incidence of high-grade gliomas has four main characteristics:

- a slight peak in incidence in childhood in the 5–9-year age group
- an increase in incidence with age
- maximum incidence at around 70–74 years of around 13 cases per 100,000 per year
- a gradual decrease in incidence among the older population.

However, the different types of glioma have different incidence profiles. Average age at diagnosis is significantly higher in GBM than in grade III tumours. Patients with AO may be younger on average than those with AA (*Table 1*).

In children, most gliomas are low grade and most are in the posterior fossa, at the back of the brain, or the diencephalic region. This means they often present with a different set of symptoms to adults. Posterior fossa tumours may cause unsteadiness and difficulties in speaking and swallowing. Diencephalic syndrome causes failure to thrive, emaciation, amnesia, sleepiness and unusual eye

TABLE 1 *Age (years) at diagnosis for types of high-grade glioma*

Study	Measure	GBM	AA	AO
Behin *et al.*, 2003[12]	Mean	53	40	
Laws *et al.*, 2003[14]	Mean	58	45 (grade III)	45 (grade III)
CBTRUS, 2004[15]	Median	64	51	48
See and Gilbert, 2004[16]	Mean		41	
Ino *et al.*, 2001[17]	Median			45.3
Fleury *et al.*, 1997[18]	Peak	60–64	60–64	45–49
ONS, 2005[13]	Peak	65–69	60–64	55–59

position. Brainstem tumours are also more common in children than in adults and tend to be more diffuse, making them more frequently inoperable.[19]

Men are more commonly affected than women, in the ratio of approximately 4:3.[13] Although occurring in all races, high-grade gliomas are less common in black and Asian populations.[1]

Molecular genetics of high-grade gliomas

In recent years, histological classification of tumours has been supplemented by a growing understanding of the molecular genetics of gliomas. Molecular classification may give a more accurate indication of prognosis than traditional phenotypic taxonomy.[20] It has been suggested that glioma classification should be reappraised to include genotypic factors.[21]

In the context of the present assessment, two features that may be relevant are, first, loss of genetic material in chromosomal arms 1p, 10q and 19q and, second, status of the MGMT gene.

–1p, –19q and –10q

Loss of genetic material in various chromosomes has been the subject of intense research in recent years, and much attention has focused on chromosomal arms 1p, 10q and 19q.

–1p and –19q are associated with oligodendroglial tumours, whereas –10q is negatively correlated with this phenotype. One or both of –1p and –19q are present in the majority of cases histopathologically categorised as AOs (–1p 50–87%; –19q 58–83%; both 40–78%).[8,17,22–28] Conversely, –10q is seldom seen: most studies report an incidence of 0–24%[8,26,27,29,30] (although 50% of one small series showed this feature[31]). Moreover, –10q is negatively associated with –1p,[8,17,31,32] leading some to suggest that the two genotypes, –1p with intact 10q, on the one hand, and intact 1p with –10q, on the other, represent two distinct subcategories of AO.[31,32] More controversially, it has been suggested that all AOs with –10q may be misdiagnosed astrocytic tumours.[33]

The opposite picture is seen in tumours with astrocytic phenotype. –1p and/or –19q are only seen in a minority of GBMs (–1p 0–24%; –19q 0–33%; both 0–14%),[8,24,25,34–37] and grade III AAs appear to be similar.[24,25,36–38] In astrocytic tumours, –10q appears to increase with tumour grade: deletions are detected in approximately 35% of AAs,[8,37,39–42] with incidence rising to around 75% in GBMs.[8,35,37,39–44] Interestingly, GBMs that have been pathologically classified as having oligodendroglial characteristics have higher rates of –1p/–19q[45] and no –10q.[46] Similarly, when the histopathology of GBMs with –1p/–19q is re-examined, oligodendroglial features are frequently identified.[47]

MGMT

O^6-Methylguanine-DNA methyltransferase (MGMT) is an enzyme that repairs DNA damage at a site commonly targeted by cytotoxic drugs, thereby inhibiting the effect of chemotherapy on tumours. The region of tumour DNA associated with promotion of MGMT sometimes shows unusual levels of methylation (hypermethylation). In these cases, MGMT activity may be decreased or absent.

Aberrant MGMT promoter methylation and/or reduced MGMT expression have been detected in a little under half of GBMs, with reported incidence from 38 to 68%.[48–56] There is some suggestion that oligodendroglial tumours may have higher rates,[28,57–59] although this has not been an invariable finding.[52] In oligodendroglial tumours, MGMT promoter hypermethylation appears to be correlated with the –1p/–19q genotype.[28,57,60]

Aetiology

There are no discernible predisposing factors in most cases. However, there is an association of brain tumours in general, including high-grade glioma, with certain rare genetic disorders such as neurofibromatosis.[1] There is also an association in hereditary immunodeficiency disorders such as ataxia telangectasia.[1]

Environmental factors can also play a role. Patients having radiotherapy to the head, as treatment of another cancer, for example, have an increased risk of developing brain cancer.[1] No definite association has been shown with a variety of suspected chemicals, such as solvents, pesticides and oil products.[1] Studies into mobile phone use have not produced any evidence of an association.[61]

Symptoms

The most common symptoms are headaches, vomiting, seizures and changes in cognitive and/or functional ability.[62] Symptoms are dependent on the size, location and degree of infiltration of the tumour. Tumour mass and swelling around it cause raised intracranial pressure, resulting in headache, nausea, vomiting and papilloedema

BOX 2 *Karnofsky Performance Status*

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalisation is indicated, although death not imminent
20	Very sick; hospitalisation necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

(on ophthalmoscopy). General neurological deficit may cause symptoms such as drowsiness, loss of consciousness, seizures, cognitive slowing, mood and personality changes. More focal neurological deficit (specific to the site of the tumour) may result in difficulties with movement, hearing, speech, ambulation, dexterity, vision and others. In children, posterior fossa tumours result in symptoms of cerebellar involvement such as lack of muscular coordination (ataxia) and rapid eyeball movements (nystagmus).[1]

Prognosis

High-grade gliomas almost never metastasise[12] but are very malignant owing to their ability to expand and infiltrate local tissue. Despite intensive research, the prognosis for patients remains very poor.[63] There are no recent population-based survival data for the UK, but the general consensus in the literature is that median survival time for AA is around 2–3 years and for GBM only 1 year.[2,12] The chance of survival is cumulative. In a study in Taiwan, patients with GBM who survived to 2 years after surgery had a conditional probability of survival for another 3 years of 40.2% in comparison with the observed 5-year survival rate for GBM of 12.4%. Likewise for AA, those surviving to 2 years had a conditional probability of living for another 3 years of 50.1% compared with the observed 5-year survival rate of 28.6%.[64] Even so, the outlook for patients with high-grade glioma remains bleak.

More recently, there have been attempts to identify specific pretreatment prognostic factors and to use them to predict response to various treatments. Thus far, however, no clear pretherapeutic, outcome-based stratification has emerged. Many pretreatment factors have been investigated but only three have consistently been shown to be significant prognostic indicators:[1,65]

- **Age**: younger patients do better and in children tumours seem to be more sensitive to cytotoxic drugs.[3] There is a known relationship between age and tumour histology [see the section 'Epidemiology of high-grade glioma' (p. 3)]
- **Performance status:** this is commonly measured on the Karnofsky Performance Status (KPS) (*Box 2*). The higher the score at diagnosis, the better is the outcome.
- **Histology of the tumour:** grade III tumours do better than grade IV and tumours with an oligodendrocytic component have improved survival.[66,67]

In addition, genetic prognostic markers have been identified. In patients with AO, combined –1p/–19q has been associated with extended overall and progression-free survival (PFS).[17,22–24,26,30,33,68] Other studies have suggested that –1p alone (with or without –19q) is a marker for enhanced survival and PFS.[31,69,70] Conversely, –10q is associated with poor survival and PFS.[17,31,32]

Some evidence shows the subgroup of GBM patients with –1p or –1p/–19q also have longer survival.[35,71] A review of a small group of GBM patients with exceptional survival all showed –1p.[72] The same team noted that AOs without –1p are analogous to GBMs in clinical profile, even when histopathological diagnosis is beyond doubt.[17] Again, –10q is associated with shorter lifespan and has reduced incidence in GBMs with long-term survival.[35,37,42,73]

Reduced MGMT expression – measured directly or by assay of promoter hypermethylation – has been associated with extended overall survival and PFS.[49,50,55,56,74]

Current service provision

Management of high-grade glioma

High-grade gliomas are incurable. Treatment therefore involves finding an appropriate balance between aggressive interventions aimed at improving survival and palliative measures designed to improve patients' comfort and quality of life (QoL).[75]

Combinations of medical symptom management, surgery, radiotherapy, chemotherapy and supportive measures are used. However, few evidence-based treatment guidelines can be drawn from the literature[63,101] such that no 'standard treatment' has clearly emerged and optimal management continues to be controversial.[14] In the UK, most patients have surgery and radiotherapy, with chemotherapy usually reserved for treatment at recurrence for some younger, fitter patients. Despite the aggressive use of surgery, radiotherapy and chemotherapy, only modest improvements in survival have been achieved for patients with malignant glioma.

Medical treatment

The aim with medical treatment is alleviation of symptoms, including analgesics for pain, corticosteroids to relieve cerebral oedema and anticonvulsants to control seizures. If surgery is impossible owing to patient condition, or tumour size or location, palliative medical management may be the extent of treatment.

Surgical treatment

High-grade gliomas are generally diffusely invasive and cannot be completely removed, even with radical resection. The extent of surgery depends on the condition of the patient and accessibility of the tumour. Debulking (partial removal) may provide symptomatic relief and, if possible, the tumour will be removed 'completely', at least at the macroscopic level.

Although there may be a macroscopic boundary to the tumour, high-grade gliomas always infiltrate. The lack of microscopic boundary renders complete excision impossible and recurrence inevitable. However, some studies have suggested that macroscopically complete or near complete resection improves both survival and neurological performance.[3,66,76–78] Advances in surgery, such as image-directed and image-guided craniotomy, have enhanced excision to the apparent tumour margin, resulting in maximal excision being recommended as standard treatment in some quarters.[12] However, the quality of the data in these studies has been challenged[67,79] and a Cochrane Review concluded that there was insufficient evidence to determine whether resection or biopsy alone provided superior outcomes.[80] In most cases, surgery is at least performed for histological diagnosis (biopsy) and alleviation of symptoms (debulking).

Perioperative complications include wound infection, seizures, intracranial bleeding, deep vein thrombosis, depression and pulmonary embolism.[67,81] Perioperative mortality is around 1.5% for first craniotomy and 2.2% for the second.[81] Even so, some patients experience improved neurological status as a result of surgery.[81] There is evidence that the impact of surgery on survival is influenced by the location of the tumour – tumours in one lobe of the brain do better than midline tumours; tumours in the frontal lobe do better than in other lobes; and those in the cortex have better outcomes than deeper ones.[67]

It has been suggested that surgery may push the tumour into a proliferative growth state due to oxygenation, but also that this may make it more sensitive to chemotherapy.[82]

Radiotherapy

There is less debate about the benefit of radiotherapy.[83] A postoperative 6-week course of external beam radiotherapy using linear accelerators is recommended as standard treatment.[83] A systematic review of radiotherapy showed a 3–4-month survival advantage for postoperative radiotherapy compared with supportive care or chemotherapy.[84] However, outcome following conventional radiotherapy is poor in older patients with poor performance status who are more disabled by the tumour.[83,85] In these cases, supportive care alone is reasonable.[83] Even in less disabled patients, the toxic effects of radiotherapy can be considerable.[85,86]

Acute adverse effects, such as swelling, skin irritation, hair loss, tiredness or nausea, occur during or immediately after treatment. Others effects, such as cognitive impairment, may occur some months later.[1] Somnolence syndrome is a common early delayed effect, occurring some weeks after radiotherapy has ended, where patients experience exhaustion, drowsiness, lethargy and memory impairment that may last several months.[1] Acute and early delayed adverse effects may be responsive to steroids. Radiation necrosis is a rare but serious late adverse effect that may be difficult to diagnose owing to similarity with GBM recurrence on scans. Encephalopathy may also affect long-term survivors, causing lack of concentration, loss of memory, unsteadiness and incontinence up to 3 years after radiotherapy. Encephalopathy is related to total radiation dose, fraction size and the age of the patient.

Chemotherapy

There has been considerable debate about the benefits of cytotoxic drugs in the treatment of

high-grade gliomas, especially when newly diagnosed. Chemotherapy is not yet considered standard treatment in the UK, although it is used more routinely in the USA.[87] Sequential categories of chemotherapy are shown in *Figure 2*.

Agents have to be lipid soluble in order to cross the blood–brain barrier. The most frequently used in adjuvant chemotherapy have traditionally been a nitrosurea agent such as carmustine [1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU)] or lomustine [1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)] as single agents or as part of combination therapy. The most commonly used combination therapy has been procarbazine, lomustine and vincristine (PCV therapy). More recently, TMZ has been used as second-line chemotherapy. It has the benefit of being administered orally, has good blood–brain barrier penetration[88] and may be less toxic.[4,89] Adverse effects of chemotherapy include haematological changes (low white blood cell count) with increased risk of infection and bleeding, fatigue, nausea and vomiting.[90]

A Cochrane Review of chemotherapy for high-grade gliomas published in 2004 showed small but clear improvements in survival when chemotherapy was used in addition to radiotherapy, compared with radiotherapy alone.[91] Meta-analysis showed an increase in absolute survival rate from 40 to 46% at 1 year and from 10 to 15% at 2 years. Median survival time increased by 2 months. There was no evidence that this improved outcome depended on tumour type, or that the relative effects of chemotherapy varied in different patient subgroups, such as age, sex, KPS or extent of tumour resection. However, since the underlying prognosis varies in all these groups, the effect of chemotherapy resulted in different absolute improvement in outcome rates.[91] The results of this meta-analysis have been criticised owing to differences in design of the RCTs included and the fact that eight of the 12 trials were published 20 or more years ago.[92] Of the four more recent trials included, only one reports a survival benefit with chemotherapy.[92]

The lack of conclusive evidence for even minimal increases in survival caused by these agents, together with the cumulative toxicity associated with both radiotherapy and chemotherapy, has led to recommendations against the use of chemotherapy during the initial treatment phase and its reserve for the treatment of recurrences.[4,94] Furthermore, tumours may develop resistance to nitrosurea-based regimens, which would render them even less effective if used in recurrence.[4]

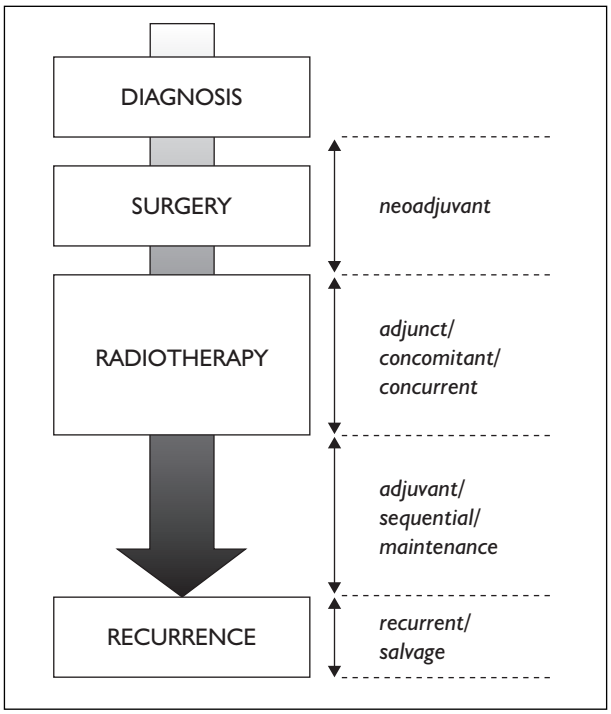

FIGURE 2 *Sequential categories of chemotherapy. Adapted from Parney and Chang.[93]*

In the subgroup of patients with oligodendroglial tumours, evidence for chemosensitivity is more positive. Around two-thirds of AOs treated with chemotherapy show radiographic response, and the contrast with the poor chemosensitivity of astrocytic gliomas is borne out in one direct comparison between tumour groups.[95–99] The improved prognosis for AO patients with –1p/–19q chromosomal losses has been directly related to increased chemotherapy in a number of series, including radiographic evidence of objective tumour response.[17,25,26,30] Conversely, AOs with –10q are less likely to respond to chemotherapy.[17]

Recurrence and progression

More than 80% of high-grade gliomas recur within 2–3 cm of the margin of the original tumour.[12] Recurrence can be defined clinically, based on patients presenting with progressive symptoms, or radiologically, based on a 25% increase in tumour size on follow-up imaging.[100] In the UK, recurrence is usually diagnosed clinically (Palmer J, Department of Neurosurgery, Derriford Hospital, Plymouth: personal communication, 2005).

Palliative care aims to improve function and QoL whereas further aggressive treatment is considered in relation to the performance status of the

patient. Re-operation at recurrence is usually reserved for small, symptomatic and easily accessible tumours[3] and is associated with similar morbidity and mortality to first surgery.[12,81] Stereotactic radiosurgery (where the radiation beam can be targeted specifically at the tumour by the use of computer imaging so that higher doses can be given while minimising toxicity[12,82]) is sometimes used at this point.[12] To avoid problems of drug resistance, chemotherapy at recurrence usually involves cytotoxic drugs not previously used, but overall the benefit remains small.[12]

Quality of life

Absolute survival differences between treatment regimens for malignant gliomas are small, making their impact on QoL particularly important. QoL in people with high-grade gliomas is difficult to measure. Specific tumour localities will affect the nature and location of adverse effects. For example, patients with left hemisphere tumours have significantly increased memory loss, poorer verbal fluency and verbal learning.[102]

Given the potential for mental and physical deterioration caused by the tumours, it is particularly difficult to measure changes in QoL over the course of the illness. One assessment found that half of patients had dropped out of completing serial QoL assessments after 6 months.[103] Those who continued in the study were younger and fitter than the rest of the population, and had a greater probability of survival. Such informative censoring gives rise to considerable scope for bias in serial QoL measurement.

This difficulty in serial measurements also means that it is difficult to ascertain the shape of any deterioration in QoL. It is not clear whether most people experience steady decline, stepwise decline or a period of relative wellness followed by a rapid decline. A longitudinal study, published only in abstract form, of 103 patients with terminal cancer undergoing palliative care assessed QoL using four measures [including Functional Assessment of Cancer Therapy (FACT) and the EQ-5D instrument] prior to death. This suggests that the decline is steady initially and rapid in the last month or two.[104] However, it is uncertain whether this pattern is similar among those specifically with glioma.

Treatments for glioma, in addition to the disease, have an impact on QoL, and it may not be possible to differentiate between tumour and treatment effects. Radiotherapy, for example, has a well-documented side-effect profile, causing hair loss, fatigue, somnolence, deterioration and cognitive problems, some of which may also be caused by tumour progression.[103] In contrast, surgery may initially, at least temporarily, increase QoL dramatically if it relieves the sometimes severe symptoms related to pressure in the cranium, such as headache.

A recent (2002) review of glioma treatments found only five randomised controlled trials (RCTs) for high-grade glioma reporting QoL outcome measures.[105] Of these, two used non-validated measures (the neuropsychological test battery and a 47-item QoL tool adapted from different questionnaires); two used a measure with limited validation (the University of Toronto measure); and one used the validated European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30/B20. The last consists of a 30-item questionnaire generic to those with cancer plus with an additional 20-item brain-specific module.

It is more common for trials in this disease area to use performance scales, particularly the KPS (*Box 2*). However the KPS has been shown to have poor correlation with self-perceived QoL.[106] In particular, it has been shown to differentiate poorly between those with better KPS scores. It is also unable to assess elements of emotional and mental well-being such as depression.[107] Further, KPS score is highly influenced by age.[107]

The Mini-Mental State Examination (MMSE), which assesses cognitive impairment, has been used to measure performance status in glioma trials; however, it is not known how this measure relates to QoL.

QoL has also been assessed using the Short Form with 36 Items (SF-36), in order to compare QoL for patients with glioma with that of patients with small cell lung cancer.[108] QoL scores in the two groups were found to be similar, although specific neurological symptoms for patients with glioma were seen.

Disease-specific measures

FACT

The general Functional Assessment of Cancer Therapy (FACT) scale has a brain subscale and both have been validated in 101 patients with high-grade gliomas.[109] The mean age of the population was young, at 41.2 years, and most

patients had undergone surgery with radiation and chemotherapy adjuncts. Validation of the measure examined the association between scores on the FACT subscales, total score and brain subscales and with other QoL measures completed at the same time [Ferran and Powers Quality of Life Index (FP-QLI); the Beck depression inventory (BDI); the State–Trait Anxiety inventory (STAI); the Norbeck Social Support Questionnaire (NSSQ); Marlowe–Crowne Social Desirability Scale; and clinician-rated KPS]. Validity coefficients were generally high. Test–retest reliability was moderate for the brain subscale ($r = 0.66$, $p < 0.001$) and high for the subscale and generic FACT together ($r = 0.78$, $p < 0.001$).

EORTC

The EORTC QLQ-C30 is a widely used generic scale for people with cancer.[110] It is a 30-item self-reported questionnaire covering the following domains: physical functioning (five items), role functioning (two items), emotional functioning (four items), cognitive functioning (two items), social functioning (two items), global QoL (two items), fatigue (three items), pain (three items), nausea and vomiting (two items) and single items for dyspnoea, insomnia, anorexia, constipation, diarrhoea and financial impact (see Appendix 1).

There is also a specific supplementary brain cancer module (BC20). A 24-item version contains four 'emotional functioning' items that are similar to those in the QLQ-C30 and so a 20-item version may be used if the two questionnaires are used in conjunction. This contains four multi-item scales (future uncertainty, visual disorder, motor dysfunction, communication deficit) and seven single items on headache, seizures, drowsiness, hair loss, itching, weakness of both legs and difficulties with bladder control (see Appendix 1).

Osoba and colleagues[106] assessed these instruments in 105 adults enrolled from three centres in the USA and UK. Eligibility was based on histological evidence of high-grade glioma, a KPS of ≥50, life expectancy of >3 months, a stable steroid maintenance dosage for at least 1 week, ability to provide informed consent and ability to complete the questionnaires. Chemotherapy or radiation therapy was allowed at study entry and throughout. All participants had high-grade glioma, either newly diagnosed (within 2 weeks of surgery, 39%) or radiologically diagnosed as recurrent (61%). They had a KPS of >50 (75% >80) and about half had GBM.[106] About 46% were being treated with chemotherapy and 10% with radiotherapy at the time. This is a relatively well population compared with that found in clinical practice, where more patients are likely to have GMB and may have poorer KPS scores. It is also not possible to assess the impact of the tumour and various treatments independently.

The BC20 has been shown to have significant internal and external validity, exhibiting reasonable test–retest stability over 1 week and also differences between patients with recently diagnosed and recurrent tumours, differences in neurological status and with varying KPS.[111]

Patients with newly diagnosed and recurrent disease were found to have significantly different scores for physical, role and cognitive functioning as well as global QoL. In addition, the brain module found differences in ratings of visual disorder, motor dysfunction, communication deficit, weak legs and bladder control between these two groups.[111]

Different impacts were associated with specific neurological impairment. Those with dysphasia also showed lower physical, role, cognitive and social functioning scores and an increase in future uncertainties, visual disorder, motor dysfunction and weakness of both legs.[111] Dysphasia was not associated with differences in emotional function or global QoL measure compared with those without dysphasia. Motor deficit *was* found to be associated with decreases in all other functioning domains, including emotional functioning, and also global QoL. The authors suggest that emotional functioning may be particularly important in maintaining global QoL. Where participants showed declining neurological status (as measured by the KPS or neurological status), significant deterioration in QoL measures was also seen.

Qualitative research about quality of life

A UK study of 105 patients undergoing surgery and radiation therapy (median age 52 years, range 21–59 years) found that of a median survival time of 10 months in the cohort, only 4 months were spent without serious disability.[85] Content analysis of semi-structured interviews found that, of those surviving beyond 6 months, 25% suffered a clinical deterioration or disability that seemed to be associated with treatment. In addition, 42% suffered from severe tiredness.

Using similar methods, the same authors undertook an interview study of 75 patients with

malignant glioma as they began radiotherapy. They found that although most understood that they had a brain tumour, only one-quarter were fully aware of the extent of their poor prognosis and as many as 43% seemed to show no awareness that they were likely to die.[112] Similar findings have been reported elsewhere.[113] Sixty-six close relatives of these patients were also interviewed and many more (67%) were aware of this poor prognosis. As the illness progressed, more patients became aware that they were dying, but the authors considered that one-quarter still showed no indication of this awareness and a further 22% were only partly aware.[112]

The authors rated patient distress as less than might be anticipated, with more than two-thirds reported as 'only occasionally depressed, anxious or dismayed and remain[ing] generally cheerful or confident'. The level of distress was moderately correlated with awareness of their prognosis. In most cases, relatives were more distressed, and two-thirds were considered to be markedly or moderately distressed.[112]

A substantial minority of these patients (42%) expressed negative comments about radiotherapy. Of the 58 patients who were interviewed again after radiotherapy, only 40% achieved a period of stability or remission. Those not doing so were more likely to view the treatment negatively. Lower levels of dissatisfaction were found about surgery (29%).[112]

The same group undertook another study with 56 of these relatives after they had been bereaved.[114] The majority (about 60%) were rated as feeling that the QoL experienced by their relative with a glioma was poor or unacceptable. About half felt that people had been satisfied with radiotherapy treatment, with a further one-fifth uncertain and the remainder unsatisfied. Views about QoL and radiotherapy were closely related. The authors argue that periods of 'normality', where patients could participate as usual in family, work or social life, were highly valued by relatives, even if these periods were short.

A qualitative study among 28 patients with high-grade gliomas categorised time spent since diagnosis as 'time of everyday life', when patients were able to continue with life, at least in some areas such as work and family activities, as they had before their diagnosis, or 'time of disease', when patients found their life dominated by their condition, either because of the extent and impact of treatment, or the tumour effects themselves.[115] They found that in about one-third of patients, life continuity was lost after diagnosis, leaving only 'time of disease'.

Another qualitative study used grounded theory to analyse interviews with 30 people with glioma and identified ways in which such patients create a sense of protection and hope. They found that the adverse effects of treatment, such as hair loss, could be interpreted by patients as a hopeful sign, as they demonstrated the potential potency of the treatment.[116] In addition, surgery can provide immediate relief from extreme symptoms, such as severe headache, and may result in what the authors describe as "post-operative euphoria which seemed to immunise the patient against intimidating information", such as the severity of their condition.

This research suggests that patient reactions to glioma and its treatment are complex. A substantial minority appear not to recognise the fatal nature of their illness. The place of denial and hope in coping with terminal illness is unclear. This may have implications for the perceived QoL of these patients. Some patients find treatment, particularly radiotherapy, unsatisfactory, especially if it fails to provide a period of disease stability. Conversely, some side-effects are borne because they are felt to indicate that the treatment may be working. For some patients, the time after treatment and diagnosis is dominated by the disease, whereas others are able to continue with aspects of their normal life activities. Such periods of normality may be highly valued by patients.

Description of the new interventions

Carmustine implants

Pharmacology

Carmustine [1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU)] is a chemotherapeutic nitrosurea, an agent that interacts with (alkylates) DNA and RNA in a way that may prevent the proliferation of tumour cells. Systemic (intra-arterial or intravenous) chemotherapy with carmustine has been a therapeutic option for patients with malignant brain tumours since the 1970s. However, studies show systemic carmustine, when used with radiotherapy (RT), confers limited benefit over RT alone.[117–123] Moreover, significant reservations have been expressed about the toxicity profile of systemic carmustine, especially when delivered intra-arterially,[124–126] contributing

to doubts about its place in routine chemotherapy for high-grade gliomas.[94]

The carmustine implant [Gliadel® carmustine wafer (BCNU-W), Link Pharmaceuticals, distributor for Guilford Pharmaceuticals] was developed in the late 1980s as a direct method of delivery to optimise exposure to the chemotherapeutic agent in the affected area of the brain, while minimising the toxicities inherent in high-dose systemic chemotherapy (*Figure 3*).

The implant is made of a biodegradable polymer impregnated with carmustine. Each wafer is round, slightly smaller than a 5-pence piece and weighs 200 mg with 7.7 mg of carmustine (3.85%) loaded evenly throughout.

Wafers are implanted directly on to the surface of the resection cavity at the time of surgery. On exposure to intracranial fluid, the wafer decomposes (the anhydride bonds in the copolymer are hydrolysed), releasing carmustine into the surrounding brain tissue. The wafers are designed to release carmustine over a 2–3-week period. Experimental models suggest that wafers produce the equivalent of a 113-fold increase in brain exposure compared with systemic delivery.[127,128] No evidence of carmustine can be detected in residual wafer fragments removed at subsequent re-operation or autopsy.[128,129] However, around one-third of patients have evidence of residual wafer material on neuroimaging performed 3 months after surgery.[130]

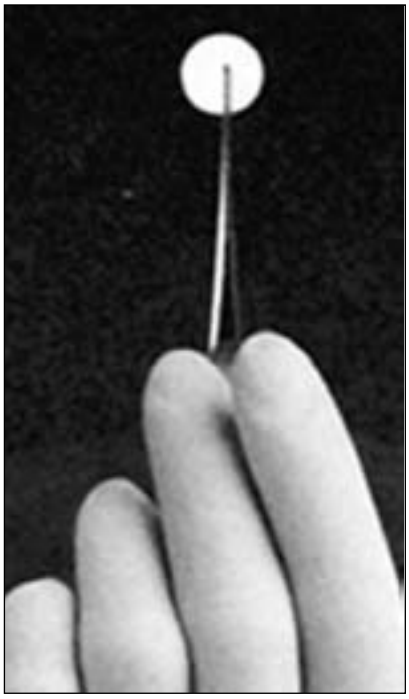

FIGURE 3 *Carmustine wafer (Gliadel®) Image source: http://www.hopkinsmedicine.org/hmn/W05/feature3.cfm*

Licensing

The FDA granted approval for the use of BCNU-W (Gliadel®, Link Pharmaceuticals) "as an adjunct to surgery … in patients with recurrent glioblastoma multiforme for whom surgical resection is indicated" in 1996. In February 2003, this was extended to permit wafer implantation in patients with newly diagnosed high-grade glioma "as an adjunct to surgery and radiation".

The first European marketing authorisation of BCNU-W was granted in France in December 1998 and, in 1999, the Mutual Recognition procedure in 10 European countries was granted for recurrent GBM. This was extended for use in newly diagnosed high-grade glioma in 2004.

Dosage

Up to eight wafers (61.6 mg of carmustine) may be implanted depending on the size of the tumour resection cavity.

Costs

The cost of BCNU-W quoted in the BNF is £687.50 per wafer, meaning that the total cost of medication is up to £5500 per patient. Cost implications of the intervention are considered in detail in the section 'Resource use' (p. 69).

Temozolomide

Pharmacology

Temozolomide (8-carbamoyl-3-methylimidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one; TMZ) is an oral prodrug, that is, it is converted within the body into an active agent. In the case of TMZ, the substance produced is monomethyltriazenoimidazolecarboxamide (MTIC). The effect of MTIC is believed to be methylation of DNA in a way that prevents the proliferation of tumour cells.[89,131] This process occurs rapidly: peak levels of TMZ in the blood are measured 30–90 minutes after a single dose, blood MTIC reaches a peak 90–120 minutes after TMZ administration and maximum levels of a by-product of DNA methylation (AIC) are shown an average of 150 minutes after administration.[132,133]

The production of MTIC occurs spontaneously when TMZ is exposed to physiological acid, which means that TMZ can be taken orally, and the active compound is made available through simple gastrointestinal absorption. Other prodrugs, such as dacarbazine, also produce MTIC, but these depend on enzymatic conversion in the liver,

which can lead to toxic effects and unpredictable availability of the active substance.

It has been suggested that patients with reduced MGMT activity may derive particular benefit from TMZ, because their DNA is less able to repair the cytotoxic damage inflicted by the drug, thus preserving its effect.[52,55,56] As a result, there is interest in agents that may silence the MGMT gene in patients who would otherwise not obtain this benefit. One such agent, O^6-benzylguanine, has been shown to enhance the sensitivity of chemoresistant gliomas to TMZ in experimental settings,[134–136] although there is also some evidence that this combination of treatments may have an unfavourable toxicity profile.[137] A Phase I clinical trial has established the tolerability of this combination in patients with recurrent gliomas[138] and a Phase II trial is under way.[139]

Loss of chromosomal arm –1p is associated with response to TMZ in oligodendroglial tumours.[140–142]

Licensing

A commercial preparation of TMZ (Temodal®, Schering Plough) was authorised for the treatment of patients with recurrent high-grade gliomas by the European Agency for the Evaluation of Medicinal Products in January 1999; this licence has recently been extended to mandate use in newly diagnosed GBM concomitantly with RT and adjuvantly as monotherapy treatment. The TMZ licence excludes children under 3 years old.

Dosage

In patients with newly diagnosed GBM, TMZ is licensed for use in conjunction with RT and is administered in two phases. During RT, a daily dose of 75 mg/m^2 is administered for 42 days. On completion of RT, there is a 28-day treatment break, followed by a second phase of up to six 28-day cycles of maintenance (adjuvant) TMZ treatment. Dosage is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. At the start of cycle 2, the dose is escalated to 200 mg/m^2/day, if haematological toxicity is within prescribed limits.

There is no separate recommended dosage for paediatric cases. A recent study[143] adopted an identical regimen to that used in adult practice, and other studies[144,145] have used an equivalent schedule to the adjuvant phase alone of therapy in adults.

Haematological surveillance is recommended throughout TMZ therapy, in view of the known risk of myelosuppression (neutropenia and thrombocytopenia).

Costs

The base cost of TMZ is £0.69/mg. In an average patient (body surface area 1.8 m^2), a full course of concomitant and adjuvant TMZ costs about £11,000.

Current service cost and impact of new treatments

Full details of our assessment of cost are given in the section 'Resource use' (p. 69). For usual care, providing surgery, RT, second-line treatment for a minority of patients, treatment of adverse effects and end of life care is estimated at an average of £16,000–17,000 per patient. This cost is calculated over the 5 years of our model; however, about three-quarters of the total costs occur in the first year. New cases of high-grade gliomas occur in 3.56/100,000 people. For a District General Hospital serving a population of 250,000 people, this represents about nine people per year, at a total cost of about £144,000–153,000. In England as a whole, a total of 1758 new cases are identified each year [see the section 'Epidemiology of high-grade glioma' (p. 3)]. This represents a cost nationally of around £28–30 million for each cohort over 5 years, with three-quarters of the costs coming in the first year.

The economic model detailed in Chapter 4 suggests that BCNU-W costs an additional £6105 per patient, including any management of adverse effects. Not all patients will be eligible for BCNU-W as tumours need to be accessible and able to be removed leaving a large enough space for the insertion of the wafers. Whittle and colleagues estimate that 25% [95% confidence interval (CI) 16 to 38] of patients presenting to their Edinburgh unit with high-grade glioma would be eligible for BCNU-W implantation, and that about 21% (95% CI 13 to 34) would receive it.[146] Using the CIs, this represents about 1–3 people per year in an average District General Hospital, at a cost of £6105–18,315 over 5 years. In England, this represents about £1.4–3.6 million over 5 years, three-quarters of the cost coming in the first year.

The economic model detailed in Chapter 4 suggest that TMZ costs, on average, an additional £8556 per patient over five years, with three-quarters of the costs coming in the first year. This takes account of patients who do not finish the complete course and the costs of treating adverse effects over and above standard care. For each

cohort of new cases identified in a year, assuming all patients to be eligible for TMZ, this represents a cost per District General Hospital of £77,004 and a cost in England of £15 million over 5 years, with three-quarters of the cost coming in the first year. If only half of the population were eligible, the cost would be £38,502 per District General Hospital and £7.5 million for England.

Chapter 3

Systematic review of effectiveness

Research questions

The following questions were addressed in this review:

1. Compared with current standard treatment, what is the clinical effectiveness of BCNU-W as adjunct treatment to surgery and radiation therapy to treat newly diagnosed high-grade glioma?
2. Compared with current standard treatment, what is the clinical effectiveness of TMZ as concomitant and adjuvant treatment to surgery and radiation therapy to treat newly diagnosed high-grade glioma?

Review team and Advisory Group

The review was carried out by a team comprising Dr Rob Anderson, Dr Matthew Dyer, Ruth Garside, Stuart Mealing, Dr Martin Pitt, Alison Price, Gabriel Rogers, Dr Margaret Somerville and Dr Ken Stein.

Experts in the field were approached to be part of an Expert Advisory Group for the project. Details are given in Appendix 2. The Advisory Group was consulted about inputs for the model and asked to comment on an early draft of the report.

General methods

The review generally adhered to the methodological guidelines published by the NHS Centre for Reviews and Dissemination (York) Report No. 4.[147] The project protocol is shown in Appendix 3.

There is no available evidence detailing the direct comparison of TMZ and BCNU-W. Because of this, separate reviews were conducted for each intervention.

Methods for systematic review of effectiveness

Inclusion and exclusion criteria

Inclusion

BCNU-W

Intervention:

- BCNU-W as an adjunct to surgery with subsequent radiation therapy with or without standard systemic chemotherapy.

Comparators:

- Placebo wafer inserted at the time of surgery with or without radiotherapy (RT).
- Surgery with or without RT and systemic chemotherapy with standard antineoplastic agents (excluding those listed in the intervention).

TMZ

Intervention:

- Surgery followed by RT with concomitant TMZ followed by an adjuvant course of temozolomide.

Comparators:

- Surgery followed by RT with or without systemic chemotherapy with standard antineoplastic agents (excluding those listed in the intervention).

Inclusion criteria common to both interventions

Population:

- Children and adults with newly diagnosed grade III or IV primary gliomas.

Study design:

- Systematic reviews.
- RCTs.
- Non-randomised evidence was also considered where it gave the best estimates of a required parameter (for example adverse effects or patient preferences) or where RCT data were scanty or uninformative.

Exclusion

BCNU-W

- Studies of BCNU-W in which treatment with carmustine other than as wafers at the time of surgery and radiation therapy took place but was not reported separately.

TMZ

- Studies in which the use of TMZ other than as an adjunct to surgery and radiation therapy took place but was not reported separately.

Exclusion criteria common to both interventions

Population:

- Not primary diagnosis of high-grade glioma (low-grade gliomas, other types of brain tumour).
- Not newly diagnosed glioma (recurrent or advanced cases).

Study design:

- Narrative or non-systematic reviews.
- Preclinical or biological studies, animal models.
- Case studies.
- Abstract only.
- Not available in English.

Assessment of the effectiveness of temozolomide and carmustine implants

Search strategy

Electronic databases were searched for published systematic reviews, RCTs, observational studies, economic evaluations and ongoing research in March 2005 and updated in August 2005. Appendix 4 shows the databases searched and the strategy in full. Bibliographies of articles were also searched for further relevant studies and the US Food and Drug Administration (FDA) website was searched for relevant material.

Observational studies were considered for inclusion to broaden the evidence base under review, as it was suspected that there would be few relevant RCTs. Moreover, it was judged that the more inclusive eligibility criteria frequently found in observational case series might result in evidence with a greater degree of generalisibility than the RCTs. Additionally, we speculated that such studies might provide longer follow-up data and more detailed description of treatment-related adverse effects.

Identification of studies

Identification of relevant studies was made in two stages. Abstracts returned by the search strategy were examined independently by two researchers (RG and GR) and screened for inclusion or exclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers (RG and GR) examined these independently for inclusion or exclusion and disagreements were resolved by discussion. The process is shown in Appendix 5.

Data extraction strategy

Data were extracted by one researcher (GR) and checked by another (RG). Actual numbers were extracted where possible. Data extraction forms for each included study are reproduced in Appendix 7.

Quality assessment strategy

Assessments of RCT quality were performed using the indicators shown below. Results were tabulated and these aspects described.

Internal validity

Sample size

- Power calculation at design.

Selection bias

- Explicit eligibility criteria.
- Proper randomisation and allocation concealment.
- Similarity of groups at baseline.

Performance bias

- Similarity of treatment other than the intervention across groups.

Attrition bias and intention to treat analysis

- All patients accounted for.
- Withdrawals specified and described.
- Analysis undertaken on an ITT basis.

Detection bias

- Blinding.
- Objective outcome measures.
- Appropriate data analysis.

We also noted any potential conflicts of interest (for example, financial support provided to studies and/or authors by manufacturers of the interventions).

For observational studies, we addressed such of these criteria as were applicable to study design, and also noted whether the study in question was prospective and whether it explicitly enrolled consecutive patients.

Systematic reviews were assessed against QUOROM guidelines.[148]

External validity

External validity was judged according to the ability of a reader to consider the applicability of findings to a patient group in practice. Study findings can only be effectively generalisable if they (a) describe a cohort that is representative of the affected population at large or (b) present sufficient detail in their outcome data to allow the reader to extrapolate findings to a patient group with different characteristics.

To assess the generalisability of included studies, we focused on the baseline factors on which high-grade glioma outcomes are known to be substantially dependent – age, performance status and tumour histology. Studies that were representative with regard to these factors were judged to have high external validity. The age range of each cohort, in particular, was seen as an index of a study's applicability to the patient population in practice.

Methods of analysis

Details of the methodology and results of included studies are tabulated and described in the text. We have presented results from RCTs and case series in the same tables; where study design renders cells inapplicable, they have been greyed out. Dashes in the tables indicate that the information was not reported. Where explicitly calculated by PenTAG, χ^2 statistics were derived using the CHIDIST function of Microsoft Excel.

Where data were available, we combined absolute survival at a fixed time point (e.g. at 12 months). Meta-analysis was undertaken to estimate a weighted treatment effect across trials. A random effects model was used to avoid the assumption of a single underlying treatment effect. This is more conservative, but incorporates an estimate of between-study heterogeneity. Without patient-level data, it was not possible to pool survival analyses.

Indirect comparison between the two interventions was considered if enough similarities in study method and population were found.

Results of the systematic review: quantity of research available

Number and type of studies identified

The inclusion/exclusion process is illustrated in Appendix 5.

Our searches returned 805 separate references relating to one or both of the interventions. From screening of abstracts, we excluded 761 of these, leaving 44 potentially relevant studies to be reviewed in full. Thirty-four further papers were excluded at this stage (see Appendix 6 for a list of these, with reasons for exclusion).

Our assessment of BCNU-W is based on six papers: two systematic reviews, two RCTs and two case series.

Our assessment of TMZ is based on four papers: two RCTs and two case series.

All of the studies identified compared the chemotherapy regimens under review with surgery and radiotherapy.

Results of the systematic review: carmustine implants

Quality of included systematic reviews

We identified two previous systematic reviews that were wholly or partially concerned with the effectiveness of BCNU-W in newly diagnosed high-grade gliomas.[149,150] These were assessed against the QUOROM statement, details of which can be found in Appendix 7. Data extraction tables are in Appendix 8.

The paper by Meldorf[150] describes itself as a meta-analysis rather than a systematic review and combines patient-level data from two BCNU-W RCTs.[130,151] No details are therefore given of search strategy, data extraction or characteristics of the included trials. Clinical heterogeneity was not assessed but the trial designs are described as "almost identical". Only survival data were analysed. Data were adjusted using a Cox proportional hazards model to account for the impact of KPS, age, country of origin and tumour type.

A total of 272 patients (240 from the Westphal trial[151] and 32 from the Valtonen trial[152]) were included in the analysis. The estimated hazard ratio for the BCNU-W group compared with placebo wafer was 0.68 (95% CI 0.53 to 0.87, $p = 0.006$) or a 32% reduction in the risk of death. The adjusted hazard ratio (HR) was 0.69 (95% CI 0.53 to 0.90, $p = 0.006$)

KPS ($\leq$70 versus >70) and age ($\geq$60 versus <60 years) were independent, statistically significant factors associated with improved survival. HRs were 1.43 (95% CI 1.09 to 1.94,

$p = 0.0002$) and 2.14 (95% CI 1.39 to 3.29, $p = 0.0005$), respectively.

As this review did not include a critical assessment of study quality, contained no subgroup analysis for tumour type and did not provide primary data about included study end-points, it was not felt to provide sufficient information to override the need for us to undertake our own systematic review. However, the meta-analysis does have the advantage of access to patient-level data.

The second systematic review identified was by Brophy and Chen at the technology assessment unit of the McGill University Health Centre in Canada.[149] This is a web-based publication and as such has not been peer reviewed.

The review provides a description of the search strategy used but it is not clear how data were extracted. Details of the inclusion criteria are not made explicit but appear to be RCTs for BCNU-W in patients with newly diagnosed or recurrent malignant gliomas. Study quality is assessed using the Jadad score and all included studies (one in recurrent disease[153] and two in newly diagnosed disease[151,152]) are defined as being "adequate". Results from the trials are presented descriptively. There is no detailed presentation of study characteristics to inform quality assessment and it is not clear that all results have been summarised. We therefore felt that this review was not sufficient to override the need for us to undertake a further systematic review.

Quality of included randomised controlled trials and case series

Two RCTs[151,152] and two observational case series[129,154] met our inclusion criteria. Design characteristics of the studies are summarised in *Table 2*.

The first RCT[152] took place in Scandinavia in 1992–93 and was followed by a worldwide trial in 1997–99.[151] The two trials are comparable in design, with analogous eligibility criteria and similar treatment protocols (for both intervention and control regimes).

The uncontrolled case series are also broadly analogous. Brem and colleagues' paper details a multicentre Phase 1 (open-label safety pilot) trial.[129] Kleinberg and colleagues provide a retrospective review of all relevant interventions undertaken in day-to-day practice at a single centre.[154] Because of the design of this study, no explicit inclusion criteria were stipulated for age and performance status of participants.

The RCT reported by Westphal and colleagues[151] and, to a lesser extent, the RCT by Valtonen and colleagues[152] and the Phase 1 series by Brem and colleagues[129] were scrutinised in detail by the FDA, as part of their authorisation process for BCNU-W for newly diagnosed high-grade gliomas. Extra evidence from the studies was presented by the manufacturer, and additional analysis was carried out by the FDA's experts. The majority of the documentation recording this process has been made publicly available on the FDA's website,[155,156] and we have considered this material where it adds to the published articles. Our data extraction tables (see Appendix 8) identify the information that has been derived from this source.

Internal validity

Measures of internal validity are given in *Table 3*.

Sample size

In the major RCT reported by Westphal and colleagues in 2003,[151] the initial protocol specified a sample size of 200 with 90% power to detect a 20% difference in 12-month survival, at two-sided significance level of 5%. When consulted during study design (1997), FDA consultees had warned that the assumed treatment effect was "overly optimistic".[155] Following a preliminary review of blinded data in 1999, the investigators amended the protocol to increase sample size to 240, powering the study to detect an 18% difference in 12-month survival. Analysis at the study's protocol-specified cut-off, by which time 240 subjects had been recruited, revealed a difference in 12-month survival of less than 10%. Post-hoc FDA analysis showed power of "only about 46%" at that stage, with the reviewer noting, "Even if the data provides 100% events, the power would increase only to 57%".[155]

The study protocol for Valtonen and colleagues' RCT[152] indicated that a maximum of 100 patients were to be enrolled; however, only 32 patients entered the trial, as the investigators were unable to source additional wafers. The study was therefore underpowered to detect significant differences in outcomes between arms.

Brem and colleagues detailed an uncontrolled multicentre Phase 1 (open-label safety pilot) trial.[129] Three centres enrolled patients until one of the centres had reached 10 subjects, at which point enrolment was discontinued in all centres, leading to a sample size of 22. Kleinberg and

TABLE 2 *Design characteristics of included studies (carmustine implants)*

Study (design)	Setting (entry dates)	Inclusion criteria				Exclusion criteria	Treatment regime		Outcomes measured	
		Age (years)	Tumour	Performance status	Other		Intervention	RT	Primary	Secondary
Westphal *et al.*, 2003[151] (RCT) (n = 240)	38 centres in 14 countries (12/1997–07/1999)	18–65	Grades III and IV	KPS ⩾60	Single, contrast-enhancing, unilateral, supratentorial tumour Surgery within 2 weeks of baseline MRI	Prior cytoreductive therapy Prior RT to the brain Known hypersensitivity to nitrosureas "Clinically significant laboratory abnormalities (in the judgement of the investigator)"	Intraoperative placement of ⩽8 wafers (i.e. ⩽61.6 mg of BCNU)	55–60 Gy: 30–33 daily fractions, 5 days/week focal (2–5-cm margin)	Survival	Time to KPS decline Time to neurological progression PFS QoL Adverse events
Valtonen *et al.*, 1997[152] (RCT) (n = 32)	4 Scandinavian university hospital neurosurgical units (03/1992–03/1993)	18–65	Grades III and IV	KPS ⩾60	Unilateral, unifocal tumour at least 1 cm in diameter	Significant renal, hepatic or haematological dysfunction Other concomitant life-threatening disease Pregnancy Hypersensitivity to radiographic contrast media	Intraoperative placement of ⩽8 wafers (i.e. ⩽61.6 mg of BCNU)	"Standard" RT (regimen not detailed)	Survival	2-year survival
Kleinberg *et al.*, 2004[154] (CS) (n = 45)	1 US university hospital oncology centre (07/1990–08/1999)	No explicit limits	Grades III and IV	No explicit limits	Surgically resectable, unilateral, contrast-enhancing tumour	Evidence of systemic disease	Intraoperative placement of ⩽8 wafers (i.e. ⩽61.6 mg of BCNU)	Regimen not uniform; most (30) patients received 59.5–60 Gy at 1.8–2 Gy/day	Surgical outcome	Survival Toxicity Steroid dosing Histopathological findings at reoperation
Brem *et al.*, 1995[129] (CS) (n = 22)	3 US centres (07/1990–08/1991)	⩾18	Grades III and IV	KPS ⩾60	Single, unilateral, supratentorial tumour of at least 1 cm^3	Significant renal, hepatic or haematological dysfunction Other concomitant life-threatening disease Pregnancy Hypersensitivity to radiographic contrast media	Intraoperative placement of ⩽8 wafers (i.e. ⩽61.6 mg of BCNU)	"Standard" RT (regimen not detailed)	Complications Functional status	Survival

CS, case series.

TABLE 3 *Internal validity measures of included BCNU-W studies*

	Randomised controlled trials		Case series	
	Westphal et *al.*, 2003[151]	**Valtonen et *al.*, 1997[152]**	**Kleinberg et *al.*, 2004[154]**	**Brem et *al.*, 1995[129]**
Power calculation at design?	Yes	No		
Proper randomisation?	Yes	Yes		
Groups similar at baseline?	Predominantly[a]	No[b]		
Investigators blinded?	Yes[c]	Yes[c]		
Outcome assessors blinded?	Yes	Yes		
Patients blinded?	Yes	Yes		
Prospective?			No	Yes
Consecutive patients enrolled?			No	Not reported
Eligibility criteria stated?	Yes	Yes	Yes	Yes
Objective outcome measures?	Predominantly[d]	Yes	Predominantly[e]	No[f]
Analysis on ITT basis?	Yes	Yes	No	Yes
All patients accounted for?	Yes	Yes	Yes	Yes
Withdrawal specified?	Yes	Yes	NA	Yes
Withdrawal reasons given?	Yes	Yes	NA	Yes
Inter-centre consistency?	Yes	Not reported	NA	No
Conflicts of interest?	Yes	Yes	Yes	Yes

ITT, intention-to-treat; NA, not applicable.
[a] Distribution of grade III tumours arguably favoured BCNU-W group (see text). Mean tumour size was larger in the BCNU-W group.
[b] All patients in placebo group had grade IV gliomas, whereas 5/16 of the BCNU-W group had grade III tumours; slight differences in KPS in favour of placebo group.
[c] Note that placebo wafers and active implants were visibly different (see text).
[d] Definition of disease progression can be dependent on assessment of treating clinician.
[e] Data extracted from historical patient notes (presumably varying quality).
[f] Some primary outcomes subjective, particularly 'severe' vs 'mild or moderate' postoperative events.

colleagues' uncontrolled case series is a retrospective review of all relevant interventions at a single university hospital oncology centre during a given period.[154] A total of 45 cases are reported, 10 of which are common to this study and the Phase 1 trial.

In total, the evidence-base includes 193 patients who received BCNU-W and 136 who had placebo wafers implanted (see *Table 4* for full details of patient characteristics).

Selection bias

Randomisation methods were identical in the two RCTs and appear relatively sound. Wafers were provided to each centre in blocks of four unmarked boxes (two BCNU-W, two placebo). Following intraoperative confirmation of eligible diagnosis, a blinded box of wafers was chosen for implantation by the investigator. However, the blinding of the wafers was imperfect (see also comments on detection bias), and it has been noted that, under such circumstances (and especially when block size is consistent), investigators can potentially manipulate a proportion of treatment allocations.[157] However, we believe this to be unlikely, and the multicentre design should minimise any impact.

Westphal and colleagues[151] report only one imbalance between trial arms in their published paper: larger mean tumour size in the BCNU-W group ($p = 0.047$). However, this is not thought to have much prognostic importance.[78] FDA assessors were concerned by asymmetry in allocation of "favourable" non-GBM diagnoses, especially anaplastic oligoastrocytomas (eight in the BCNU-W arm versus three in the placebo arm). As histopathology is a greater predictor of patient outcome than any current therapy, this may be significant despite the small absolute numbers. In addition, the diagnoses of one referee pathologist were considered definitive in the trial and dictated the classification of cases in all subsequent analyses. By way of verification and sensitivity analysis, FDA assessors requested that the data be re-examined on the basis of the alternative trial referee pathologist's diagnoses. This re-analysis showed an increased imbalance in distribution of grade IV tumours (88 BCNU-W versus 99 placebo) which, if accurate, could further bias the trial in favour of the intervention.

TABLE 4 *Patients' characteristics at baseline in included BCNU-W studies*

Study	Sample size	Age (years)	Sex (% M:F)	Histology (%)	KPS	Extent of surgery (%)			Subgroups analysed	Follow-up (months)
						Total	Partial	Lobectomy		
Westphal *et al.*, 2003[151]	Total 240 BCNU-W 120 Placebo 120	Mean: BCNU-W 52.6 Placebo 53.6 Range: BCNU-W 21–72 placebo 30–67	BCNU-W 63:37 Placebo 70:30	Grade IV: BCNU-W 84 Placebo 88 Grade III: BCNU-W 16 Placebo 12	Median: BCNU-W 80 Placebo 90 Range: BCNU-W 60–100 Placebo 60–100	BCNU-W 47 Placebo 41	BCNU-W 52 Placebo 55 Mean % of tumour resection: BCNU-W 89.9 Placebo 88.3	BCNU-W 2 Placebo 3	GBM only	⩾12 Range 12–30
Valtonen *et al.*, 1997[152]	Total 32 BCNU-W 16 Placebo 16	Median: BCNU-W 55.5 Placebo 53.0 Range: BCNU-W 36–67 Placebo 36–65	BCNU-W 50:50 Placebo 63:38	Grade IV: BCNU-W 69 Placebo 100 Grade III: BCNU-W 31 Placebo 0	Median: BCNU-W 75 Placebo 90 Range: BCNU-W 60–100 Placebo 40–100	BCNU-W 6 Placebo 6	BCNU-W 88 Placebo 94	BCNU-W 6 Placebo 0	GBM only	⩾24
Kleinberg *et al.*, 2004[154]	45	Median 57 Range 34–77	Not reported	Grade IV 87 Grade III 13	<70 20 ⩾70 80	Not reported	Not reported	Not reported	GBM only	Median 16.8
Brem *et al.*, 1995[129]	22	Mean 60 Range 45–86	68:32	Grade IV 95 Grade III 5	Mean 84.3 Range 40–100	14	64	23	None	Mean 7

In Valtonen and colleagues' RCT,[152] all patients in the placebo group had GBM, whereas five (31.3%) of the BCNU-W group had grade III tumours. Subgroup analyses on GBM-only patients are presented, eliminating this bias at the expense of further diminishing an already substantially underpowered sample. The authors also note a "slight difference" in baseline KPS that might cause bias in favour of the intervention, but do not report any test of the significance of this discrepancy.

Bias in patient selection is always possible in uncontrolled case series. However, this is more properly considered as an issue of external validity (the extent to which biased selection of participants may compromise the applicability of its findings) and is discussed in the section 'External validity' (p. 23).

Performance bias
In Westphal and colleagues' RCT,[151] there was potential for bias in the administration of additional conventional (systemic) chemotherapy, which was permitted by protocol only in patients with AO tumours, known to be especially chemosensitive.[158,159] Four patients with AO received chemotherapy (2/6 in the BCNU-W group and 2/5 in the placebo group) together with four patients with AOA (3/8 in the BCNU-W group and 1/3 in the placebo group). A small bias in favour of the intervention is possible, particularly in long-term analysis.

Treatment such as repeat tumour resection and 'salvage' chemotherapy was permitted by all studies at investigators' discretion after diagnosis of tumour progression/disease recurrence. Although the effectiveness of individual modes of second-line therapy remains uncertain, treatment of recurrent tumours may confer survival benefit, especially in younger, fitter patients and those with more chemosensitive tumour types.[160,161] Late performance bias confounding survival rates in the BCNU-W trials is therefore a possibility. The impact of treatment order is unknown.

The FDA's analysis of Westphal and colleagues' trial reports the frequency of repeat surgical procedures (for post-implantation complications, and also for disease progression). There is a higher rate of reoperation in the BCNU-W arm: 40 versus 31.7% ($p = 0.178$). The discrepancy is greater in non-GBM cases; the majority of patients with grade III tumours in the BCNU-W group underwent reoperation (10/19 = 52.6%), but surgical reintervention was undertaken in less than one-quarter of comparable patients in the placebo group (3/14 = 21.4%) ($p = 0.0698$). There were also discrepancies favouring the BCNU-W arm in frequency of post-recurrence chemotherapy (14.2 versus 10.0%; $p = 0.322$) and other treatments [BCNU-W reimplantation (two versus none), brachytherapy (one versus none) and stereotactic radiosurgery (one versus none)]. Although none of these differences is statistically significant at conventional levels, all apparent asymmetries favour the BCNU-W group, and it is possible that small imbalances, in combination, could provide survival advantage for that group.

Valtonen and colleagues[152] do not report post-study treatment.

In uncontrolled case series, the treatment provided is only relevant as an issue of generalisability and so is discussed in the section 'External validity' (p. 23).

Attrition bias and intention-to-treat analysis
Westphal and colleagues report that three patients withdrew from their RCT, two were lost to follow-up and one withdrew consent.[151] It is not clear from which arm of the trial these patients withdrew. Patients who withdrew were censored alive at time of last contact in survival analyses.

Valtonen and colleagues had complete follow-up in their small RCT,[152] as did Brem and colleagues in their uncontrolled study.[129] One patient was lost to follow-up in Kleinberg and colleagues' case series and was excluded from analysis.[154]

Detection bias
Blinding. Both RCTs are described as "double-blind". In their discussion of Westphal and colleagues' RCT,[151] the FDA observed that the physical characteristics of the placebo wafers differed in colour and friability from those containing carmustine (presumably, this would also have been true in Valtonen and colleagues' trial[152]). As a result, individual investigators would have been able to distinguish between, but not identify, trial arms. It was also possible to unblind treatment allocation at treating centres, in the event that an individual investigator deemed access to this information necessary for management of adverse events. There is no report of whether this occurred.

Assessment. Overall survival is the main outcome measure in the RCTs and appears to have been assessed consistently. However, both RCTs have definitions of disease progression that are partially

dependent on the subjective assessment of treating clinicians and this is the basis on which PFS times are calculated:

- The overriding criterion is radiological evidence of tumour growth of a specified magnitude. Although in principle this is an objective measure, considerable inter-observer variability has been shown in radiological assessment of tumour response to chemotherapy.[162]
- Each study also includes an alternative definition of progression based on the patient's symptomatic state: "a documented clinical/neurological decline". Such a definition is open to interpretation on the part of treating clinicians.[163]

This is a potential source of bias if imperfect blinding allowed outcome assessors to discern treatment allocation. However, PFS results were ultimately very similar in each arm of the major RCT [see the section 'Effectiveness (all patients)' (p. 26)].

Analysis. There is concern about the statistical methods adopted in the presentation of Westphal and colleagues' results.[151] In particular, the following issues should be considered:

- In the published report of the trial, analyses are stratified according to the country in which treatment took place. The stated justification for this was that randomisation was stratified by centre, because wafers were sent to each participating unit in sets. The authors argued that, although analysis by centre would have introduced an excessive degree of stratification to the model, it was hoped that stratification by country would prove sufficient to capture any variation between centres without excessively multiplying levels of stratification.

FDA reviewers criticised this method, especially as it had not been pre-specified in the study protocol. They demonstrated that this mode of stratification was uniquely well suited to maximise the apparent effectiveness of BCNU-W, and provided results of unstratified analyses that tended to generate less significant results. Full details of this debate are given in transcripts of the FDA hearing at which the extension of BCNU-W's licensed indication was considered.[156]

In reporting results from this trial below, we have provided both published (stratified by country) and protocol-specified (unstratified) analyses, where both are available. We are reticent about relying on published findings alone where they are noticeably different from those generated by unstratified tests (for example, where stratified analyses provide *p*-values which achieve significance but unstratified analyses do not).

- The FDA reviewers also criticised the trialists' analysis of two secondary outcome measures: time-to-decline of KPS and time-to-progression on neurological indices. Published results were based on analyses that counted death as an event. When the FDA repeated the analysis with deaths censored, much of the data were lost and statistical significance was no longer apparent. These end-points are clearly not independent of the primary (survival) analysis. Consequently, the presented statistics are flawed.

External validity

A priori inclusion/exclusion criteria and treatment design are shown in *Table 2*. Baseline patients' characteristics including age, sex, tumour type, performance status and extent of surgery are shown in *Table 4*.

The generalisability of the included studies may be compromised by the age profile of the evidence base; both included RCTs excluded patients over 65 years old, whereas in practice one-third of patients with high-grade gliomas fall into this category [see the section 'Epidemiology of high-grade gliomas' (p. 3)].

The age profile of Brem and colleagues' case series (mean 60, range 45–86 years) appears more representative of the affected population than the other included studies.[129] The retrospective case series reported by Kleinberg and colleagues is the only study that reports the use of BCNU-W in clinical practice.[154] Although formal eligibility criteria would not have applied to their patient selection process, the profile of the reported cohort (median age 57, range 34–77 years) suggests the intervention may have been used preferentially in younger patients.

External validity may also be affected by the exclusion of patients with low performance indices. Those with multifocal or deeply infiltrative tumours were also excluded, but as BCNU-W implantation is contingent on physical tumour characteristics, these patients are also ineligible for BCNU-W in clinical practice. Based on participation in Westphal and colleagues' RCT,[151] Whittle and colleagues estimated that 25% (95% CI 16 to 38%) of patients presenting to their Edinburgh unit with high-grade glioma would be

eligible for BCNU-W implantation, with about 21% (95% CI 13 to 34%) actually receiving it.[146] Although increasing the upper age limit could enhance generalisibility, BCNU-W use in practice is also limited to larger, accessible tumours.

Finally, post-recurrence treatment provided in included studies compared with clinical practice was considered. Reoperation rates in the BCNU-W and placebo arms of Westphal and colleagues' 2003 RCT were 40% and 31.7%, respectively.[151] In the case series by Brem and colleagues, nine patients (40.9%) underwent reoperation (one twice).[129] Kleinberg and colleagues reported that 15 patients (33.3%) had repeat tumour resection, of whom four (8.9%) proceeded to a third operation.[154] These rates appear high in comparison with reoperation rates in published series from units in Germany (17.0%),[164] Turkey (21.1%),[165] and the USA (15.3%),[166] in UK practice, as few as 10% of patients may receive repeat resection at recurrence (Palmer J, Department of Neurosurgery, Derriford Hospital, Plymouth: personal communication, 2005). These higher rates of re-intervention may reflect a younger, fitter cohort in the trials compared with clinical practice. Such patients respond better to aggressive treatment.

Summary of study quality

A summary of the major FDA criticisms of Westphal and colleagues' RCT[151] is shown in *Table 5*.

A summary of the quality of included BCNU-W studies is given in *Box 3*.

Results of included randomised controlled trials and case series

Outcome measures

The outcome measures for which we have extracted data are described and discussed below.

TABLE 5 *Summary of FDA criticism BCNU-W RCT evidence*

Area of concern	FDA critique	Likely direction of bias
Sample size calculation	This was based on 90% power to detect 20% survival difference at 12 months. FDA felt that this was an optimistic treatment effect on which to base calculation; the actual difference was about 10% and the FDA calculated that actual power was about 46%. The possibility of a Type II error remains	Placebo
Selection bias	Higher numbers of AOs in the active arm (BCNU-W 8 vs 3 in placebo arm). Long-term survivors (n = 11 at August 2002, up to 56 months follow-up) in the trial are 5/8 AOs in the BCNU-W arm and 1/3 AOs in the placebo arm. Despite the small absolute numbers of tumours with better prognostic histology, the FDA felt that this could have a significant impact on the results, especially as absolute difference in survival was small. Subgroup analysis of GBM found no difference in survival. In addition, when the population was re-examined by another central pathologist's diagnoses, the imbalance of tumour types increased (88 GBM vs 99 placebo)	BCNU-W
Performance bias	Treatment at recurrence: higher numbers of reoperation, especially in non-GBM cases, and also chemotherapy, reimplantation of BCNU-W, brachytherapy and stereotactic radiosurgery. None of these is statistically significant but in each case the difference favours BCNU-W and impact could be cumulative	Not clear. Possibly BCNU-W
Detection bias: blinding	Active and placebo wafers differed in colour and friability. Blinding is therefore compromised. Investigators were also permitted to unbind allocation if they felt this was needed to address adverse effects. It is not reported whether or not this happened. Given that the primary outcome is objective (survival), this may not have an impact, however, it may affect choice of secondary treatment	Not clear
Statistical analysis	Median survival, estimated by Kaplan–Meier curves, was adjusted for country, although this was not a per protocol analysis. This calculation gives a significant median survival advantage (p = 0.03) not seen with the per protocol analysis (p = 0.08) The FDA found that this particular stratification maximised the apparent treatment effect of BCNU-W	BCNU-W
Outcome measures	In the published results, analyses of time to KPS decline and time to progression counted death as an event. These outcomes are not independent of the primary outcome, death. When analyses were repeated by the FDA censoring death, differences were no longer significant	BCNU-W

BOX 3 *Summary of quality of included BCNU-W studies*

- The evidence base is limited to four studies, including two RCTs (193 patients receiving BCNU-W).
- Both RCTs were underpowered.
- Randomisation and allocation concealment were probably adequate in the RCTs. However, there are imbalances at baseline in both RCTs, especially in grade III tumours of types that may be more responsive to chemotherapy.
- As active and placebo implants used in the RCTs had different physical characteristics, blinding may have been compromised.
- Survival, as a primary outcome measure, is relatively resistant to detection biases. However, there is room for subjectivity in the definition of secondary outcome measures such as PFS.
- Intention-to-treat methods have been rigorously adopted in the major RCT.
- All included studies allowed treatment at the investigator's discretion in the post-study period, so late performance bias may confound survival rates.
- Questionable statistical methods, which tended to enhance the apparent effectiveness of the intervention, were used in the published report of the major RCT.
- The external validity of the evidence-base is limited by exclusion of older patients.

Overall survival

All included studies considered survival duration as a primary or secondary outcome of interest. Survival duration is defined in various terms in the studies, with different authors describing their start-point as randomisation,[151] surgery[152] or histological diagnosis.[154] However, as all three of these definitions relate to the intraoperative period, we have assumed effective equivalence across all included studies in use of the term **survival**.

All studies report survival in terms of median duration, using the Kaplan–Meier method for estimation. The RCTs test for difference between trial arms using the log-rank method. Kaplan–Meier survival curves are also presented in each paper.

Cox proportional hazards models were also fitted and reported in the RCTs, to account for the effect of known prognostic variables.

Periodic survival rates

Most included studies present some data showing what proportion of their patients survived to one or more time point. Estimates presented in the published studies do not represent absolute proportions surviving, but are calculated on the basis of survival data censored at the relevant juncture. As low numbers are censored in all the survival data under review, this should be inconsequential. However, there are implications for significance testing. Where data are censored in the manner of a life-table analysis, a log-rank statistic is most appropriate to test for differences between groups as it takes account of the duration for which all individual patients survived. Point estimates of absolute survival provide the kind of cross-categorised frequency data that call for a standard test of association (χ^2/Fisher's exact test). Tests of this sort dichotomise subjects (alive/dead) and discard information about exactly how long each survived. We present both types of estimate with their appropriate significance test where data was available.

Twelve-month survival

We have presented 12-month survival separately because this is the measure used most consistently across the evidence base and the one with the most detailed available data.

Progression-free survival

The investigators in several of the included studies collected data on PFS as a secondary outcome measure.

In assessing the extent to which PFS is both informative and consistent as an outcome measure, there are three main issues:

- **Start-point**. As with overall survival, the start-point for PFS duration is taken to be surgery, and this is consistent in included studies.
- **End-point**. The definition of the moment at which a patient is categorised as suffering disease progression/recurrence is crucial to measurement of PFS. Each study has its own characterisation, but all are substantially based on the standardised definition proposed by Macdonald and colleagues in 1990: "$\geqslant$25% increase in size of enhancing tumor or any new tumor on CT or MRI scans, or neurologically worse, and steroids stable or increased".[100] There are margins for inconsistency in the subjective interpretation of neurological decline and/or assessment of steroid dosage.
- **Follow-up regime**. Systematic differences in follow-up will have a significant effect on the detection of disease progression. For example, more frequent neuroimaging will inevitably lead to prompter detection of tumour growth, with a consequent decrease in time-to-progression outcomes. The same may apply to the frequency of clinical assessment, although one might like to assume that a patient with significant neurological decline would come to the timely

TABLE 6 *Median survival estimates in included BCNU-W studies*

Study	Median survival (months) (95% CI)		Effectiveness			
	BCNU-W	Placebo	Kaplan–Meier method: HR (95% CI)	Log-rank: *p*	Cox proportional hazards model	
					HR (95% CI)	*p*
Westphal *et al.*, 2003[151]	13.9 (12.1 to 15.3)	11.6 (10.2 to 12.6)	0.71 (0.52 to 0.96)[a]	0.03[a]	0.72 (0.53 to 0.98)[a]	0.03[a]
			0.77 (0.57 to 1.03)[b]	0.08[b]	–	0.08[b]
Updated analysis[c]:	*13.8 (12.1 to 15.1)*	*11.6 (10.2 to 12.7)*	*0.73 (0.56 to 0.95)*	*0.02*	–	
Valtonen *et al.*, 1997[152]	13.4 (9.7 to ?[d])	9.2 (8.7 to 10.4)	–	0.012	0.27 (0.11 to 0.68)	0.006
Kleinberg *et al.*, 2004[154]	–					
Brem *et al.*, 1995[129]	9.7					

[a] Stratified by country (published statistic).
[b] Unstratified (protocol-specified statistic extracted from material presented to the FDA[155]).
[c] Updated unstratified analysis of survival data available at 16 August 2002 (extracted from material presented to the FDA[155]).
[d] Insufficient data to calculate upper CI.

attention of his or her physician, regardless of planned follow-up schedule. Where we report PFS data, below, we have also presented summaries of end-points and surveillance regimes, in order to facilitate comparison between studies.

Where appropriate, we have also considered post-progression survival (estimated by subtracting median PFS from median overall survival). In the context of newly diagnosed gliomas, an intervention could be effective by delaying disease progression and/or by prolonging survival, and it may be important to distinguish between the relative contributions of each kind of effect.

Effectiveness (all patients)

Overall survival

Median survival estimates in included studies are collected in *Table 6*.

In both RCTs, Kaplan–Meier estimates of median survival time were longer in patients treated with BCNU-W (median months gained were 2.3 in Westphal and colleagues[151] and 4.2 in Valtonen and colleagues[152]). Both published papers report this difference to be statistically significant by the log-rank test.

The 9.7-month median survival reported by Brem and colleagues[129] is noticeably shorter than that presented in other series. As noted in the section 'External validity' (p. 23), this cohort is older and this may account for the discrepancy in median survival. Kleinberg and colleagues do not report results for combined tumour grades; their GBM-only results are presented in the section 'Effectiveness (GBM only)' (p. 30).[154]

Westphal and colleagues' reported results are stratified by country [see the section 'Internal validity' (p. 18)].[151] The FDA repeated the test without stratifying the data, in line with the study protocol. Evidence of effectiveness was therefore diminished, in terms of both HR (with 95% CIs rising to encompass unit) and log-rank statistic ($p = 0.08$). Other analyses, stratified by the prognostic factors tumour type, KPS and age, also showed no significant difference between the arms ($p = 0.14$, 0.67 and 0.103, respectively.)

Figure 4 shows the Kaplan–Meier survival curves for all patients in the RCT reported by Westphal and colleagues.[151] A difference in survival rate between the arms becomes apparent at around 10 months (by which time about 30% of the cohort have died).

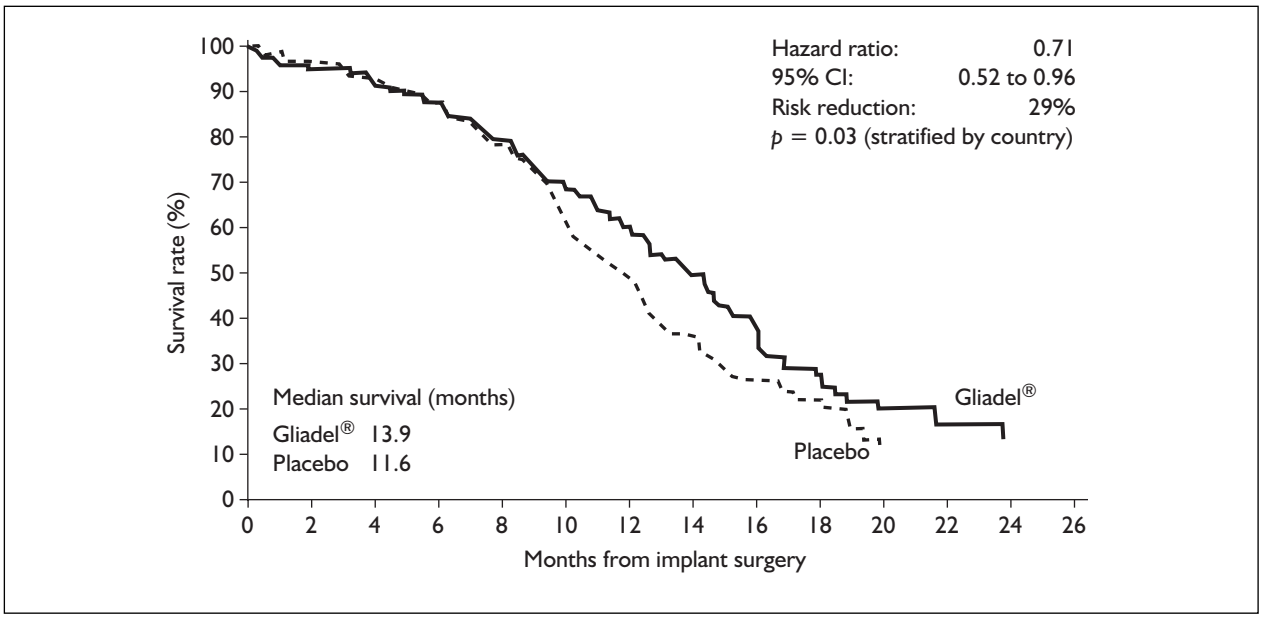

FIGURE 4 *Kaplan–Meier curves depicting overall survival. Adapted from Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC,* et al. *A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma.* Neuro-oncology *2003;**5**:79–88 with kind permission of Duke University Press.*

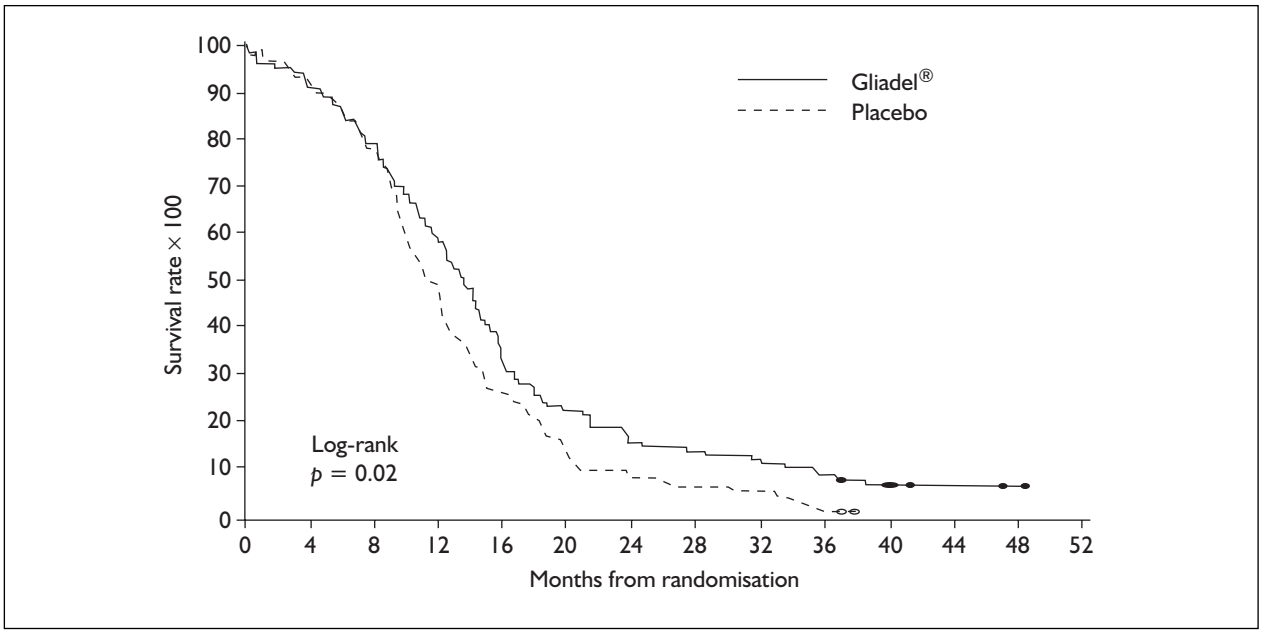

FIGURE 5 *Kaplan–Meier curves depicting long-term overall survival. Adapted from material presented to the FDA.*[155]

Despite doubts about the published trial evidence, subsequent long-term data (up to 16 August 2002, slightly more than 2 years after the protocol-specified cut-off date) presented to the FDA led them to authorise BCNU-W for newly diagnosed patients. In this analysis, the difference between the treatment groups appeared significant by the unstratified log-rank test ($p = 0.02$). *Figure 5* shows the survival curve depicting these long-term data. This difference was maintained when removing chemosensitive anaplastic oligoastrocytoma (AOA) patients from the analysis ($p = 0.03$) (three of these were randomised to the placebo and seven to the BCNU-W group). **[Confidential information removed.]**

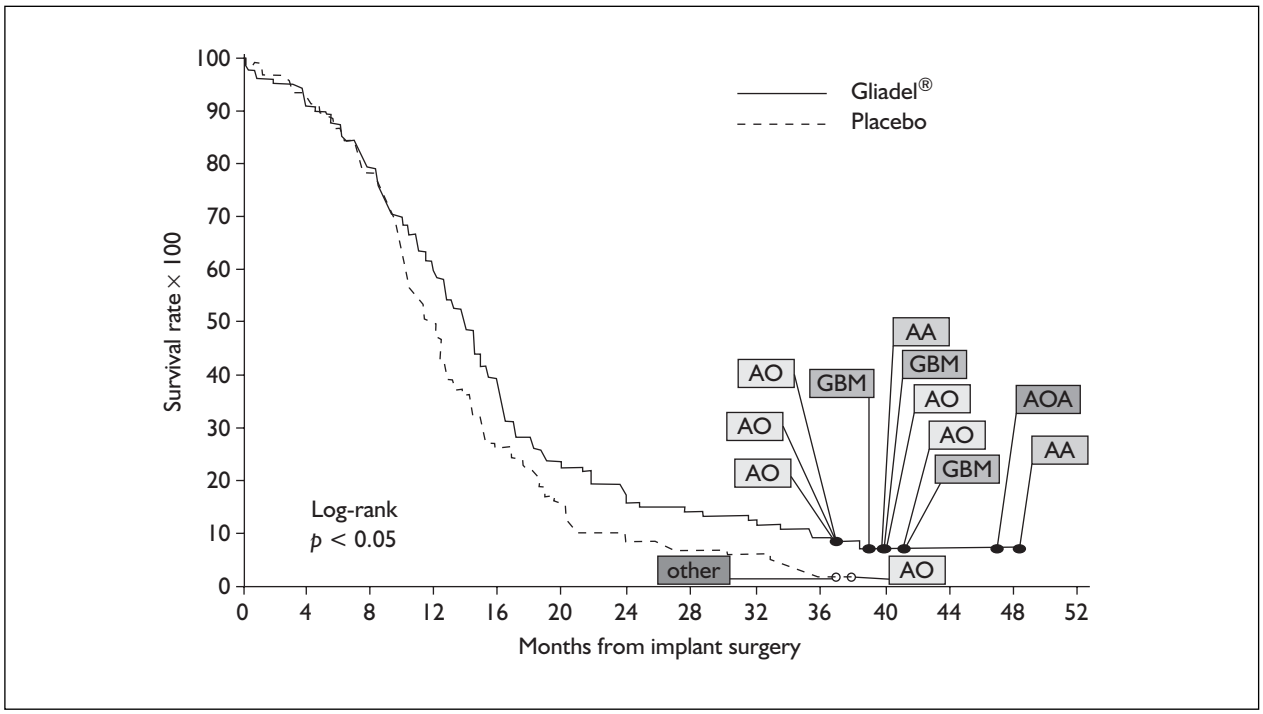

FIGURE 6 *Kaplan–Meier curves depicting tumour pathology of long-term survivors. Adapted from package insert and modified by PenTAG, with permission.*

However, tail effects may be important in long-term follow-up. At 2 years, 80% of the study cohort had died and there was no significant difference in survival between the two groups using the unstratified analysis. After this time, the results are driven by a small number of long-term survivors. Subgroup analysis for those with GBM still shows no difference in survival at long-term follow-up (see *Table 10*).

Figure 6 shows the long-term Kaplan–Meier curves with surviving patients identified by tumour pathology at the point at which they have been censored (i.e. survival at last contact). Grade III tumours, especially those with an oligodendroglial character, predominate.

It would be informative to assess the chromosomal status of these long-term survivors, with particular reference to the genotype that has been associated with improved survival (–1p/–19q with intact 10q). It would be interesting to know whether the three long-term survivors with grade IV tumours share these chromosomal features, in common with the GBM patients with exceptional survival in other series.[72,73]

Periodic survival rates

Details of survival rates 12, 18, 24 and **[Confidential information removed]** months after surgery are given in *Table 7*.

In the RCTs, a greater proportion of patients treated with BCNU-W survived to each juncture reported. Twelve-month survival rates are discussed in more detail below.

Twelve-month survival

Twelve-month survival data are collected in *Table 8*. In this instance, we have access to absolute survival numbers from the two RCTs, which are included in the FDA's analysis of the evidence base.

Despite applying stratification methods detailed above, Westphal and colleagues were unable to demonstrate any significant 12-month survival advantage with BCNU-W over placebo.[151]

In Valtonen and colleagues' RCT, absolute survival proportions and survival rates are identical (indicating that no observations are censored in the latter calculation).[152] In spite of very limited sample sizes, test statistics are significant by both methods, suggesting that, in this small cohort at least, BCNU-W provided real 1-year survival benefit. Once more, the estimate from Brem and colleagues' case series is lower than those presented elsewhere, again, perhaps owing to poorer baseline prognosis.[129]

Using survival numbers, we performed a meta-analysis of the odds ratios for 12-month survival in

TABLE 7 *12-, 18-, 24- and 36-month survival estimates[a] in included BCNU-W studies*

Study		Survival (%) (95% CI)			
		12 months	**18 months**	**24 months**	**36 months**
Westphal *et al.*, 2003[151]	BCNU-W	59.2 (50.4 to 68)	–	**[Confidential information removed]**	
	Placebo	49.6 (40.6 to 58.6)	–		
Valtonen *et al.*, 1997[152]	BCNU-W	62.5	–	31.3	$p^b = 0.012$
	Placebo	18.8	–	6.3	$p^c = 0.172$
Kleinberg *et al.*, 2004[154]	BCNU-W	–	–		
Brem *et al.*, 1995[129]	BCNU-W	36	18		

[a] All estimates calculated on the basis of survival data censored at the relevant juncture.
[b] Log-rank test performed on survival data from each arm censored at the specified juncture (published statistic).
[c] Fisher's exact test performed on proportion surviving in each arm at the specified juncture (statistic extracted from additional findings and analysis contained in material presented to the FDA[155]).

TABLE 8 *12-month survival estimates in included BCNU-W studies*

Study	Absolute survival: *n* (%)[a]			Survival analysis: % (95% CI)[b]		
	BCNU-W	**Placebo**	***p***	**BCNU-W**	**Placebo**	***p***
Westphal *et al.*, 2003[151]	71 (59.2)	59 (49.2)	0.120[c]	59.2 (50.4 to 68)	49.6 (40.6 to 58.6)	0.108[e]
Valtonen *et al.*, 1997[152]	10 (62.5)	3 (18.8)	0.029[d]	62.5	18.8	0.0087[f]
Kleinberg *et al.*, 2004[154]	–			–		
Brem *et al.*, 1995[129]	–			36		

[a] Number of patients surviving at 12 months (data extracted from Link submission[168] for Westphal *et al.* and material presented to the FDA[155] for Valtonen *et al.*).
[b] Survival data censored at 12 months (published statistic).
[c] χ^2 test (calculated by PenTAG).
[d] Fisher's exact test (statistic extracted from material presented to the FDA[155]).
[e] Log-rank test stratified by country (published statistic).
[f] Unstratified log-rank test (statistic extracted from material presented to the FDA[155]).

the two RCTs. *Figure 7* provides a Forest plot depicting our results. No significant treatment advantage was found. The test for heterogeneity was borderline.

Progression-free survival

PFS data are collected in *Table 9*.

Neither RCT demonstrated any improvement in PFS with BCNU-W.[151,152] The submission provided by Link Pharmaceuticals to the National Institute for Health and Clinical Excellence (NICE), reports that progression was defined by neuroimaging in 70% of cases in the major trial.[168] While tumour regrowth may precede symptomatic decline in these cases, scans could be undertaken in response to 'clinical suspicion of tumour progression', so the two may be conflated.

Neither case series reports PFS.

We also considered post-progression survival (estimated by subtracting median PFS from median overall survival). From the data reported by Westphal and colleagues,[151] we calculated a median life expectancy following recurrence of 8 months for patients treated with BCNU-W compared with 5.7 months for those who received placebo wafers. In the trial reported by Valtonen and colleagues,[152] post-progression survival was more than doubled in the BCNU-W group at 5.6 versus 2.5 months.[152]

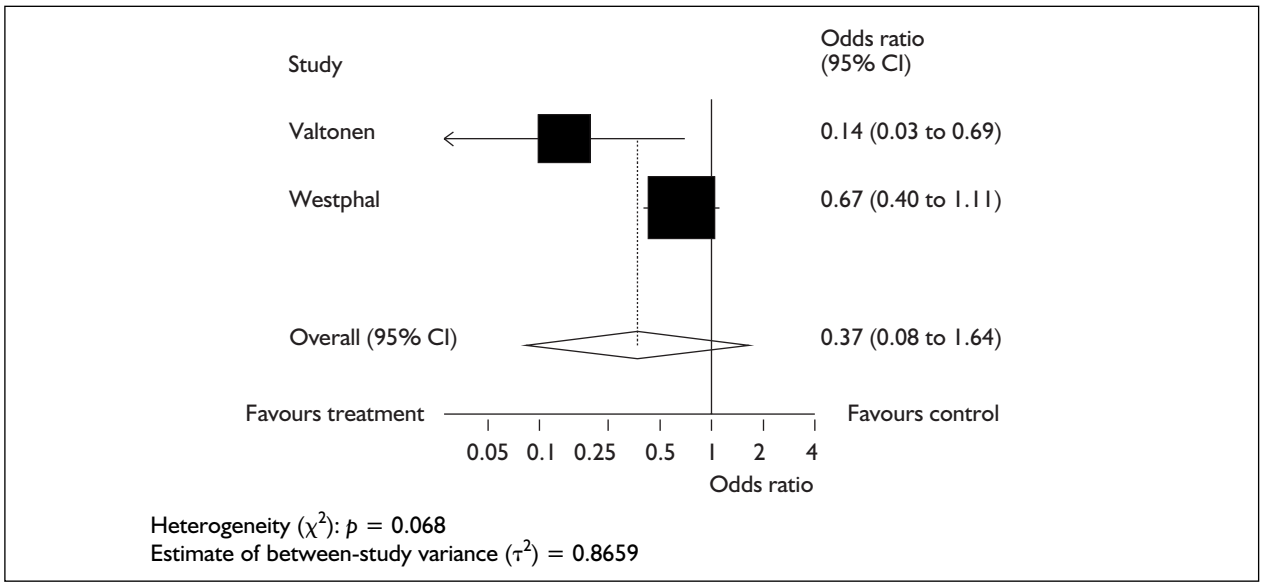

FIGURE 7 *Forest plot showing odds ratio for 12-month survival in BCNU-W RCTs (random effects model)*

TABLE 9 *Median time-to-progression estimates in included BCNU-W studies*

Study	Definition of progression	Surveillance regime	Months (95% CI)	*p*
Westphal *et al.*, 2003[151]	Tumour growth ⩾25% and/or New lesions on MRI, and/or "A documented clinical/ neurological decline"	Frequency of clinical evaluations not reported MRI performed: • at baseline and within 48 h of surgery • at 3 months postoperatively • "If there was clinical suspicion of tumor progression"	BCNU-W 5.9 (4.4 to 8.3) Placebo 5.9 (4.7 to 7.4)	0.90
Valtonen *et al.*, 1997[152]	"Changes on contrast-enhanced CT or MRI scan and/or KPS"	3-monthly assessment (including CT/MRI)	BCNU-W 7.8 (3.2 to 9.7) Placebo 6.7 (3.0 to 9.9)	0.467
Kleinberg *et al.*, 2004[154]	–	–	BCNU-W	–
Brem *et al.*, 1995[129]	–	–	BCNU-W	–

We are unable to undertake significance testing on these second-order measures without access to more extensive data. As neither RCT demonstrated a benefit in terms of PFS, any claimed treatment effect must be due to differences in survival after disease progression. However, post-recurrence survival benefit may be influenced by asymmetry in post-study treatment [see the section 'Internal validity' (p. 18)].

Effectiveness (GBM only)

Overall survival (GBM only)

Median survival estimates from GBM-only subgroup analyses in included studies are collected in *Table 10*.

Westphal and colleagues[151] presented a stratified-by-country analysis that did not demonstrate a significant survival advantage for GBM patients treated with BCNU-W. *Figure 8* shows the Kaplan–Meier survival curves for treatment and placebo groups. Results reported from the investigators' Cox proportional hazards regression suggested that, once known baseline factors were accounted for, the effect of treatment allocation became significant. However, the FDA's unstratified recalculation showed no significant evidence of a treatment effect.

FDA assessors requested that these data be re-examined on the basis of the 'central' referee

TABLE 10 *Median survival estimates in included BCNU-W studies: GBM only*

Study	Median survival (months) (95% CI)		Effectiveness			
	BCNU-W	Placebo	Kaplan–Meier method: HR (95% CI)	Log-rank: *p*	Cox proportional hazards model	
					HR (95% CI)	*p*
Westphal *et al.*, 2003[151]	13.5 (11.4 to 14.8)	11.4 (10.2 to 12.6)	0.76 (0.55 to 1.05)[a]	0.10[a]	0.69 (0.49 to 0.97)[a]	0.04[a]
			0.82 (0.60 to 1.11)[b]	0.20[b]	–	0.20[b]
Updated analysis:[c]	*13.1* (11.4 to 14.7)	*11.4* (10.2 to 12.6)	*0.78* (0.59 to 1.03)	*0.08*	–	0.045
Valtonen *et al.*, 1997[152]	12.3 (10.4 to 17.9)	9.2 (8.7 to 10.4)	–	0.008	0.27 (0.10 to 0.71)	0.008
Kleinberg *et al.*, 2004[154]	12.8 (9.6 to 15.9)					
Brem *et al.*, 1995[129]	–					

[a] Stratified by country (published statistic).
[b] Unstratified (protocol-specified statistic extracted from additional material presented to the FDA's Oncologic Drugs Advisory Committee[155]).
[c] Updated analysis of survival data available at 16 August 2002 (extracted from additional material presented to the FDA's Oncologic Drugs Advisory Committee[155]).

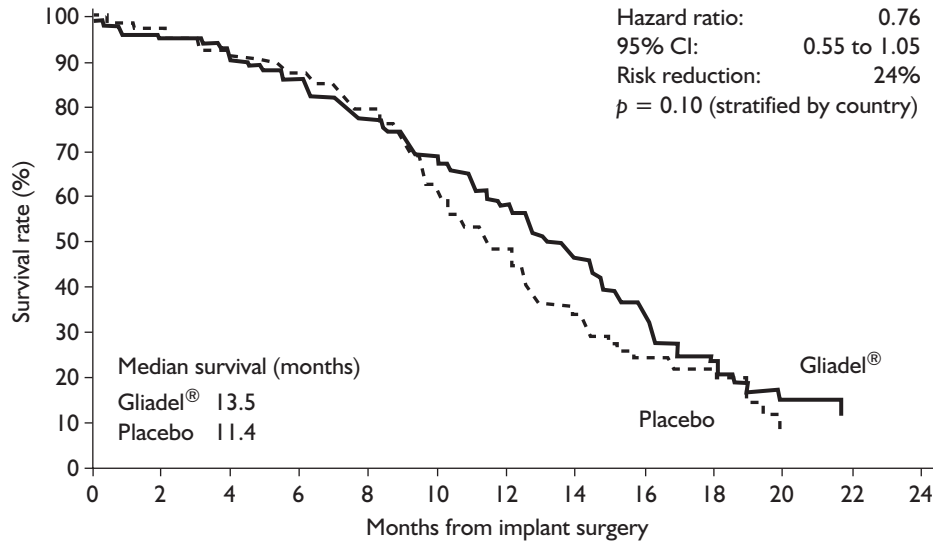

FIGURE 8 *Kaplan–Meier curves depicting overall survival of GBM-only subgroup. Adapted from Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC,* et al. *A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma.* Neuro-oncology *2003;**5**:79–88 with kind permission of Duke University Press.*

TABLE 11 *6-, 12-, 18- and 24-month survival estimates[a] in included BCNU-W studies (GBM only)*

Study		Survival (%) (95% CI)			
		6 months	12 months	18 months	24 months
Westphal *et al.*, 2003[151]	BCNU-W	–	57.4 (47.8 to 67.1)	–	–
	Placebo	–	48.6 (39 to 58.1)	–	–
Valtonen *et al.*, 1997[152]	BCNU-W	–	54.5	–	18.2 { $p^b = 0.126$
	Placebo	–	18.8	–	6.3 { $p^c = 0.549$
Kleinberg *et al.*, 2004[154]	BCNU-W	–	–	–	–
Brem *et al.*, 1995[129]	BCNU-W	–	–	–	–

[a] All estimates calculated on the basis of survival data censored at the relevant juncture.
[b] Log-rank test performed on survival data from each arm censored at the specified juncture (published statistic)
[c] Fisher's exact test performed on proportion surviving in each arm at the specified juncture (statistic extracted from additional findings and analysis contained in material presented to the FDA[155]).

TABLE 12 *12-month survival estimates in included BCNU-W studies (GBM only)*

Study	Absolute survival:[a] *n* (%)			Survival analysis: % (95% CI)[b]		
	BCNU-W	Placebo	*p*	BCNU-W	Placebo	*p*
Westphal *et al.*, 2003[151]	58 (57.4)	52 (49.1)	0.229[c]	57.4 (47.8 to 67.1)	48.6 (39.0 to 58.1)	0.206[e]
Valtonen *et al.*, 1997[152]	6 (54.5)	3 (18.8)	0.097[d]	54.5	18.8	0.059[f]
Kleinberg *et al.*, 2004[154]	–			–		
Brem *et al.*, 1995[129]	–			–		

[a] Number of patients surviving at 12 months (data extracted from material presented to the FDA's Oncologic Drugs Advisory Committee[155]).
[b] Survival data censored at 12 months (published statistic).
[c] χ^2 test (calculated by PenTAG).
[d] Fisher's exact test (statistic extracted from material presented to the FDA's Oncologic Drugs Advisory Committee[155]).
[e] Log-rank test stratified by country (published statistic).
[f] Unstratified log-rank test (statistic extracted from material presented to the FDA's Oncologic Drugs Advisory Committee[155]).

pathologist's diagnoses [see the section 'Internal validity' (p. 18)]. The observed difference in median survival between the arms for GBM patients fell to 1 month and the log-rank *p*-value rose to 0.4.[155] No similar subgroup analysis was undertaken for subjects classified as non-GBM by the 'central' referee pathologist. However, it can be inferred from the effect of reclassification on GBM results that treatment effect may be increased in these patients (although numbers would remain small).

Periodic survival rates (GBM only)
Details of survival rates for GBM-only subgroups 6, 12, 18 and 24 months after surgery are given in *Table 11*. Additional details for 12-month survival data are collected in *Table 12*. In the RCTs, reported differences in survival are not significant.

As in the overall population, we undertook meta-analysis of the odds ratios for 12-month survival in the GBM-only subgroup of the two RCTs. *Figure 9* provides a Forest plot depicting our results. The pooled odds ratio of 0.61 (95% CI 0.30 to 1.23) suggests no significant treatment benefit. The test for heterogeneity is non-significant.

Progression-free survival (GBM only)
PFS figures for a GBM-only subgroup were available from the extended data from the major BCNU-W trial that was presented to the FDA. This showed no significant difference between the

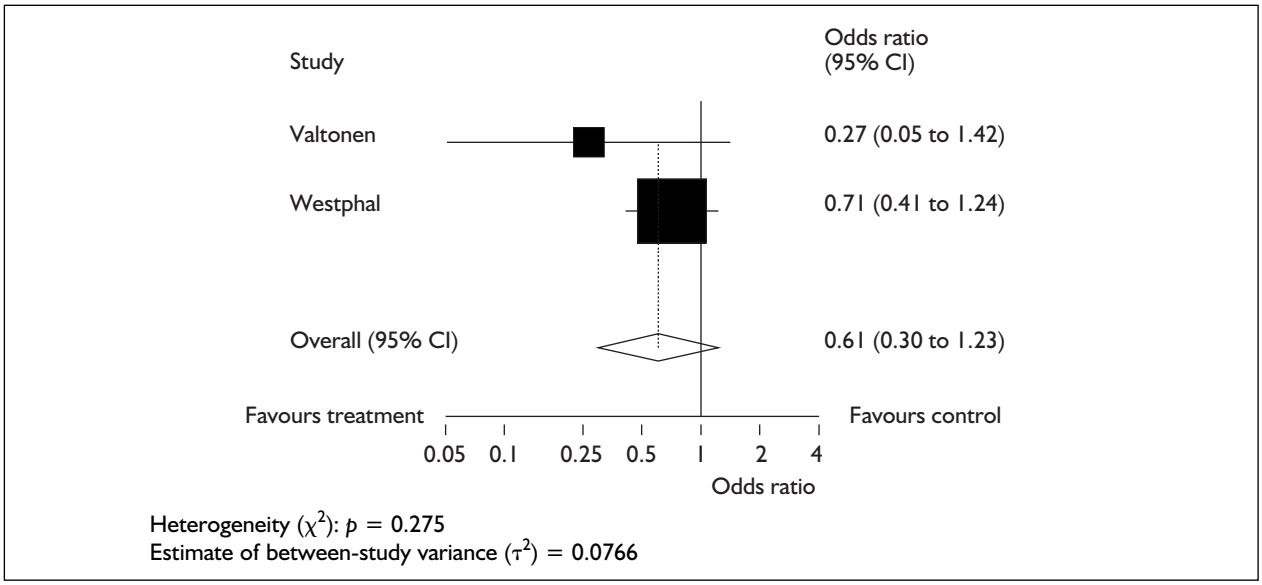

FIGURE 9 *Forest plot showing odds ratio for 12-month survival in BCNU-W RCTs (GBM only) (random effects model)*

arms; 5.8 months (95% CI 3.9 to 8.3) for BCNU-W versus 5.7 months (95% CI 3.6 to 6.6) for placebo; p = 0.621 (stratified log-rank).[155]

Adverse effects

Data from included studies

Each of the included studies of BCNU-W assessed adverse effects (AEs) according to their own criteria. In Westphal and colleagues' RCT, participating units collected incidence data for any treatment-emergent AEs, but concentrated on 23 prespecified complications (listed in *Box 4*).[151] Events were dichotomised as serious (severe or life-threatening) or non-serious (mild or moderate). The trial authors then standardised AE reports using COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms, a coding dictionary for adverse effects used by the FDA) classifications.

Valtonen and colleagues also used COSTART categories in their RCT to amalgamate AE data, with severity classified on a four-point scale (mild, moderate, severe, life-threatening).[152] The results were reported for all grades of severity and for a subgroup of serious (severe/life-threatening) events. Similarly, the case series by Brem and colleagues classified AEs as severe, moderate or mild, but the last two categories are amalgamated in reported results, also effectively divided into serious and non-serious.[129] Kleinberg and colleagues' case series provides less detailed information on AEs suffered by their patients; this may be due to the retrospective design of their study.[154]

BOX 4 *Adverse effects routinely monitored in Westphal and colleagues' RCT*[151]

- Anaemia
- Aphasia
- Brain oedema
- Confusion
- Convulsions
- Deep thrombophlebitis
- Fever (in the absence of infection)
- Headache
- Hemiplegia
- Hydrocephalus
- Infection
- Intracranial abscess
- Leukopenia
- Meningitis
- Nausea
- Pain body whole
- Pulmonary embolus
- Thrombocytopenia
- Vomiting
- Healing abnormalities (i) – fluid, CSF or subdural collections
- Healing abnormalities (ii) – CSF leaks
- Healing abnormalities (iii) – wound dehiscence, breakdown or poor healing
- Healing abnormalities (iv) – scalp or wound effusions

In theory, the categories of serious and non-serious AEs drawn from these studies should be broadly equivalent to grades 1/2 and 3/4, respectively, of the US National Cancer Institute Common Toxicity Criteria (NCI CTC) [as used in TMZ trials – see the section 'Adverse effects' (p. 49)]. However, the absence of any objective, uniform standard for the classification of event

TABLE 13 *Adverse effects reported in included BCNU-W studies: severe or life-threatening [effects occurring in ⩾5% of patients in any series (either arm in RCTs)]*

	Median (data points) (%)	
Adverse effect	**BCNU-W**	**Placebo**
Body as a whole		
Abscess	5.0 (5.0[a])	2.5 (2.5[a])
Aggravation reaction	70.8 (70.8[a])	69.2 (69.2[a])
Fever	5.8 (5.8[a])	4.2 (4.2[a])
Headache	5.8 (5.8[a])	5.8 (5.8[a])
Infection	4.8 (4.5, 5.0[a])	2.5 (2.5[a])
Cardiovascular system		
Deep thrombophlebitis	4.2 (4.2[a])	5.8 (5.8[a])
Pulmonary embolus	7.3 (6.3, 8.3[a])	7.3 (6.3, 8.3[a])
Thrombophlebitis	3.5 (0.8[a], 6.3)	4.0 (1.7[a], 6.3)
Metabolic and nutritional disorders		
Diabetes mellitus	6.3 (6.3)	0.0 (0.0)
Musculoskeletal		
Spondylitis VIII–IX	6.3 (6.3)	0.0 (0.0)
Nervous system		
Aphasia	8.3 (4.2[a], 12.5)	2.5 (0.0, 5.0[a])
Brain oedema	5.8 (4.5, 5.8[a], 6.3)	3.3 (0.0, 6.7[a])
Coma	1.7 (0.0, 3.3[a])	5.0 (5.0[a])
Confusion	12.4 (6.7[a], 18.2)	3.3 (3.3[a])
Convulsion	13.6 (6.3, 13.6, 33.3[a])	18.3 (0.0, 36.7[a])
Depression	6.3 (6.3)	0.0 (0.0)
Grand mal convulsion	5.0 (5.0[a])	4.2 (4.2[a])
Hemiplegia	23.5 (15.8[a], 31.3)	20.0 (15.0[a], 25.0)
Hydrocephalus	6.3 (6.3)	0.0 (0.0)
Meningitis	6.3 (6.3)	6.3 (6.3)
Somnolence	2.5 (2.5[a])	5.0 (5.0[a])
Speech disorder	5.0 (5.0[a])	1.7 (1.7[a])
Stupor	4.0 (1.7[a], 6.3)	1.7 (0.0, 3.3[a])
Tremor	5.0 (5.0[a])	1.7 (1.7[a])
Other		
Rapid deterioration	6.3 (6.3)	0.0 (0.0)
Respiratory system		
Pneumonia	3.5 (2.5[a], 4.5)	5.0 (5.0[a])
Special senses		
Visual field defect	6.3 (6.3)	0.0 (0.0)

[a] Data extracted from the most extensive RCT under review: Westphal and colleagues (2003).[151]

limits interpretation and generalisation of these results.

Results from all studies are given in *Table 13*, which lists serious AEs occurring in at least 5% of patients in any study, and *Table 14*, which lists AEs occurring at any severity level in 10% or more of patients in any study. The tables detail the incidence of each AE in the studies that report them, and the median of these values. In view of the potential for between-study variability in the reporting of AEs and the small sample size in other series, it may be most informative to concentrate on findings from the major RCT. Accordingly, we have identified all data points drawn from Westphal and colleagues[151] in our tables.

By far the most common serious AE is that classed as 'aggravation reaction', a term used only by

TABLE 14 *Adverse effects reported in included BCNU-W studies: all reported [effects occurring in ⩾10% of patients in any series (either arm in RCTs)]*

	Median (data points) (%)	
Adverse effect	**BCNU-W**	**Placebo**
Body as a whole		
Aggravation reaction	81.7 (81.7[a])	79.2 (79.2[a])
Asthenia	21.7 (21.7[a])	15.0 (15.0[a])
Fever	17.5 (17.5[a])	17.5 (17.5[a])
Headache	27.5 (27.5[a])	36.7 (36.7[a])
Infection	11.4 (4.5, 18.3[a])	20.0 (20.0[a])
Pain	13.3 (13.3[a])	15.0 (15.0[a])
Unspecified	12.5 (12.5)	12.5 (12.5)
Cardiovascular system		
Deep thrombophlebitis	10.0 (10.0[a])	9.2 (9.2[a])
Unspecified	18.8 (18.8)	6.3 (6.3)
Digestive system		
Constipation	19.2 (19.2[a])	11.7 (11.7[a])
Nausea	21.7 (21.7[a])	16.7 (16.7[a])
Vomiting	12.7 (4.5, 20.8[a])	15.8 (15.8[a])
Haemic and lymphatic		
Unspecified	0.0 (0.0)	12.5 (12.5)
Metabolic and nutritional disorders		
Healing abnormality	10.2 (4.5, 15.8[a])	11.7 (11.7[a])
Nervous system		
Amnesia	9.2 (9.2[a])	10.0 (10.0[a])
Aphasia	17.5 (17.5[a])	18.3 (18.3[a])
Brain oedema	15.8 (9.1, 22.5[a])	19.2 (19.2[a])
Confusion	20.8 (18.2, 23.3[a])	20.8 (20.8[a])
Convulsion	43.9 (33.3[a], 54.5)	37.5 (37.5[a])
Depression	15.8 (15.8[a])	10.0 (10.0[a])
Hemiplegia	40.8 (40.8[a])	44.2 (44.2[a])
Necrosis	13.6 (13.6)	
Neuropathy	6.7 (6.7[a])	10.0 (10.0[a])
Somnolence	10.8 (10.8[a])	15.0 (15.0[a])
Speech disorder	10.8 (10.8[a])	8.3 (8.3[a])
Unspecified	62.5 (62.5)	37.5 (37.5)
Respiratory system		
Pneumonia	13.3 (8.3[a], 18.2)	7.5 (7.5[a])
Skin and appendages		
Alopecia	10.0 (10.0[a])	11.7 (11.7[a])
Rash	11.7 (11.7[a])	10.8 (10.8[a])
Special senses		
Unspecified	12.5 (12.5)	0.0 (0.0)
Urogenital system		
Urinary tract infection	11.0 (8.3[a], 13.6)	10.8 (10.8[a])

[a] Data extracted from the most extensive RCT under review: Westphal and colleagues (2003).[151]

Westphal and colleagues.[151] The FDA investigation found that this had been used in non-US centres only, and was used to describe the kind of disease progression that was captured as an end-point in the trial (see Sponsor Table 45 on p. 51 of the FDA Clinical Review[155]). It therefore does not appear to provide additional information.

One AE was found to have significantly increased incidence in one arm of the RCT by Westphal and colleagues; intracranial hypertension was reported in 11 patients (9.2%) in the BCNU-W group and two patients (1.7%) in the placebo group ($p = 0.019$).[151] The study authors emphasise that this complication emerged 6 months or more after

TABLE 15 *Selected postoperative complications in BCNU-W RCT and other reported series*

Study	Design	Tumours	N	Incidence of AEs (%)		
				Postoperative seizure	Abscess	CH/ stroke
Lee *et al.*, 1990[169]	R	AA, med, met	321	1.8	–	–
Cabantog and Bernstein 1994[170]	R	GBM, AA	207	1	1.9	1
Suri *et al.*, 1998[171]	R	GBM, AA	511	5.9	–	–
Sawaya *et al.*, 1998[172]	P	GBM, AA, LGG	327	2.5	1.5	0.5
Brell *et al.*, 2000[173]	R	GBM, AA, med	200	4	1.5	3
Buckner *et al.*, 2001[174]	P	GBM, AA	275	2	–	–
Westphal *et al.*, 2003[151]	P	GBM, AA	BCNU-W: 120	9.2	3.3	5.0
			Placebo: 120	13.3	1.7	2.5

CH, cerebral haemorrhage; LGG, low-grade glioma; med, medulloblastoma; met, metastasis; P, prospective; R, retrospective. Adapted from FDA.[155]

wafer implantation in most cases, and conclude that the events were more likely to be related to tumour recurrence than to the intervention. Other interpretations are possible, such as interaction between the BNCU-W and radiotherapy.

Use of a placebo wafer may be a consideration as we cannot be certain that this has no AEs. Comparing incidence of AEs between arms may mask any increase in complications that is attributable to the implantation of wafers in general. To investigate this possibility, FDA analysts compared the incidence of three key postoperative AEs (seizures, abscesses and cerebral haemorrhage/stroke) in Westphal and colleagues' RCT with data in other published surgical series. Their findings are shown in *Table 15*. Although the rate of all selected complications appeared to be higher in the study under scrutiny, FDA reviewers emphasised that the apparent difference could be attributed to variations in AE collection in the presented series.[155]

Case reports of adverse effects

We also identified literature reporting the occurrence of noteworthy complications arising after BCNU-W implantation as trials may not identify rare but significant AEs.

Tumour bed cysts

Two separate US units have reported a total of six occurrences of intracranial cyst formation at the site of tumour resection and BCNU-W implantation. Patients developed symptomatic mass effect 1–9 weeks after surgery and required high-dose steroid therapy and/or reoperation for drainage. One patient later died of opportunistic infection secondary to steroid-related immunosuppression.[175,176] Although cyst formation is a known complication of intracerebral tumours, the relatively rapid onset in each of these cases has been taken as evidence that they were a direct complication of wafer implantation. It is speculated that such events may be an inflammatory response to the implants themselves.[175]

Cerebral oedema

Two instances of critical cerebral oedema following BCNU-W implantation, one fatal, have been reported.[177] Gottfried and colleagues have shown that a significant increase in cerebral oedema is to be expected postoperatively and 1 month after BCNU-W implantation, although the cases reviewed in their series were all asymptomatic.[178] Brain oedema may necessitate reoperation and, in some cases, removal of residual wafer material.

Wound infection

One unit has reported a high incidence of post-craniotomy surgical site infections, affecting nine of the 32 patients in their series (28%).[179] The BCNU-W product package insert reports that there was an increased incidence of healing abnormalities in the multicentre RCT assessing BCNU-W in recurrent gliomas: 15 of 110 (14%) of the treatment group, compared with six of 112 (5%), suffered this complication [$p = 0.041$ (χ^2 test, calculated by PenTAG)]. This finding was not included in the published report of the trial.[153] Similarly, Subach and colleagues found increased frequency of wound infections in their retrospective case-matched cohort study: four of 22 (18%) of the treatment group, compared with one of 45 (2%) of the control cohort, suffered this complication [$p = 0.022$ (Fisher's exact test, calculated by PenTAG)].[180] They suggested that wound-related complications were likely to be a result of inhibition of epithelial cell growth and

BOX 5 *Summary of results from systematic review of carmustine implants*

In the BCNU-W RCT, reported by Westphal and colleagues:[151]

1. **Overall survival results**, calculated at the protocol-specified cut-off date of at least 12 months after surgery (range 12–30 months) suggest that the intervention is not associated with statistically significant survival benefit –
   (a) median of 2.3 (95% CI –0.5 to 5.1) life-months gained in treatment arm
   (b) unstratified hazard ratio of 0.77 (95% CI 0.57 to 1.03)
   (c) $p = 0.08$ by unstratified log-rank
   (d) However, analysis stratified by country in the published analysis shows a statistically significant result ($p = 0.03$).
2. Results show no benefit in terms of **PFS**:
   (a) median of 0 (95% CI –3.0 to 3.6) progression-free months gained in treatment arm
   (b) $p = 0.90$ by unstratified log-rank.
3. The **GBM-only subgroups** showed no statistically significant survival advantage:
   (a) median of 2.1 (95% CI –1.2 to 4.6) life-months gained in treatment arm
   (b) unstratified hazard ratio of 0.82 (95% CI 0.60 to 1.11)
   (c) $p = 0.20$ by unstratified log-rank.
4. **Long-term outcome** data provide some evidence of survival benefit, but tail effects may apply. Overall survival in GBM-only subgroup is not significantly different to placebo:
   (a) median of 2.2 (95% CI 0.6 to 4.9) life-months gained in treatment arm [HR = 0.73 (95% CI 0.56 to 0.95); $p = 0.02$ by unstratified log-rank]
   (b) median of 1.7 (95% CI –1.2 to 4.5) life-months gained in GBM-only treatment arm [HR = 0.78 (95% CI 0.59 to 1.03); $p = 0.08$ by unstratified log-rank].
5. **Adverse effects**:
   (a) intracranial hypertension was the only AE found to have significantly increased incidence in the BCNU-W arm (9.2 vs 1.7%; $p = 0.019$); however, the event occurred long after surgery in most cases
   (b) across the whole trial, the incidence of postoperative seizures, abscesses, cerebral haemorrhages and strokes, although similar in both arms, appeared high in comparison with other published surgical series. This could be due to variations in AE collection, but it may reflect AEs associated with the implantation of wafers (active or placebo).

The additional included studies add little to the evidence base. Valtonen and colleagues' RCT appears to be broadly consistent with the larger trial, but the very small sample size makes it difficult to draw any conclusions.[152] The results reported in Brem and colleagues' uncontrolled case series are consistently less positive than those presented in other series, which may reflect the higher age of their cohort.[129]

fibroblast proliferation caused by diffusion or leakage of carmustine. This study was carried out in those with recurrent gliomas.

A summary of results from a systematic review of carmustine implants is given in *Box 5*.

Results of the systematic review: temozolomide

We did not identify any previous systematic reviews relating to the use of TMZ in newly diagnosed high-grade gliomas.

Although TMZ is licensed for use in children aged 3 years and older, we did not identify any studies of TMZ in paediatric populations that met our inclusion criteria.

Quality of included randomised controlled trials and case series

Two RCTs and two observational case series met our inclusion criteria. Design characteristics are summarised in *Table 16*.

The RCT reported by Stupp and colleagues in 2005 is a relatively large, multicentre trial conducted under the joint supervision of EORTC and the National Cancer Institute of Canada (NCIC).[181] A subgroup analysis of a sample from this cohort according to genetic status (MGMT methylation) has also been published.[56]

Athanassiou and colleagues' 2005 RCT, which was conducted across several Greek oncology departments, investigated a higher dose regimen for adjuvant TMZ (two 5-day courses of 150 mg/m^2/day per 28-day cycle, instead of one 5-day block at 150–200 mg/m^2/day).[182]

Both included observational studies were prospective case series. Stupp and colleagues' 2002 paper[183] describes a two-centre, open-label Phase II pilot study and Lanzetta and colleagues' 2003 study[184] details a review of all relevant interventions at a single university neurosurgical department during a given period.

Internal validity

Indicators of internal validity are given in *Table 17*.

TABLE 16 *Design characteristics of included studies (TMZ)*

Study (design)	Setting (entry dates)	Inclusion criteria				Exclusion criteria	Treatment regime		Outcomes measured	
		Age (years)	Tumour	PS	Other		Intervention (TMZ)	RT	Primary	Secondary
Stupp *et al.*, 2005[181] (RCT) (n = 573)	85 centres in 15 countries (08/2000–03/2002)	18–70	Grade IV only	WHO PS ⩽2	Adequate haematological, renal and hepatic function	Unstable or increasing dose of corticosteroids <14 days before randomisation	Daily TMZ (75 mg/m^2/day) during RT (⩽7 weeks) + Adjuvant TMZ for first 5 days of ⩽6 28-day cycles at 150 mg/m^2/day (escalated to 200 mg/m^2/day if tolerated)	60 Gy: 2 Gy/day, 5 days/weeks for 6 weeks focal (2–3 cm margin)	Survival	PFS Safety QoL
Athanassiou *et al.*, 2005[182] (RCT) (n = 130)	Multiple (?5) Greek oncology departments (01/2000–12/2002)	⩾18	Grade IV only	KPS ⩾60	Adequate haematological, renal and hepatic function	"Poor medical condition because of non-malignant systemic disease or acute infection" Any medical condition that could interfere with oral administration of TMZ	Daily TMZ (75 mg/m^2/day) during RT (6 weeks) + Adjuvant TMZ (150 mg/m^2/day) on days 1–5 and 15–19 of ⩽6 28-day cycles	60 Gy: 2 Gy/day, 5 days/week for 6 weeks focal (2–2.5 cm margin)	PFS Survival	Safety
Lanzetta *et al.*, 2003[184] (CS) (n = 24)	Single Italian neurosurgical department (10/1999–03/2001)	⩾18	Grade IV only	ECOG PS <2	Adequate haematological, renal and hepatic function Life expectancy ⩾12 weeks at study entry	Previous chemotherapy Any medical condition interfering with oral administration of TMZ Previous or concurrent malignancies at other sites Other severe underlying disease Pregnancy	Daily TMZ (75 mg/m^2/day) during RT (6 weeks) + Adjuvant TMZ for first 5 days of ⩽6 cycles at 200 mg/m^2/day	60 Gy: 2 Gy/day, 5 days/week for 6 weeks	Safety	Survival Tumour response QoL

continued

TABLE 16 *Design characteristics of included studies (TMZ) (cont'd)*

Study (design)	Setting (entry dates)	Inclusion criteria				Exclusion criteria	Treatment regime		Outcomes measured	
		Age (years)	Tumour	PS	Other		Intervention (TMZ)	RT	Primary	Secondary
Stupp *et al.*, 2002[183] (CS) (n = 64)	2 Swiss university hospitals (entry dates not reported)	⩾18	Grade IV only	ECOG PS ⩽2	Adequate haematological, renal and hepatic function ⩽28 days since surgery (biopsy or resection)	Other severe underlying disease Any medical condition that could interfere with the oral administration of TMZ Previous or concurrent malignancies at other sites	TMZ (75 mg/m^2/day) during RT (6–7 weeks) for 5 (patients 1–16) or 7 (patients 17–) days/week + Adjuvant TMZ for first 5 days of ⩽6 28-day cycles at 200 mg/m^2/day	60 Gy: 2 Gy/day, 5 days/week for 6 weeks focal (2–3 cm margin)	Safety	Survival

CS, case study; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

TABLE 17 *Internal validity measures of included TMZ studies*

	RCTs		Case series	
	Stupp et *al.*, 2005[181]	**Athanassiou et *al.*, 2005[182]**	**Lanzetta et *al.*, 2003[184]**	**Stupp et *al.*, 2002[183]**
Power calculation at design?	Yes	No		
Proper randomisation?	Yes	Methods not reported		
Groups similar at baseline?	Predominantly[a]	Yes		
Investigators blinded?	No	No		
Outcome assessors blinded?	Not reported	Not reported		
Patients blinded?	No	No		
Prospective?			Yes	Yes
Consecutive patients enrolled?			Not reported	Not reported
Eligibility criteria stated?	Yes	Yes[b]	Yes[b]	Yes[b]
Objective outcome measures?	Predominantly[c]	Predominantly[c]	Predominantly[d]	Yes
Analysis on ITT basis?	Yes	No	No	Yes
All patients accounted for?	No	Yes	Yes	No
Withdrawal specified?	Yes	Yes	Yes	Yes
Withdrawal reasons given?	Yes	Not in full	Yes	Yes
Inter-centre consistency?	Not reported	Not reported	NA	Not reported
Conflicts of interest?	Yes	No	No	Yes

ITT, intention-to-treat.
[a] Significantly more patients in the RT only group were receiving corticosteroids at the time of randomisation (see text).
[b] Exclusion criteria are not necessarily completely reported.
[c] Definition of disease progression can be dependent on assessment of treating clinician.
[d] Definition of tumour response and disease progression substantially dependent on assessment of treating clinicians.

Sample size

Stupp and colleagues' RCT is the largest under review here, with 573 participants (286 RT only; 287 RT + TMZ).[181] The study was designed with 80% power at a significance level of 0.05 to detect a 33% increase in median survival (HR for death, 0.75), assuming that 382 deaths occurred during the study period. These assumptions were realised in the trial (HR = 0.63; 480 deaths).

A total of 130 patients were enrolled in Athanassiou and colleagues' smaller RCT.[182] Twenty patients were excluded from analysis [for details, see the section 'Attrition bias and intention-to-treat analysis' (p. 41)]; of those that were included, 57 received RT + TMZ and 53 received RT alone. The paper does not report any details of *a priori* sample size calculation.

Stupp and colleagues' uncontrolled case series includes 64 patients.[183] Lanzetta and colleagues report on the 21 patients who received relevant treatment at their institution during the course of their study.[184]

In total, our evidence base comprises 429 patients who received TMZ in addition to RT and 339 who had RT alone under control conditions.

Selection bias

In Stupp and colleagues' multicentre RCT, randomisation was performed centrally, with patients stratified according to performance status, extent of previous surgery and treatment centre.[181] Exact methods are not reported, so it is not possible to appraise whether they were appropriate (especially whether the allocation sequence was adequately concealed from investigators). Randomisation took place after surgery in this trial with patients enrolled within 6 weeks of histological diagnosis [which we take to be synonymous with surgery, as in the BCNU-W trials; see the section 'Outcome measures' (p. 24)]; this has implications as regards interpretation of the findings [see the section 'Internal validity' (p. 18)].

In Hegi and colleagues' subgroup analysis based on MGMT methylation status of participants from the same trial, it is demonstrated that the sample analysed were representative of the wider cohort in terms of overall survival ($p = 0.23$ by the log-rank test).[56]

Athanassiou and colleagues did not report their randomisation methods.[182]

In Stupp and colleagues' RCT, more patients in the RT only group than in the RT + TMZ group

were receiving corticosteroids at the time of randomisation [75% versus 67%; $p = 0.0363$ (χ^2 statistic calculated by PenTAG)].[181] It has been suggested that steroid dependency is a reliable indicator of shorter survival in patients with high-grade gliomas, although the evidence is limited.[185,186] Steroid medication is unlikely to have an impact on survival, but it is possible that it indicates poorer patient condition. However, the performance status index (WHO) between the arms was similar.

Although Stupp and colleagues' RCT was explicitly limited to patients with GBM, around 7–8% of subjects were found to have grade III tumours when histological slides were subjected to central pathological review. Grade III cases appear to be fairly evenly distributed between arms. However, around 15% of cases were not submitted for central review, and an undetected imbalance of tumour histology amongst these is conceivable. Precise final diagnoses are not presented, so the distribution of the most chemosensitive grade III tumours (those with an oligodendroglial component) is unknown. Any asymmetry could have an impact on apparent treatment effect. Subgroup analysis of confirmed GBM cases would have been extremely helpful.

There were no significant differences in baseline factors in the RCT reported by Athanassiou and colleagues.[182] Once again, a proportion of patients (4.6%) were found to have grade III tumours; these subjects were excluded from analysis [see comments on intention-to-treat (ITT) considerations].

As above, we consider selection bias as an issue of external validity in uncontrolled case series [see the section 'External validity' (p. 42)].

Performance bias

The risk of performance bias is particularly important in open-label RCTs. As all included studies allowed treatment at the investigator's discretion in the post-study period, that is, after diagnosis of tumour progression/disease recurrence, this may be a concern. Late performance bias confounding survival rates may be possible [see analogous discussion with regard to BCNU-W studies in the section 'Internal validity' (p. 18)].

In the larger RCT, by Stupp and colleagues, reoperation was undertaken in 23% of each arm.[181] Post-recurrence chemotherapy was given to 58% of the RT + TMZ group and 72% of the RT-only group. The chemotherapeutic agent was TMZ in 60% of patients in the RT-only group and 25% of patients in the RT + TMZ group. However, the authors emphasise that the "response to salvage chemotherapy was not recorded as part of our study". This is a shortcoming as overall survival benefit is the primary outcome. The effectiveness of TMZ as second-line chemotherapy has not been conclusively established.[2] However, unmonitored crossover may confound any evidence as to survival advantage in the first-line use of TMZ.

Similarly, in the RCT by Athanassiou and colleagues, salvage TMZ was administered in 18.9% of the RT-only arm (none of the TMZ group received a second course at recurrence). No details are given of reoperations or other second-line treatment.[182]

The case series by Lanzetta and colleagues[184] and Stupp and colleagues[183] do not report post-study treatment.

Attrition bias and intention-to-treat analysis

Stupp and colleagues report that 178 (62%) of the RT + TMZ arm withdrew from treatment compared to only 26 (9%) of the RT only group [$p < 0.0014$ (χ^2 statistic calculated by PenTAG)].[181] Although these numbers include patients who withdrew because of disease progression, there is still a clear imbalance between the arms when analysis is limited to discontinuations for other reasons (toxic effects/decision by patient/unspecified): 70 (24%) of the RT + TMZ group versus 9 (3%) of the RT-only group [$p < 0.001$ (χ^2 statistic calculated by PenTAG)]. It should be emphasised that, owing to the potentially extended period of adjuvant therapy, ≤34 weeks for the RT + TMZ group compared with ≤6 weeks for the RT-only group, an increased number of treatment withdrawals is to be expected. The bias that might be introduced by this asymmetry is minimised by the authors' consistent ITT approach (although, owing to postoperative randomisation, the treatment pathways that define the two ITT groups discount surgical treatment; see the section 'Detection bias', p. 42).

Athanassiou and colleagues did not adopt ITT principles, excluding from analysis a total of 20 patients as ineligible (five who were randomised but not treated, six who had ineligible histology and nine who received off-protocol RT).[182] Any asymmetry in drop-out may tend to inflate survival rates in the group with most excluded patients but, because the arm from which these

subjects were discounted is not specified, it is not possible to account for any possible impact on results.

Detection bias

Blinding. Neither RCT was blinded, with no placebo used in the control arms. This means that response to therapy may have been affected by treatment allocation, and any placebo effect of the intervention cannot be accounted for. However, this should have no effect on the main outcome of survival.

Assessment. Overall survival is the main outcome measure in the RCTs, and appears to have been assessed consistently. However, as in the BCNU-W papers, each of the included TMZ studies features definitions of disease progression (on the basis of which PFS times are calculated) that may be dependent on the subjective assessment of treating clinicians [see discussion in the section 'Internal validity (p. 18)]. Such ambiguities could be a source of bias, and may be a cause for concern in non-blinded RCTs. Studies in which outcome assessors are not blinded to treatment allocation may suffer an increased risk of Type I error (see, for example, the investigation of Noseworthy and colleagues[187]).

Randomisation took place after surgery in both RCTs and, since performance status was one of the trial entry criteria, patients dying or suffering significant complications following surgery may not have been considered for inclusion. Assuming adequate randomisation, this effect would apply equally to both arms. However, all estimates of outcome are likely to appear inflated in comparison with trials of this or other interventions that enrol subjects at the time of surgery.

Analysis. In general, statistical methods appear sound. As stated above, subgroup analysis for patients with confirmed GBM would have been useful in Stupp and colleagues' RCT.[181] Neither RCT reports absolute numbers of survivors at given periods (all published proportion-surviving estimates are calculated on the basis of survival data censored at the relevant juncture), which is a limitation.

External validity

A priori inclusion/exclusion criteria and treatment design are shown in *Table 16*. Baseline patients' characteristics including age, sex, tumour type, performance status and extent of surgery are shown in *Table 18*.

There are very few data in the included studies that apply to older people. Stupp and colleagues' RCT excluded patients over 70 years old.[181] Athanassiou and colleagues appear not to have applied an upper age limit to their RCT (although it is possible that inclusion criteria are not completely reported).[182] Their study does not provide detailed data on the age profile of their recruited cohorts, reporting age as a dichotomised variable (≤50 versus >50 years) only. The authors state that higher age was one of the "unfavorable baseline characteristics" of their patients in comparison with other series (they cite Stupp and colleagues' 2005 RCT[181] and 2002 case series[183]). The proportion of over-50s (82% across both arms) does appear high when compared with the age profiles reported in other included studies. Nevertheless, without more detailed information on study demographics, it is difficult to draw conclusions about the generalisability of findings.

Furthermore, Athanassiou and colleagues[182] state that, in comparison with Stupp and colleagues' cohort,[181] their patients were more likely to have low preoperative performance status, and were less likely to undergo total surgical resection (with more biopsy-only procedures). This may make their findings more applicable to the general clinical population.

Neither included case series describes exclusion of older patients. However, the maximum ages reported by Stupp and colleagues[183] and Lanzetta and colleagues[184] (70 and 75 years, respectively) seem low.

Finally, Stupp and colleagues' failure to report confirmed GBM cases separately is an issue for external as much as internal validity. Without knowing what influence tumour grade had on observed treatment effect, it is difficult to apply these data to grade III or IV patients with confidence.[181]

Summary of study quality

A summary of the quality of included TMZ studies is given in *Box 6*.

Results of included studies

Outcome measures

The outcomes for which we have extracted and considered data – overall survival, periodic survival rates, 12-month survival and PFS – are the same as those used in the analysis of BCNU-W [as detailed in the section 'Outcome measures' (p. 24)] and, in the main, the same considerations apply.

TABLE 18 *Patients' characteristics at baseline in included studies (TMZ)*

Study	Sample size	Age (years)	Sex (% M:F)	Histology (%)	Performance status (%)	Days from diagnosis to treatment	Extent of surgery			Subgroups analysed	Follow-up (months)
							Total (%)	Partial (%)	Biopsy (%)		
Stupp *et al.*, 2005[181]	Total 573 RT + TMZ 287 RT only 286	Median: RT + TMZ 56 RT only 57 Range: RT + TMZ 19–70 RT only 23–71 ⩾50: RT + TMZ 69% RT only 72%	RT + TMZ 63:37 RT only 64:36	Confirmed GBM: RT + TMZ 92 RT only 93	WHO PS 0: RT + TMZ 39 RT only 38 WHO PS 1: RT + TMZ 47 RT only 49 WHO PS 2: RT + TMZ 13 RT only 12	Median: RT + TMZ 35 RT only 35 Range: RT + TMZ 12–75 RT only 14–90	RT + TMZ 44 RT only 45	RT + TMZ 39 RT only 40	RT + TMZ 17 RT only 16	By age By sex By WHO PS By extent of surgery By baseline steroid use By genetic (MGMT) status	Median 28
Athanassiou *et al.*, 2005[182]	Total 130 Excluded 20 RT + TMZ 57 RT only 53	>50: RT + TMZ 84% RT only 79%	RT + TMZ 64:36 RT only 61:39	–	KPS ⩽80: RT + TMZ 53 RT only 68 KPS >80: RT + TMZ 47 RT only 32	Mean: RT + TMZ 34 RT only 36 Range: RT + TMZ 28–41 RT only 29–43	RT + TMZ 18 RT only 15	RT + TMZ 40 RT only 43	RT + TMZ 42 RT only 42	KPS ⩽80	Median 11
Lanzetta *et al.*, 2003[184]	24	Median 44 Range 25–75	63:37	–	ECOG PS: 0–1 85 2 15 KPS: ⩾90 67 ⩽80 33	Median 25 Range 14–45	–	85	15	–	Median 18
Stupp *et al.*, 2002[183]	64	Median 52 Range 24–70	61:39	Confirmed GBM: 95.3	ECOG PS: 0–1 86 2 14	Median 25 Range 14–45	23	34	42	Confirmed GBM	Median 23

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

BOX 6 *Summary of quality of included TMZ studies*

- The evidence base comprises 429 patients receiving TMZ in the four included studies – two RCTs and two case series.
- One of the RCTs is adequately powered (meeting all assumptions on which *a priori* sample size calculation was based).
- The RCTs enrolled and randomised patients after surgery, thereby excluding patients who died perioperatively or suffered complicated recoveries.
- Neither RCT reports randomisation methods.
- Both RCTs are open label and so may be susceptible to performance bias.
- Open-label RCTs are also susceptible to detection bias, especially for the secondary outcome, PFS, which may be judged subjectively. The primary outcome, survival, should not be affected.
- By design, all included studies were limited to patients with GBM; however, pathological reviews revealed that a proportion of the enrolled cohort had grade III tumours. Their inclusion may distort reported treatment effect. No subgroup analysis of confirmed GBM cases was provided in Stupp and colleagues' RCT.
- Late performance bias is possible as all included studies allowed treatment at the investigator's discretion in the post-study period (including the use of second-line TMZ in the control group).
- ITT methods have been rigorously adopted in the major RCT.
- The external validity of the evidence-base is limited by study entry criteria. The smaller RCT may be more applicable to the population at large, as it appears to be based on an older patient group, who were more likely to have low baseline performance and less likely to have undergone extensive tumour resection. However, the study was based on a relatively small sample and is underpowered to provide robust findings.

TABLE 19 *Median survival estimates in included TMZ studies*

Study	Median survival (months) (95% CI)		Effectiveness			
	RT + TMZ	RT only	Kaplan–Meier method: HR (95% CI)	Log-rank: *p*	Cox proportional hazards model	
					HR (95%CI)	*p*
Stupp *et al.*, 2005[181]	14.6 (13.2 to 16.8)	12.1 (11.2 to 13.0)	0.63 (0.52 to 0.75)	<0.001	0.54 (0.45 to 0.64)	<0.001
Athanassiou *et al.*, 2005[182]	13.4 (9.5 to 17.1)	7.7 (5.3 to 9.2)	–	<0.0001	0.66	0.0003
Lanzetta *et al.*, 2003[184]	15.7 (10.3 to 30.5)					
Stupp *et al.*, 2002[183]	16.0 (10.9 to 21.2)					

One dissimilarity is the measurement of time-to-event outcomes. Whereas the BCNU-W trials began measuring these outcomes at the time of surgery, TMZ studies adopted a later start-point.

Stupp and colleagues' published report of the EORTC/NCIC RCT does not provide any relevant definitions.[181] However, according to Schering-Plough's submission to NICE, survival was "measured from the date of randomisation until death".[90] We assume that PFS was defined with a similar start-point, although this is not explicitly stated. The precise juncture at which randomisation took place is unclear. The study protocol stipulated that treatment (i.e. RT ± TMZ) had to begin within 1 week of randomisation, and that the median time from diagnosis to the commencement of RT was 5 weeks. Accordingly, we estimate that randomisation took place around 4 weeks after surgery.

In the RCT reported by Athanassiou and colleagues, survival and PFS were explicitly estimated from the date at which patients commenced RT (an average of 35 days after diagnosis).[182]

Effectiveness (all patients)

Overall survival

Median survival estimates in included studies are collected in *Table 19*. Both RCTs show significant increases in survival with RT + TMZ compared with RT alone.

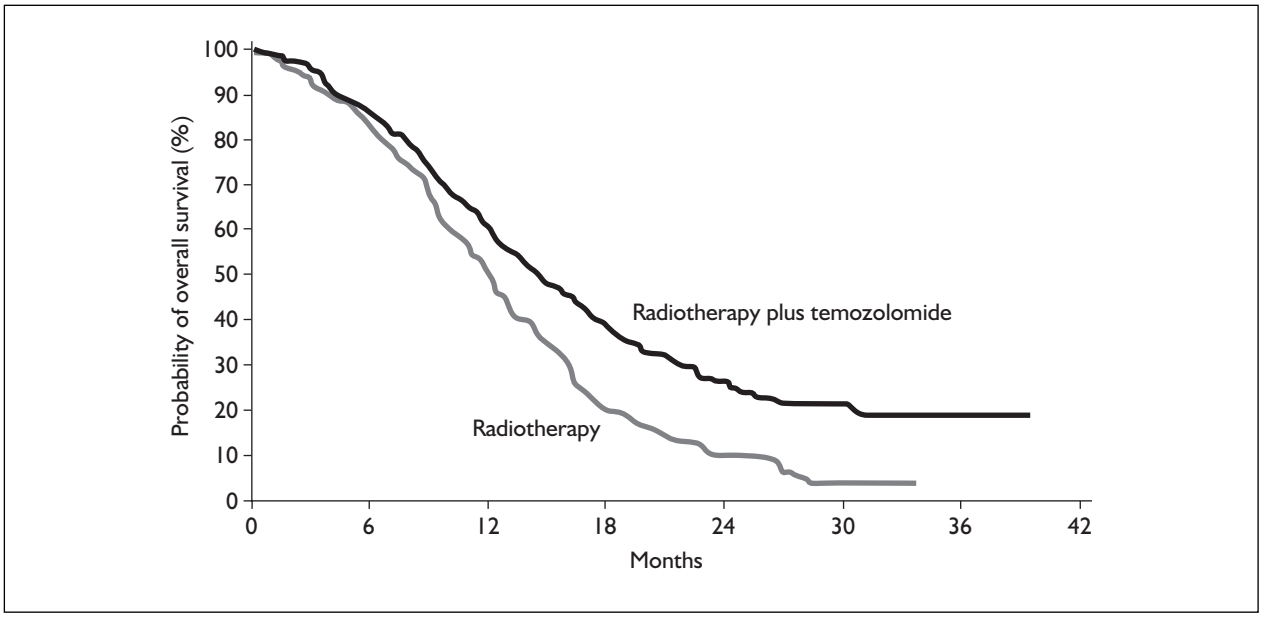

FIGURE 10 *Kaplan–Meier curve depicting overall survival. Adapted from Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ,* et al. *Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.* N Engl J Med *2005; **352**:987–996. © 2005 Massachusetts Medical Society. All rights reserved.*

TABLE 20 *6-, 12-, 18- and 24-month survival estimates[a] in included TMZ studies*

Study		Survival (%) (95% CI)			
		6-month survival	**12-month survival**	**18-month survival**	**24-month survival**
Stupp *et al.*, 2005[181]	RT + TMZ	86.3 (82.3 to 90.3)	61.1 (55.4 to 66.7)	39.4 (33.8 to 45.1)	26.5 (21.2 to 31.7)
	RT only	84.2 (80.0 to 88.5)	50.6 (44.7 to 56.4)	20.9 (16.2 to 26.6)	10.4 (6.8 to 14.1)
Athanassiou *et al.*, 2005[182]	RT + TMZ	80.2 (70.4 to 91.4)	56.3 (44.1 to 71.6)	24.9 (14.7 to 42.1)	–
	RT only	58.3 (46.4 to 73.3)	15.7 (8.2 to 30.1)	5.4 (1.5 to 19.6)	–
Lanzetta *et al.*, 2003[184]	RT + TMZ	–	58	36	–
Stupp *et al.*, 2002[183]	RT + TMZ	–	58 (46.0 to 70.0)	36 (24.0 to 50.0)	31 (19.0 to 44.0)

[a] All estimates calculated on the basis of survival data censored at the relevant period.

The estimate provided by Athanassiou and colleagues is slightly shorter than that in the other studies.[182] However, the start-point from which they measured survival was the commencement of RT [see the section 'Outcome measures' (p. 42)], which may slightly shorten time-to-event measures in comparison with other studies. In addition, the authors state that the studied population included those with poorer baseline characteristics than other trials, and this may affect overall survival.

In both RCTs, unadjusted measures of relative effectiveness suggest that TMZ treatment confers significant survival benefit (median months gained 2.5 in Stupp and colleagues[181] and 5.7 in Athanassiou and colleagues[182]). In each case, this association was preserved when Cox multivariate regressions were fitted to adjust for confounding factors at baseline.

Figure 10 shows the Kaplan–Meier survival curves for all patients in the major EORTC/NCIC RCT reported by Stupp and colleagues.[181] This appears to show a steadily widening difference in survival probability between the trial arms.

Periodic survival rates

Details of survival rates 6, 12, 18 and 24 months after surgery are given in *Table 20*. In the RCTs, a greater proportion of patients treated with TMZ

TABLE 21 *12-month survival estimates in included TMZ studies*

	Absolute survival: *n* (%)[a]			Survival analysis: % (95% CI)[b]		
Study	**TMZ + RT**	**RT only**	***p*[c]**	**TMZ + RT**	**RT only**	***p***
Stupp *et al.*, 2005[181]	174 (60.6)	144 (50.3)	0.0133	61.1 (55.4 to 66.7)	50.6 (44.7 to 56.4)	–
Athanassiou *et al.*, 2005[182]	–	–	–	56.3 (44.1 to 71.6)	15.7 (8.2 to 30.1)	–
Lanzetta *et al.*, 2003[184]	–			58		
Stupp *et al.*, 2002[183]	–			58 (46 to 70)		

[a] Number of patients surviving at 12 months (data extracted from Schering-Plough submission[90]).
[b] Survival data censored at 12 months (published statistic; no *p*-values reported for difference).
[c] χ^2 test (calculated by PenTAG).

TABLE 22 *Median time-to-progression estimates in included TMZ studies*

Study	Definition of progression	Surveillance regime	Months (95% CI)	*p*
Stupp *et al.*, 2005[181]	Increase in tumour size by 25%; and/or Appearance of new lesions; and/or Increased need for corticosteroids	During RT: weekly clinical review Commencing 21-28 days after RT: • 3-monthly evaluation (including CT/MRI) • clinical review every adjuvant TMZ cycle (RT + TMZ group only)	TMZ + RT 6.9 (5.8 to 8.2) RT only 5.0 (4.2 to 5.5)	<0.001
Athanassiou *et al.*, 2005[182]	⩾25% tumour growth on MRI/CT; and/or Any new tumour on MRI/CT; and/or Neurological progression (not defined); and/or Clinical progression (not defined)	During RT: weekly clinical review During year 1: • 2-monthly evaluation (including CT/MRI) • clinical review every adjuvant TMZ cycle (RT+TMZ group only) During year 2: 3-monthly evaluation (including CT/MRI)	TMZ + RT 10.8 (8.1 to 14.7) RT only 5.2 (3.9 to 7.4)	<0.0001
Lanzetta *et al.*, 2003[184]	–	–	TMZ + RT:	–
Stupp *et al.*, 2002[183]	–	–	TMZ + RT:	–

survived to each time point. For the trial by Stupp and colleagues, there is an overlap in CIs at 6 and 12 months, but not for longer term follow-up. Survival at 2 years with RT + TMZ is high at 26.5%. For the Athanassiou trial, CIs overlap at 6 months only. Log-rank tests for the significance are not reported. Twelve-month survival rates are discussed in more detail below.

Twelve-month survival

Twelve-month survival data are collected in *Table 21*. The RCTs report that the proportion of patients who survived 1 year was greater for those who received TMZ. Log-rank tests for significance are not reported. Our χ^2 test for difference in absolute survival proportions in Stupp and colleagues' trial are significant ($p = 0.013$).

Progression-free survival

PFS data are collected in *Table 22*. Both RCTs found a significant increase in PFS in their RT + TMZ groups. The median 10.8 months' PFS reported by Athanassiou and colleagues is noticeably longer than that achieved in other trials and, in particular, the result reported by Stupp and colleagues.[181,182] This could be explained by hidden heterogeneity in the underlying patient populations or differences in surveillance leading

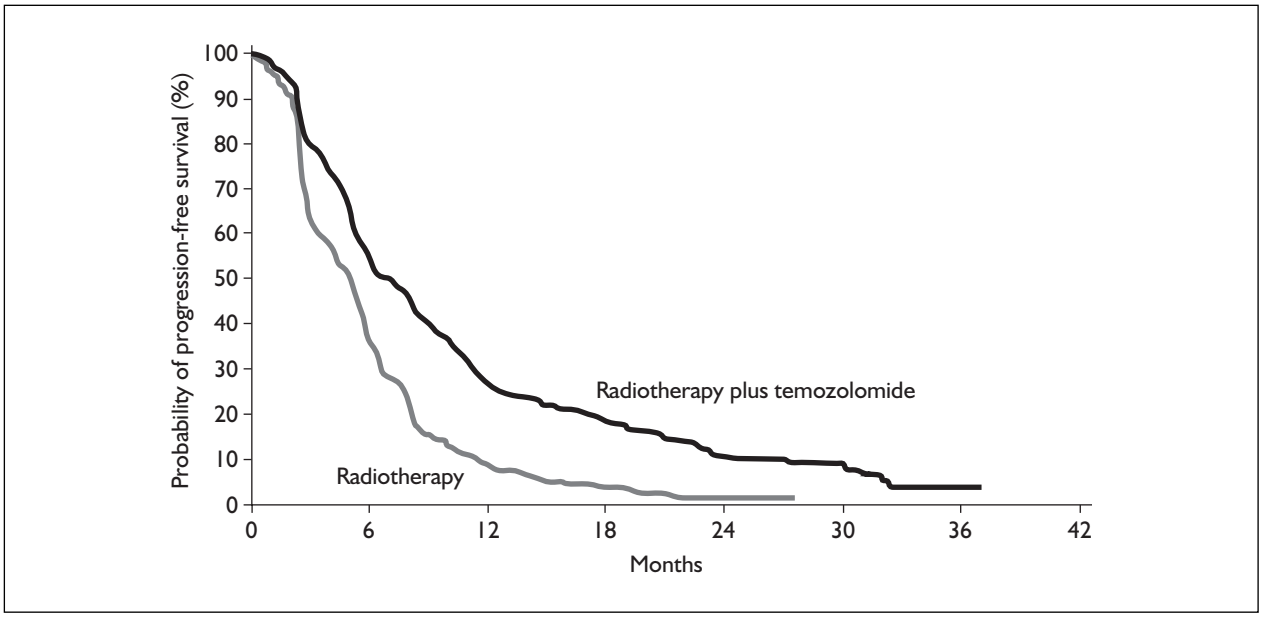

FIGURE 11 *Kaplan–Meier curves depicting progression-free survival. Adapted from Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ,* et al. *Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.* N Engl J Med *2005;**352**:987–996. © 2005 Massachusetts Medical Society. All rights reserved.*

to inconsistent detection of progression (length–time bias). Alternatively, the novel TMZ regime under evaluation by Athanassiou and colleagues may be effective at delaying disease progression.

Stupp and colleagues present Kaplan–Meier curves illustrating PFS and these are reproduced in *Figure 11*.[181] It appears that there is little progression-retarding benefit in the most seriously ill patients, the 20% or so whose disease recurs within the first 3 months of treatment. However, the remainder of patients seem to have a higher probability of delayed progression with RT + TMZ. As we note in the section 'Detection bias' (p. 42), detection bias, to which unblinded RCTs are known to be susceptible, is a possibility.

In both RCTs, there is very little difference between arms in post-progression survival, which we estimated by subtracting median PFS from median overall survival. From the data reported by Stupp and colleagues, we calculate a median life expectancy following recurrence of 7.7 months with RT + TMZ and 7.1 months with RT only.[181] Post-progression survival was shorter in the trial reported by Athanassiou and colleagues at 2.6 and 2.5 months, respectively.[182] This suggests that the apparent survival advantage of TMZ accrues in the stable phase of disease and that there is no residual survival benefit following disease recurrence. However, as we noted earlier (p. 32), there is the possibility performance bias related to second-line treatment.

In the case series by Lanzetta and colleagues, median duration of "tumour response" and "stable disease" is reported as 17 months.[184] While this is broadly equivalent to PFS, the reported figure relates only to those patients who responded to treatment and so time-to-progression across the whole cohort is not known.

Effectiveness: GBM only

All of the included TMZ studies were designed to exclude patients with grade III tumours and so, in theory, all findings reported should only relate to those with GBM. However, as we noted in our discussion in the section 'Selection bias' (p. 40), those studies that attempted to verify tumour pathology found that a minority (7–8%) of participants had grade III tumours. Because the studies fail to report subgroup analyses for those patients with confirmed GBM only, it is impossible to tell whether the overall results are representative of the effectiveness of the intervention in this population.

The only attempt at addressing this problem comes in Stupp and colleagues' Phase II trial, which reports no difference in median survival and 1- and 2-year survival rates in an analysis excluding six 'ineligible' patients including three with grade III tumours.[183]

TABLE 23 *Median survival and PFS with TMZ according to MGMT promoter methylation*

	RT + TMZ	RT only	HR (95% CI)	p^a
Methylated MGMT promoter				
n (% of arm)	46 (43)	46 (46)		
Median survival (months) (95% CI)	21.7 (17.4 to 30.4)	15.3 (13.0 to 20.9)	0.51 (0.31 to 0.84)	<0.007
Median PFS (months) (95% CI)	10.3 (6.5 to 14.0)	5.9 (5.3 to 7.7)	0.48 (0.31 to 0.75)	0.001
2-year survival rate[b] (%) (95% CI)	46.0 (31.2 to 60.8)	22.7 (10.3 to 35.1)		
Unmethylated MGMT promoter				
n (% of arm)	60 (57)	54 (54)		
Median survival (months) (95% CI)	12.7 (11.6 to 14.4)	11.8 (9.7 to 14.1)	0.69 (0.47 to 1.02)	0.06
Median PFS (months) (95% CI)	5.3 (5.0 to 7.6)	4.4 (3.1 to 6.0)	0.62 (0.42 to 0.92)	0.02
2-year survival rate[b] (%) (95% CI)	13.8 (4.8 to 22.7)	<2[c]		

[a] Log-rank.
[b] Survival data censored at 24 months (published statistic; no *p*-values reported for differences).
[c] All of the patients in this subgroup died before or had follow-up of <2 years.

Schering-Plough's submission to NICE contains an unpublished figure depicting treatment effect in various subgroups of Stupp and colleagues' RCT, including patients with confirmed GBM.[90,181] No numerical data are reported. However, we estimate from the graph that the HR (RT + TMZ versus RT only) in the GBM-only subgroup was in the region of 0.66 (95% CI 0.54 to 0.80). This suggests the survival benefit with TMZ is slightly weaker in the licence-indicated GBM-only population than in the reported cohort [HR = 0.63; see the section 'Overall survival' (p. 44)]. However, there is substantial overlap between CIs and, without access to detailed data, it is impossible to draw categorical conclusions. We would also caution that the 'Other' group in this analysis is not synonymous with the grade III population. Because patients have been dichotomised into those with confirmed GBM and all others, the latter group contains patients with a confirmed diagnosis of non-GBM pathology, but also those whose diagnoses had not been verified. These latter patients constitute 72% of the group, making it unwise to think of this subgroup as representing non-GBM cases.

Effectiveness: subgroup analysis according to MGMT status

Hegi and colleagues[56] undertook genetic subgroup analysis of Stupp and colleagues' RCT.[181] It should be noted that this is a selected population with data available for only 207 of the original 573 recruited patients. Survival and PFS estimates are given in *Table 23*.

In the subgroup with reduced MGMT activity (as indicated by promoter methylation), there were significant and substantial differences between the trial arms: TMZ was associated with median survival benefit of 6.4 months and a median PFS gain of 4.4 months. The median survival of 21.7 months and 2-year survival rate of 46% for those with promoter methylation who received TMZ are very high.

The effectiveness of TMZ was more ambiguous in the subgroup with normal MGMT activity (unmethylated promoter). Overall survival gain was slim (0.9 months) for the RT + TMZ group compared with the RT-only group and did not reach conventional levels of significance. PFS was significantly improved by TMZ, but the observed benefit was <1 month. The validity of this measure in an unblinded trial is problematic [see the section 'Internal validity' (p. 37)].

It is possible that the effectiveness of TMZ in the full cohort (as reported by Stupp and colleagues[181]) is substantially driven by the subgroup of patients with reduced MGMT activity. There is little evidence that the ~55% of patients without this genetic profile derive any significant benefit from TMZ. Hegi and colleagues suggest that the effectiveness of treatments with different mechanisms of action should be assessed in these patients or, alternatively, they should be enrolled in studies investigating agents that may silence the MGMT gene before administration of TMZ.[56] Caution should be taken in interpreting these results, however, owing to the selected nature of the tested population and the difficulties that have been found in reproducing the test identifying MGMT promoter methylation.

TABLE 24 *Haematological toxicities for RT + TMZ in included TMZ studies: grade 3 or 4*[a]

	Leukopenia	Lymphocytopenia	Neutropenia	Thrombocytopenia	Anaemia	Infections
Stupp *et al.*, 2005[181]						
RT + TMZ phase (*n* = 284)	7 (2.5%)	NR	12 (4.2%)	9 (3.2%)	1 (0.4%)	9 (3.2%)
Adjuvant TMZ phase (*n* = 223)	11 (4.9%)	NR	9 (4.0%)	24 (10.8%)	2 (0.9%)	12 (5.4%)
Athanassiou *et al.*, 2005[182]						
RT + TMZ phase (*n* = 57)	2 (3.5%)	NR	NR	3 (5.3%)	NR	NR
Adjuvant TMZ (240 cycles)	[5] [2.1%]	NR	NR	[12] [5.0%]	NR	NR
Lanzetta *et al.*, 2003[184]						
RT + TMZ phase (*n* = 21)	NR	15 (71.4%)	2 (9.5%)	3 (14.3%)	1 (4.8%)	0
Adjuvant TMZ phase (*n* = 19)	NR	12 (63.2%)	2 (10.5%)	4 (21.1%)	1 (5.3%)	0
Stupp *et al.*, 2002[183]						
RT + TMZ phase (*n* = 62)	NR	49 (79.0%)	4 (6.5%)	4 (6.5%)	2 (3.2%)	3 (4.8%)
Adjuvant TMZ phase (*n* = 49)	NR	34 (69.4%)	3 (6.1%)	7 (14.3%)	1 (2.0%)	0

NR, not reported.
[a] AE grades assessed according to NCI CTC (see Appendix 9).

Adverse effects

All included studies classified AEs according to NCI CTC (see Appendix 9[188]). Definitions of relevant categories and grades are detailed in Appendix 9.

Haematological toxicity

Haematological abnormalities secondary to myelosuppression (reduced bone marrow activity) tend to be reported as a discrete subset in studies of TMZ. This is because they have been known to be a principal side-effect of the drug since the initial Phase 1 trial of TMZ.[189] As both RCTs under review report zero incidence of these AEs in the control arms of their trials, reported haematological toxicities for only those patients treated with RT + TMZ are summarised in *Table 24* (numbers in square brackets indicate a number of treatment cycles, rather than number of people). Increased susceptibility to infection is the overriding risk of these haematological abnormalities and we have detailed these where reported. Each study reports separate incidence figures for the concomitant and adjuvant phases of TMZ administration and, because it is not possible to establish which patients contribute to more than one data point, overall totals cannot be produced. Similarly, the possibility that patients may have suffered from more than one type of AE makes it impossible to calculate the proportion who experienced any such complication.

Stupp and colleagues report that the total incidence of "severe myelosuppression" seen at any stage in their RT + TMZ group was 16%, and that this led to the premature discontinuation of TMZ in 5% of cases.[181]

Such toxicities are potentially severe. One patient in the RT + TMZ arm of the RCT reported by Athanassiou and colleagues experienced serious infection after grade 3/4 myelotoxicity and died as a result of sepsis.[182] Stupp and colleagues reported that in their RCT two patients in the RT + TMZ group died of cerebral haemorrhage. However, the authors emphasise that this was in the absence of any identifiable coagulation disorder or thrombocytopenia.[181]

Non-haematological adverse effects

Reported incidence of other AEs is given in *Table 25*, which lists grade 3/4 AEs occurring in at least 5% of patients in any series, and *Table 26*, which lists AEs occurring at any severity level in 10% or more of patients in any series. We have identified all data points drawn from the most substantial RCT under review in our tables.

TABLE 25 *Non-haematological adverse effects reported in included TMZ studies – grade 3 or 4[a] [effects occurring in ⩾5% of patients in any series (either arm in RCTs)]*

	Median (data points) (%)	
Adverse effect	**RT + TMZ**	**RT only**
RT ± concomitant TMZ phase		
Fatigue	4.9 (3.2, 6.6[b])	4.9 (4.9[b])
Adjuvant TMZ phase		
Fatigue	4.2 (2.0, 6.3[b])	
Nausea/vomiting	3.8 (1.4,[b] 6.1)	
Any phase/unspecified		
Fatigue	13.2 (13.2[b])	7.0 (7.0[b])
Infection	7.0 (7.0[b])	2.8 (2.8[b])

[a] AE grades assessed according to NCI CTC (see Appendix 9).
[b] These values are those extracted from the largest RCT under review: Stupp and colleagues (2005).[181]

TABLE 26 *Non-haematological adverse effects reported in included TMZ studies: all reported [effects occurring in ⩾10% of patients in any series (either arm in RCTs)]*

	Median (data points) (%)	
Adverse effect	**RT + TMZ**	**RT only**
RT ± concomitant TMZ phase		
Fatigue	14.3 (12.9, 14.3, 32.4[a])	26.2 (26.2[a])
Rash	6.0 (1.6, 10.5[a])	5.9 (5.9[a])
Vision	14.6 (14.6[a])	13.6 (13.6[a])
Nausea/vomiting	13.9 (11.3, 13.9,[a] 33.3)	3.8 (3.8[a])
Adjuvant TMZ phase		
Fatigue	16.3 (14.3, 16.3, 31.7[a])	
Vision	10.5 (10.5[a])	
Nausea/vomiting	19.5 (16.3, 19.5,[a] 28.6)	
Any phase/unspecified		
Fatigue	50.9 (50.9[a])	29.7 (29.7[a])
Other constitutional symptoms	13.6 (13.6[a])	7.0 (7.0[a])
Rash	10.3 (5.3, 15.3[a])	7.0 (7.0[a])
Vision	22.3 (22.3[a])	17.5 (17.5[a])
Nausea/vomiting	29.6 (29.6[a])	4.2 (4.2[a])

[a] These values are those extracted from the largest RCT under review: Stupp and colleagues (2005).[181]

Incidence of nausea/vomiting in patients treated with TMZ occurred despite antiemetic medication being compulsory or discretionary in all studies' treatment regimes.

Stupp and colleagues provide a more detailed breakdown of AEs occurring during their RCT in a Supplementary Appendix to their paper.[181] The data for effects sustained at any time during the entire study period are given in *Table 27*, along with χ^2 statistics for differences between arms. With the single exception of grade 3 or 4 visual disturbances, where numbers are very small in both groups, all specified AEs occurred more frequently in the RT + TMZ arm than in the RT-only group. Grade 2 fatigue, rash and nausea/vomiting and grade 3 or 4 fatigue, unspecified constitutional symptoms and infection were significantly more common in the RT + TMZ arm.

Athanassiou and colleagues state that their study was unable to detect any late neurological AEs because of the short duration of follow-up.[182]

Reporting of AEs is haphazard in the case series under review. Lanzetta and colleagues do not provide any detail other than haematological effects reported above.[184] Two of the first 15 patients in Stupp and colleagues' case series developed opportunistic infections (*P. carinii* pneumonia)

TABLE 27 *Non-haematological adverse effects[a] reported in the major TMZ RCT[181]*

Adverse effect	*n* (%)					
	Grade 2			Grade 3/4		
	RT + TMZ (*n* = 287)	RT only (*n* = 286)	*p*[b]	RT + TMZ (*n* = 287)	RT only (*n* = 286)	*p*[b]
Fatigue	108 (37.6)	65 (22.7)	<0.001	38 (13.2)	20 (7.0)	0.013
Other constitutional	27 (9.4)	18 (6.3)	0.166	12 (4.2)	2 (0.7)	0.007
Rash/dermatological	35 (12.2)	17 (5.9)	0.009	9 (3.1)	3 (1.0)	0.081
Infection	7 (2.4)	5 (1.7)	0.564	20 (7.0)	8 (2.8)	0.021
Vision	59 (20.6)	44 (15.4)	0.107	5 (1.7)	6 (2.1)	0.756
Nausea/vomiting	79 (27.5)	9 (3.1)	<0.001	6 (2.1)	3 (1.0)	0.316

[a] Adverse effects assessed according to NCI CTC (see Appendix 9).
[b] χ^2 test (calculated by PenTAG).

during concomitant RT + TMZ.[183] In response, the investigators introduced compulsory antibiotic prophylaxis and saw no further instances of this complication. They also report one patient who died of "chemotherapy overdose" (thrombocytopenia, neutropenia, septicaemia) after mistakenly receiving 200 mg/m^2 of TMZ for 30 consecutive days during the adjuvant therapy phase (rather than in monthly 5-day cycles).

Treatment discontinuation due to toxicity

In Stupp and colleagues' RCT, 31 patients (11% of the RT + TMZ group) discontinued TMZ because of toxic effects (14 during concomitant therapy and 17 during adjuvant phase).[181] Athanassiou and colleagues report that two patients (3.5%) discontinued their adjuvant TMZ regime because of toxicity.[182] Four patients (6.3%) withdrew from TMZ owing to toxic effects in Stupp and colleagues' case series[183] and Lanzetta and colleagues report an 8.3% drop-out rate.[184]

Case reports

We also reviewed case report literature to identify rare but significant AEs that may not be captured in the trial data.

Hartmann and colleagues present an immunological study of three cases of TMZ-related haematological toxicity.[190] Although each patient recovered, the authors note that neutrophil function remained impaired for up to 6 weeks after TMZ had been discontinued.

Su and colleagues report the case of a woman with inoperable AA who received TMZ and developed severe haematological dysfunction, culminating in treatment-related myelodysplastic syndrome, progressing to acute leukaemia, from which she died.[191] Fatal myelosuppressive complications have also been reported in a study of TMZ for low-grade gliomas.[192]

In studies of TMZ as salvage therapy at tumour recurrence (reviewed in detail elsewhere[2]), the incidence of grade 3/4 haematological toxicities seems comparable to that identified in our review. The range of rates reported is: anaemia 1–4, leukopenia 2–7, lymphocytopenia 55–58, neutropenia 0–5 and thrombocytopenia 6–13%.[193–197]

For non-haematological AEs, a syndrome of TMZ-induced neurological 'flare' has been described by Rosenthal and co-workers.[198] They report eight patients (at least 2% of those receiving TMZ in their unit) experiencing a sudden and unexpected deterioration in neurological status within a few days of commencing TMZ. Symptoms included weakness, dysphagia, headache, confusion and convulsions. Cerebral oedema was detectable on neuroimaging in some cases, leading the authors to suggest that the syndrome may represent an acute inflammatory response to the cytotoxic effects of TMZ. It is emphasised that this syndrome is not associated with a poor prognosis and, indeed, may be an indication of effective cytotoxic action.

Islam and colleagues report an isolated case of haemorrhagic cystitis, which was amenable to treatment, but necessitated discontinuation of TMZ.[199]

In post-recurrence, salvage TMZ, the incidence of non-haematological toxicities appears comparable to those described here. For example, the range of rates reported for grade 3/4 fatigue is 2–17% and for nausea/vomiting is 0–25%.[193–197]

BOX 7 *Summary of results from systematic review of temozolomide*

In the largest TMZ RCT, reported by Stupp and colleagues:[181]

1. The intervention is associated with a small but significant **survival** benefit:
   (a) median of 2.5 (95% CI 0.2 to 5.6) life-months gained in treatment arm
   (b) unstratified HR of 0.63 (95% CI 0.52 to 0.75), $p < 0.001$ by unstratified log-rank.
2. Long term survival with TMZ is favourable at 26.5% at 2 years (vs 10.4% in the control arm).
3. The intervention is also associated with significant benefit in terms of **PFS**:
   (a) median of 1.9 (95% CI 0.3 to 4.0) progression-free months gained in treatment arm, $p < 0.001$ by unstratified log-rank.
4. **Subgroup analysis** of patients with reduced MGMT activity showed that there was a significant survival effect in this population:
   (a) median of 6.4 (95% CI 4.4 to 9.5) **life-months gained** in the treatment arm
   (b) unstratified HR of 0.51 (95% CI 0.31 to 0.84), $p < 0.007$
   (c) median of **PFS** advantage of 4.4 (95% CI 1.2 to 6.3) months
   (d) unstratified HR 0.48 (95% CI 0.31 to 0.75), $p = 0.001$.

   No significant treatment effect was seen in any outcome for those with normal MGMT activity.
5. **Adverse effects**:
   (a) 16% of the TMZ group experienced severe myelosuppression during the trial
   (b) grade 2 (moderate) fatigue, rash and nausea/vomiting were significantly more common in the TMZ arm
   (c) grade 3/4 (severe, life-threatening or disabling) fatigue, unspecified constitutional symptoms and infection were significantly more common in the TMZ arm
   (d) 11% of the treatment group discontinued TMZ because of toxic effects.

The RCT reported by Athanassiou and colleagues[182] describes an older cohort who were more likely to have low preoperative performance status and less likely to have undergone aggressive surgery. This worse baseline prognosis, while reflected in outcomes in the control group, is substantially attenuated in the treatment arm, with a net result of increased relative effectiveness:

1. median of 5.7 (95% CI 0.3 to 11.8) months overall survival gained in treatment arm ($p < 0.0001$)
2. median of 5.6 (95% CI 0.7 to 10.8) progression-free months gained in treatment arm ($p < 0.0001$)
3. 56.3% of patients receiving TMZ survived 12 months after commencement of RT, compared with 15.7% in the control arm.

The two additional uncontrolled case series add little to the evidence base.

A summary of results from the systematic review of TMZ is given in *Box 7*.

Indirect comparison of carmustine implants and temozolomide

As no direct comparison of BCNU-W and TMZ has been identified, we considered whether indirect comparison of these treatments would be valid, particularly in relation to issues raised by Song and colleagues.[200,201] For the studies in this report, we felt that there were a number of challenges to those aspects of quality and similarity in population and design that would be needed to make such a comparison. These are summarised in *Box 8*. We have not therefore attempted indirect comparison between TMZ and BCNU-W.

BOX 8 *Reasons for not undertaking indirect comparison of the interventions*

Condition	Evidence against condition
Internal validity of trials If there is uncertainty about the reliability of the trials under review, it is not feasible to compare their findings with any confidence. Song and colleagues state "biases in trials will inevitably affect the validity of the adjusted indirect comparison."[200]	As detailed in our appraisal of the methodological quality of included studies [sections 'Internal validity' (pp. 18 and 37, for BCNU-W and TMZ, respectively)], the RCTs under review are susceptible to bias. The BCNU-W RCT was underpowered, and there may have been asymmetry between trial arms at baseline, especially with regard to distribution of prognostically favourable tumour types. The TMZ RCT was importantly undermined by its open-label design, which may inflate the apparent effectiveness of the intervention. If, as a result of methodological shortcomings, these trials misrepresent the true effectiveness of the interventions, any comparison between the two sets of results will reproduce, and possibly exaggerate, such distortions.

continued

BOX 8 *Reasons for not undertaking indirect comparison of the interventions (cont'd)*

Condition	Evidence against condition
Consistency of treatment effect In presenting commonly used methods for indirect comparison, Bucher and colleagues state that it is necessary for the magnitude of treatment effect to be constant across differences in the populations' baseline characteristics.[202] If it can be assumed that each of the interventions being compared has the same relative efficacy in all patients, then it is possible to disregard acknowledged or occult heterogeneity across respective control and treatment groups.	This assumption cannot be met in this case. In the BCNU-W RCT, the intervention appeared to have a lesser effect in patients with GBM than it did in others (although numbers were small and CIs wide in the latter group). The genetic subgroup analysis of the TMZ RCT suggests that reduced MGMT activity is a predictive marker not only for absolute survival gain, but also for relative treatment effect [see the section 'Effectiveness: subgroup analysis according to MGMT status' (p. 48)]. This shows that the magnitude of treatment effect was influenced by baseline variables in the trial. In all the subgroups that can be ordered, treatment effect is greater in the better prognosis group. These findings suggest that, in high-grade glioma, cohorts contain patients with different degrees of baseline chemosensitivity. As a result, heterogeneity across trial populations will result in estimates of treatment effect that vary widely.
Homogeneity of patient cohorts The comparability of cohorts under review is prerequisite for any comparison between trials.	The populations of the RCTs under review vary in a number of key aspects: • **Diagnosis**: By design, the BCNU-W RCT included patients with grade III tumours (about 15% of subjects) in addition to grade IV. The TMZ RCT was explicitly confined to grade IV tumours; however, 7–8% of subjects were found to have grade III tumours on pathology review. Comparing the results of the TMZ trial to the entire BCNU-W cohort would unduly favour the latter, as it contains a greater proportion of subjects with better prognosis. Conversely, comparing the TMZ results to the GBM-only population from the BCNU-W trial would reverse the imbalance of grade III patients and so exaggerate the relative effectiveness of TMZ. • **Surgery**: The BCNU-W trial randomised patients at the time of tumour resection, whereas selection and randomisation of patients for the TMZ RCT took place after patients had undergone surgery and postoperative recovery. This has important effects: (i) survival is the primary outcome measure for effectiveness but is not measured consistently across trials because of differences in the start-point from which survival time was measured; and (ii) surgical mortality and morbidity are effectively excluded from the TMZ trial, which may exclude a small number of patients with worse prognosis. • **Extent of surgery**: BCNU-W implantation requires all patients to undergo extensive tumour removal, and tumours must be relatively large and accessible; TMZ is administered to patients who may only have undergone diagnostic biopsy. Extent of surgery may have a prognostic influence. This issue is emphasised by Schering-Plough in their submission to NICE.[90] They argue that, in order to make an effective comparison between the two RCTs, it would be necessary to concentrate exclusively on the subgroup of the TMZ trial who underwent complete resection. Although this is based on their erroneous assertion that all patients in the BCNU-W trial underwent macroscopically total tumour resection (the majority were judged to have had 'subtotal' resections), this highlights the difficulty of identifying appropriate subgroups to compare across trials. The kind of comparison that Schering-Plough propose is simplistic.[200]

continued

BOX 8 *Reasons for not undertaking indirect comparison of the interventions (cont'd)*

Condition	Evidence against condition
Homogeneity of control arms Indirect comparison suggests that it is feasible to assess the relative effectiveness of interventions A and B on the basis of trial A versus control and trial B versus control. However, in order for this comparison to be valid, the equivalence of the control arms across both trials has to be assumed. One way of viewing this, as Song and colleagues suggest, is to ask whether it is valid to assume that the result of trial A versus control would have been observed in trial B versus control if intervention A had replaced B in the latter.[201]	In addition to the differences between the overall patient cohorts, there are several ways in which the control arms of the RCTs under review appear to vary: • As noted in the section 'Data from included studies' (p. 33), there is a possibility that the implantation of placebo wafers had some effect on the BCNU-W control arm. This is not an issue in the TMZ trial. In comparisons between the two treatments, it would not be possible to account for any influence this discrepancy may have. • There is no placebo control in the TMZ trial. The impact of this cannot be quantified, although it is possible that an inflated treatment effect is seen. On the other hand, there are a number of similarities between the two control arms. In particular, the median survival in each group appears similar (11.6 months in the BCNU-W RCT, compared with 12.1 months in the TMZ trial), as does the 12-month survival rate (49.6 and 50.6%, respectively) and median PFS (5.9 and 5.0 months, respectively). However, any statistical homogeneity between the two groups may or may not be the results of true clinical comparability, and, as stated above, the outcome measures used are not equivalent in any case.

Chapter 4

Cost-effectiveness

Aim of the economic evaluation

We aimed to assess separately, based on available data, the cost–utility of BCNU-W and TMZ as chemotherapy additions to RT and surgery for newly diagnosed patients with high-grade gliomas who are suitable for surgery.

Research questions

What is the cost-effectiveness of:

- BCNU-W as adjuvant treatment to surgery and RT compared with placebo-wafer and surgery and RT in newly diagnosed high-grade gliomas?
- TMZ as adjuvant and concomitant treatment to surgery and RT compared with surgery and RT alone in newly diagnosed high-grade gliomas?

Systematic review of cost-effectiveness studies

Methods

Search strategy and critical appraisal methods

Electronic databases were searched using the strategy shown in Appendix 4.

Inclusion and exclusion criteria

Studies were included if they were complete economic evaluations:

- of TMZ as adjuvant and concomitant chemotherapy to surgery and RT
- of BCNU-W as adjuvant chemotherapy to surgery and RT
- in newly diagnosed high grade gliomas
- cost–utility studies
- relevant to the UK setting.

Existing cost-effectiveness evidence

Published cost-effectiveness studies

Of the few published economic evaluations of treatments for patients with high-grade glioma, none that are true cost-effectiveness analyses have focused on treatment comparisons relevant to the scope of this report.

Four studies have reported resource use and cost data in relation to treatment of people with malignant glioma with TMZ. Wasserfallen and colleagues conducted a 'cost-identification study' alongside a Phase 2 trial, collecting resource use data on 35 adults with high-grade glioma who received concomitant and adjuvant TMZ following debulking surgery and 11 patients following biopsy.[203] However, the study was set in Switzerland and no control group cost data were collected or reported. A subsequent study by Wasserfallen and colleagues, based on the same trial, only reported results for those who had initially received TMZ for recurrent malignant glioma.[204] Moreover, they did not perform an incremental analysis, instead reporting average cost-effectiveness and cost–utility ratios for a number of patient subgroups (with KPS used as a crude proxy for utility values).

Greanya and colleagues conducted a true cost-effectiveness analysis that compared surgery with RT + TMZ, with surgery with RT and lomustine for patients with recurrent glioma, in a Canadian setting.[205] This was a retrospective study based on the patient records of 50 patients who had received TMZ and 28 who had received lomustine. Despite measuring no significant differences in outcomes, incremental cost-effectiveness ratios (ICERs) were calculated.

The only cost-effectiveness analysis of TMZ set in the UK is a decision model-based analysis reported in the 2001 HTA report by Dinnes and colleagues.[2] However, their findings are of limited value in the current analysis since they were concerned with the treatment of recurrent (rather than newly diagnosed) malignant glioma.

There are as yet no published economic evaluations of treatment comparisons involving BCNU-W. Finally, although there is a published cost–utility analysis of alternative treatments for malignant glioma, this was based in the USA and was restricted to comparing alternative RT protocols.[206]

Published UK cost analyses and resource use studies

Two published analyses assess the resource consumption related to treating high-grade

glioma in the UK NHS context.[207,208] Although published in 1998, the data collection periods for both studies are over 10 years old. The paper by Latif and colleagues assessed the costs of managing 236 glioma patients (158 with GBM, 78 with AA) at a dedicated neuro-oncology clinic (Western General Hospital, Edinburgh), using the neurosurgical and oncological case file data on patients treated between 1989 and 1995.[208] The report by Bloor and colleagues was a retrospective study of 103 adult glioma patients who were diagnosed in two oncology centres during 1990 or 1991 (Royal Marsden Hospital, Surrey, and West Glasgow Hospitals NHS Trust).[207]

Neither of these studies are very well reported, lacking full identification of both resource usage by resource type and source of unit costs, but the papers provide useful indicators of the main categories of resource use that should be included in any comprehensive cost-effectiveness analysis of alternative treatments for high grade glioma in the UK NHS context.

The resource types that accounted for most of the direct care costs for these patients were surgery/operating theatre costs, neurosurgical and other inpatient bed-days, RT and outpatient hospital visits. Bloor and colleagues highlighted the generally low community care costs (mean £456 per patient, or 4% of total costs).[207] They also noted the potential importance of auxiliary services (such as speech therapy, occupational therapy, psychology and physiotherapy), but missing data prevented them from quantifying the potential significance of such costs. Finally, this is the only study to have reported use of hospice care: 62 of the 103 patients were admitted to a hospice, for a mean of 26 days (median 14, range 1–164).

More recently, Iyer and colleagues conducted an audit of the use of operating theatre time in neurosurgery at the Royal Preston Hospital.[209] This study provides useful background data on the overall operating theatre time resource demands of intracranial tumour surgery, and also its relative importance within the overall workload of such surgical centres.

Cost-effectiveness studies provided by industry

Two economic analyses were submitted to NICE by the industry sponsors of Gliadel® (BCNU-W) and Temodal® (TMZ):

- a report of a modelling-based cost–utility analysis of debulking surgery with BCNU-W versus debulking surgery with placebo wafers
- a report of a trial-based cost-effectiveness analysis of RT with concomitant and adjuvant TMZ versus RT only.

The analyses are of variable quality. The tables in Appendices 10 and 11 show their detailed compliance with NICE methodological requirements,[210] and, where decision models have been used, the quality of the decision model which is assessed using the criteria proposed by Sculpher and colleagues.[211]

The sections below provide our overall appraisal of each industry-submitted analysis.

Economic evaluation of BCNU-W submitted by Link Pharmaceuticals Ltd

Design

The economic evaluation of BCNU-W is based on a very simple model of the underlying disease process. The model divides post-surgery survival into two main phases: 'stable disease' (pre-progression) and 'disease progression' (after the recurrence of tumour). It further assumes a constant QoL (utility) for time lived in the 'stable' state, and then a continuous linear decline in utility between the time of disease progression and death (*Figure 12*).

A similar model was used by Dinnes and colleagues in the 2001 HTA report on TMZ for recurrent malignant glioma.[2]

Conducted by

The analysis was conducted by Link Pharmaceuticals Ltd.

Overall appraisal

Although this economic analysis is based on a sensible decision model structure, the main ICER generated [£28,000 per quality-adjusted life-year (QALY)] uses both incomplete cost estimates and questionable survival assumptions that bias the result in favour of BCNU-W.

The omission of all costs other than the cost of the BCNU-W themselves will underestimate the incremental cost implications of the new treatment. In particular, their analysis ignores the additional healthcare costs that would accrue during any added weeks of life due to the treatment, which they estimate at 8.2 additional weeks with stable disease, plus 3.3 additional weeks with disease progression.

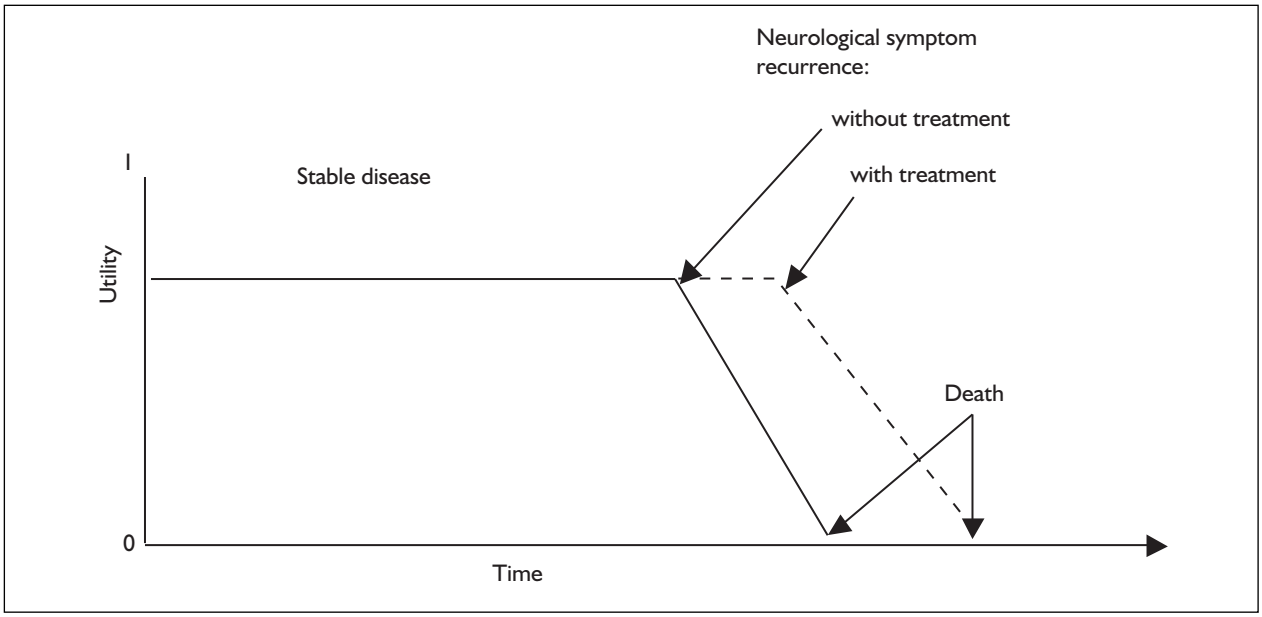

FIGURE 12 *Model of the natural history of malignant glioma*

Our critical appraisal of the BCNU-W RCT by Westphal and colleagues [see the section 'Effectiveness (all patients)' (p. 26)] shows that, in contrast to the published conclusions, there is little evidence of a statistically significant benefit from BCNU-W treatment, in terms of either overall survival or progression-free survival (see the first major limitation below).[151] Also, for the economic analysis, the time at which QoL, and hence utility, is deemed to decline is assumed to be when neurological performance scores decline. Although this seems plausible, it should be noted that for all of the other measures of disease progression/tumour recurrence there was no significant difference between treatment and placebo patients in the unstratified analysis.[151] Lastly, even if these measures of survival or progression could be relied upon as indicators of QoL, and if the trial had conclusively demonstrated a benefit, it would be incorrect to use the medians of PFS instead of the means in this analysis (see the third major limitation below).

Major limitations of industry analysis of BCNU-W

The assumption of an increase in both symptom-free survival and overall survival with BCNU-W relative to placebo

The assumption of an increase in either type of survival critically depends on (a) which measure of disease or symptom progression is used and (b) whether the analysis is conducted according to the trial protocol: unstratified by country. Our critical appraisal of the main BCNU-W RCT [see the section 'Effectiveness (all patients)' (p. 26)] shows no proven statistically significant benefit from BCNU-W treatment, in terms of either overall survival or PFS.[151]

Also, the various definitions of PFS are vulnerable to bias. A re-analysis by the FDA has shown that, if those instances of neuroperformance decline due to patient deaths are excluded, there is then a significant difference in only one of the 11 neuroperformance indicators (see Appendix 8).

Omission of all costs other than the cost of BCNU-W

Although the possible impact of treating higher rates of cerebrospinal fluid leaks and cerebral hypertension is explored in the sensitivity analysis, no other costs post-surgery are included in the analysis. Given that the analysis includes increased mean survival for those receiving BCNU-W, at least the estimated healthcare costs in added weeks of life should have been included.

Use of median rather than mean times to decline in neuroperformance

In the model, the assumed advantage in symptom-free weeks due to treatment with BCNU-W is 8.2 weeks. However, this is the difference in the mean of the 11 **median** times to neurological performance decline in each arm of the trial. For economic analysis, the **mean** of the mean times to any particular measure of decline should be used. Such a re-analysis might generate an advantage which is smaller or larger than the 8.2 weeks used in the reported analysis.

Other limitations

Given the simple two-stage model used, the utility values attached either to time lived before or after the recurrence of neurological symptoms will have a major impact on the overall result. The assumption of a utility weight of 0.8 for symptom-free post-operative survival is loosely based upon baseline KPS of patients in the main RCT[151] and UK population norms on the EQ-5D instrument for 45–54-year-olds.[212] It is questionable whether people awaiting the recurrence of a terminal disease, including some weeks spent receiving RT (with consequent immunosuppression effects) and also possible seizures following the craniotomy, would have a health-related QoL which is equivalent to the normal population of the same age. KPS is known to be a poor proxy for QoL.[107]

There is currently no good research evidence on the temporal pattern of decline in QoL following symptom or tumour recurrence in this patient group, for example, whether it is approximately linear or not and whether declines in overall QoL are linked to specific types of decline in neurological function.

The industry submission on BCNU-W did not discount costs or effects, as stipulated by NICE, in any of their analyses. However, given the relatively short mean survival of patients with high-grade gliomas, this is unlikely to affect greatly their main cost-effectiveness estimates.

A summary of the industry submission is given in *Box 9*.

Economic evaluation of TMZ submitted by Schering-Plough Ltd

Design

This is a trial-based study, using patient-specific cost and effectiveness data from the same RCT, by Stupp and colleagues.[181] **[Confidential information removed.]**

Conducted by

[Confidential information removed.]

Overall appraisal

Basing the analysis directly on actual effectiveness and resource data from a relevant trial is usually to be commended. However, this multi-centre trial was conducted in a number of countries **[Confidential information removed].** Patterns of medical practice and resultant resource consumption may therefore be different to what would occur for similar patients in the UK NHS.

No cost per QALY results are presented. **[Confidential information removed.]**

Also, the estimation and presentation of outcomes and resource use restricted to the 2-year time horizon (of the trial's data collection) is unjustified, and probably biases the results in favour of TMZ (see the discussion of major weaknesses below). This includes the main ICER result of £19,440 per life-year, that is given prominence in both the Executive summary and the Discussion of economic analysis (Section 3.5, p. 43 in the submission to NICE).

BOX 9 *Industry submission economic analysis of BCNU-W: summary critique*

Strengths

1. The structure of the decision model is simple, and broadly reflective of available evidence on the main disease stages of malignant glioma.
2. The analysis meets the majority of current NICE methodological requirements for cost-effectiveness analyses of health technologies, and provides a probabilistic sensitivity analysis based on uncertainty surrounding four of the main model parameters.

Limitation

1. Evidence for PFS advantage and overall survival benefit in the RCT on which the assessment is based is questionable.
2. The omission of any treatment costs other than the cost of the wafers themselves will bias the cost-effectiveness results in favour of BCNU-W. The omission of treatment costs in any added months of survival is particularly critical.
3. Their use of the decline in 11 measures of neuroperformance to define symptom progression is flawed because (a) if neuroperformance declines owing to death are excluded, there is no statistically significant advantage in symptom-free survival (FDA analysis), and (b) the incremental PFS used in the economic analysis is incorrectly based on the **median** times to neuroperformance decline rather than the mean times to decline on these measures.
4. The derivation of the base-case utility weight of 0.8 for symptom-free survival is not well justified. Nevertheless, PenTAG's estimation of these utility weights, using a choice-based method in conjunction with comprehensive symptom and impact descriptions, yielded similarly high utility values (0.81–0.86) for different phases of stable disease.

TABLE 28 *Main cost-effectiveness results in the TMZ submission (undiscounted)*

	Extrapolated survival of full trial cohort[a]	Extrapolated survival of economic subgroup[b]
Assuming no difference in costs after 2 years	**[Confidential information removed]**	
Assuming 'significant difference' in costs after 2 years		

LY, life-year.
[a] Using a generalised gamma distribution.
[b] Using a Weibull distribution.

Only the results and validity of the extended time-horizon analyses should therefore be considered. However, the validity of these analyses is difficult to judge because the submission has not fully described how survival was extrapolated beyond 2 years. Different statistical methods are used for extrapolating the full cohort results and the economic subsample: the generalised gamma distribution and a Weibull distribution respectively. Reasons for this are not given.

As either the full cohort or economic subgroup survival estimates can be used, and because there are two different assumptions about how treatment costs differ after 2 years, this still creates a 2×2 matrix of possible ICERS as shown in *Table 28*.

[Confidential information removed.]

Nevertheless, it is possible to fit a variety of Weibull curves to the 2-year survival data, each of which has an excellent fit (R^2 all >97%) and yet which also generate vastly different mean survival estimates. Also, given the uncertainty that generally surrounds the 'tail' of survival curves where, typically, small numbers are at risk, statisticians strongly warn about "over-interpretation of the right-hand part of the survival curve" (see Altman,[213] p. 386). The fitting of standard distributions is one example of how such over-interpretation can occur. It is clear that, in the absence of a larger trial which follows up high-grade glioma patients for 3 or 4 years, the estimates of mean extrapolated survival should be subject to extensive sensitivity analysis. **[Confidential information removed.]**

[Confidential information removed.]

Major limitations in the industry analysis for TMZ

The cost-effectiveness results relating to 2-year restricted survival are questionable for two reasons:

1. **[Confidential information removed.]**
2. Lack of control or adjustment for post-progression differences in treatment. **[Confidential information removed.]**

Other limitations

Resource use data were only available from a subsample of patients, **[Confidential information removed]** (224 of the 573 patients in the full trial). **[Confidential information removed.]** Given that one or two patients with extremely high costs can substantially alter the mean costs of small groups, this may be an important omission.

[Confidential information removed.] Their analysis complied with most of these requirements, except:

1. Health effects were not measured in QALYs, but in life-years gained.
2. **[Confidential information removed.]**
3. **[Confidential information removed.]**

Illustrative re-analysis

As already discussed, the analyses presented in the industry submission in effect compare the costs and effects of a sequence of treatments given both initially and following tumour recurrence. Because of this, it is highly plausible that both the incremental costs and incremental survival are partly driven by differing treatment choices during disease progression, rather than the choice of treatment when the gliomas were newly diagnosed.[160,161]

An alternative analysis of the cost-effectiveness of TMZ for newly diagnosed high-grade glioma could assume that the effectiveness of treatments for newly diagnosed glioma is restricted to extending PFS. Indeed, there is no good evidence that TMZ, or any other chemotherapy treatment delivered as first-line therapy for newly diagnosed tumours, offers any benefit in slowing the rate of disease progression after recurrence.

TABLE 29 *Two-year restricted survival results in industry analysis of TMZ (economic subgroup)*

Phase of survival	Survival (years) RT only	RT + TMZ	Incremental life-years
2 years restricted mean overall survival *of which:* Mean progression-free survival Mean survival with progression	**[Confidential information removed]**		
Proportion surviving at 2 years (economic subsample)			
Source: **[Confidential information removed]**.			

TABLE 30 *Extrapolated survival results in industry analysis of TMZ (economic subgroup)*

Phase of survival	Survival (years) RT only	RT + TMZ	Incremental life-years
2 years restricted mean overall survival *of which:* Mean progression-free survival Mean survival with progression	**[Confidential information removed]**		
Source: **[Confidential information removed]**.			

TABLE 31 *Cost-effectiveness results with post-progression costs and extrapolated survival gains either included (industry analyses) or excluded (PenTAG re-analysis)*

	Results when both pre- and post-progression costs are included (as per submitted analysis)		Results when only pre-progression costs are included in analysis	
	Full cohort	Economic subgroup	Full cohort	Economic subgroup
Life-years gained, extrapolated	**[Confidential information removed]**		**[Confidential information removed]**	
Incremental costs				
ICER	£11,003/LY	£12,818/LY		
Progression-free life-years gained, extrapolated				
Incremental costs				
New ICER				
LY, life-year; PFLY, progression-free life-year.				

[Confidential information removed.]:

1. **[Confidential information removed.]**
2. **[Confidential information removed.]**

[Confidential information removed.]

A summary of the industry submission is given in *Box 10*.

PenTAG cost–utility model

Structure of the model

Previous studies, such as that by Dinnes and colleagues[2] on TMZ for recurrent high-grade glioma, have generally adopted a survival curve approach such as Q-TWiST. Q-TWiST (quality-adjusted time without symptoms of disease or toxicity of treatment) produces a quality-adjusted

BOX 10 *Industry submission economic analysis of temozolomide – summary critique*

Strengths

1. The analysis is based upon a recent Phase 3 RCT which produced patient-specific survival data and resource use data (for a subgroup) relating to largely the same group of patients.
2. The analysis meets the majority of current NICE methodological requirements for cost-effectiveness analyses of health technologies.

Limitations

1. **[Confidential information removed]**. Also, no decision model is used. This makes it difficult to compare properly their cost-effectiveness analysis with the PenTAG analysis.
2. The multi-centre trial on which the analysis is based was carried out in a number of countries with health systems that are substantially different to the UK NHS. This has particular implications for the transferability of resource use data.
3. The validity of the main ICER reported is limited because it is restricted to survival and cost data only up to 2 years post-randomisation.
4. The validity of the other ICERs reported is very hard to judge, **[Confidential information removed]**:
   (a) **[Confidential information removed]**
   (b) **[Confidential information removed]**
5. No attempt has been made **[Confidential information removed]**, to adjust for the fact that patients in the RT only (control) arm of the trial received substantially higher levels of salvage chemotherapy (especially TMZ).

survival result. Three distinct health states are considered:

1. time with toxic effects (TOX)
2. time without symptoms or toxicity (TWiST)
3. disease progression until death or censoring (PROG).

The utility value attached to the TWiST state is one. This is a limitation, particularly in the case of high-grade gliomas, as it assumes that patients spend time in a health state corresponding to perfect health, unlikely with terminal cancer. The Q-TWiST method also depends on sequential health states with patients moving through them in a fixed order, which might not be the case for gliomas.

Average time values needed to calculate the output score are usually found by partitioning Kaplan–Meier information through recording the number of people in each state for each time period, and drawing separate curves for each of the health states. This is not possible for TMZ and BCNU-W as patient-level data are not available. Finally, the method relies on the utility weights for each state being independent of time. In the case of high-grade glioma, patients' physical condition degenerates as the tumours grow. The Q-TWiST approach was therefore rejected, as it was felt to lack the necessary flexibility and realism in relation to the QoL of this patient group.

A Markov model can also be used to provide a simple framework for analysis and has been adopted in previous studies.[214] It offers more flexibility to accommodate more realistic QoL values and was chosen over the Q-TwiST approach in this case. A Markov (state transition) model therefore was developed in Microsoft Excel. The structure was informed by the clinical progression of the disease and best practice for treatment and uses the health states described in *Table 32*.

The model estimates incremental cost–utility for concomitant and adjuvant TMZ, or concomitant BCNU-W in the treatment of newly diagnosed high-grade gliomas compared to treatment with surgery and RT alone. The base case uses costs for 2004 and takes the perspective of the UK NHS. A cohort of 1000 people with operable grade III and IV gliomas is modelled for 5 years. The average age of the cohort is 55 years, based on the mean of those participating in the main RCTs informing the model. A relatively short cycle length of 1 week was chosen to capture the complexity of the process and maintain flexibility in the model. This short cycle time also renders half-cycle correction unnecessary. Five years was considered sufficient time to capture all critical effects and costs and by the end of this time almost all the modelled cohort are dead. The impact of running the model for different periods is assessed in sensitivity analysis.

The influence diagram is shown in *Figure 13*. Arrows represent transitions between the states and boxes show health states through which members of the cohort pass.

During each cycle, a patient is assumed to be in one of the states. Patients move between states

TABLE 32 *Markov states and allowable transitions*

Markov state	Definition	Allowable transitions from this state to:
Surgery	Intracranial surgery to debulk the tumour (partial or full resection), including preoperative hospital stay	Death Postoperative recovery
Postoperative recovery	Postoperative inpatient hospital stay	Postoperative recovery Radiotherapy Death
Radiotherapy	Standard outpatient 6-week course of radiotherapy at 5 fractions per week, each of 2 Gy	Stable disease Radiotherapy Progression Death
Stable disease	Post-radiotherapy and before symptomatic diagnosis of tumour progression	Stable disease Progression Death
Progression	Tumour progression or recurrence, as identified by recurrence of symptoms	Progression Death
Death	Patient's death	None (absorbing state)

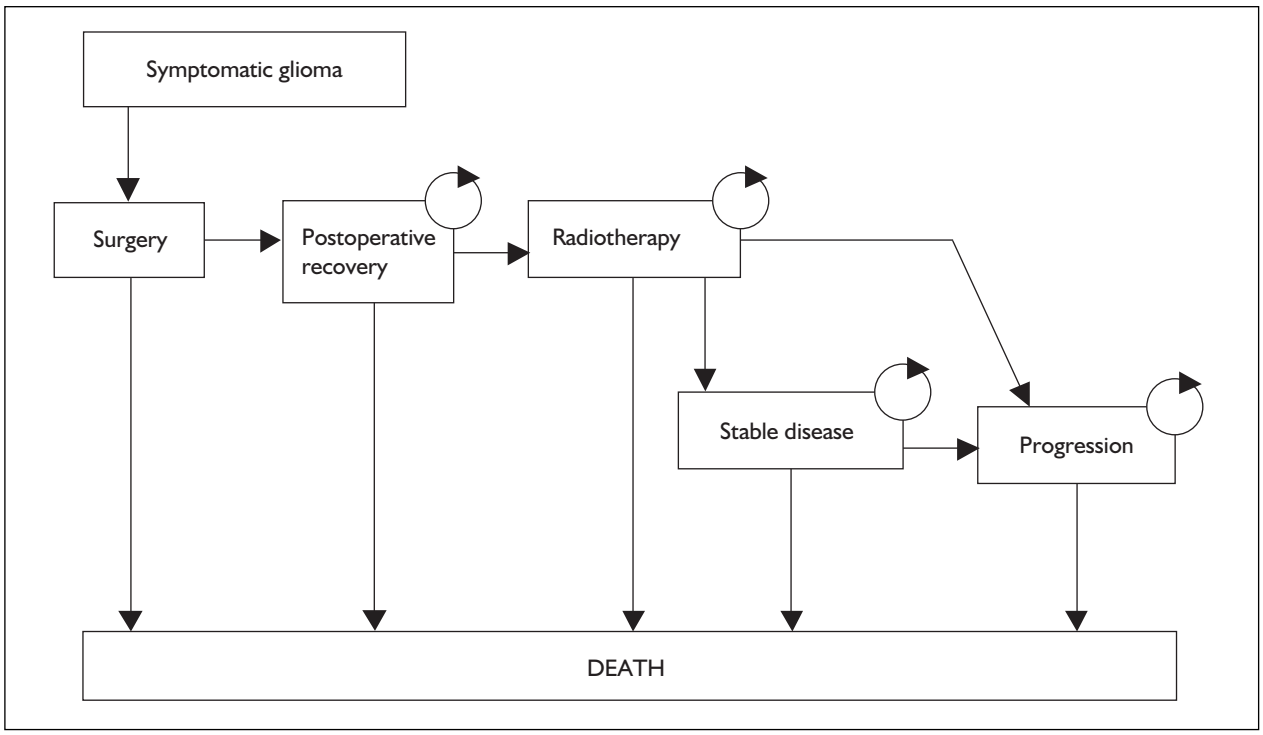

FIGURE 13 *Influence diagram for model of patients with newly diagnosed high-grade glioma*

once during each cycle. This means that if a patient is currently in the 'stable disease' state, for example, then during the next cycle they can either die, move to the 'progressive' state or stay in the 'stable' state.

The 'surgery' and 'postoperative recovery' states are tunnel states. Patients remain in them for a fixed period, during which they only leave the state if they die. After that fixed period, all patients still alive move to another state. The health states and pathways are the same for both treatments being investigated, although the length of stay in the 'postoperative recovery' tunnel state differs depending on whether the patient is from the BCNU-W or TMZ trial. This difference is

based on trial data. In all cases, 1 week is spent in the surgery state.

All patients enter the model having been diagnosed with symptomatic glioma. All patients modelled are suitable for surgery which occurs in week one of the model. 'Post-operative recovery' is the time spent between surgery and RT and depends on the treatment being received. The difference in time that patients spend in this state is due to different methods of randomisation used in the trials of BCNU-W and TMZ. Median time spent in the 'post-operative recovery' state for patients receiving TMZ is 5 weeks (control range 2.0–12.9 weeks, treatment range 1.7–10.7 weeks).[181] Patients receiving BCNU-W had a median state occupancy of 2 weeks since randomisation took place at time of surgery. All patients still alive after this period of convalescence receive RT for a maximum of 6 weeks.

Once the course of RT is finished, patients remain in the 'stable disease' state until they either die or the disease progresses. Once they enter the 'progressive' state, patients remain there until death. While the model does not contain a health state to allow for patients receiving subsequent surgery or chemotherapy after disease progression, this option is taken into account when evaluating the costs associated with the 'progressive' state. In addition, as the transitions used are based on trial data, where a proportion of patients received second-line therapy, the curves already incorporate any survival influence such treatment may cause.

The transition from 'radiotherapy' to 'progression' allows patients to move between actual health states in a non-sequential way by bypassing the 'stable disease' state.

Model assumptions

All patients receive surgery soon after a high-grade glioma is diagnosed, followed by RT a median of 5 weeks later for the TMZ model and 2 weeks later for the BCNU-W model (see above). However, current UK practice is affected by long waiting times for RT, which may be as long as 12 weeks (Palmer J: personal communication, 2005). The potential impact of this on the model is unclear. Long waiting times have an unknown impact on QoL, as waiting for treatment may be stressful and initial symptoms remain unresolved. However, the detrimental impact of treatment on QoL is also postponed. There may be an impact on survival by delayed treatment and some patients may die before receiving RT treatment.

Owing to limitations of the data, we modelled the progression of a mixture of patients with grade III and IV gliomas. Although TMZ is currently only licensed for use in grade IV tumours, an estimated 7–8% of patients included in the main RCT had their tumour reclassified as grade III at central pathological review.[181] The results are not presented separately in this trial. The outcomes for patients with grade III gliomas may be considerably different and we explored possible alternative outcomes through sensitivity analysis. Data from the main BCNU-W trial suggest that there may be no survival advantage to patients with grade IV tumours[151] (*Figure 5*). Sensitivity analysis is used to explore the impact of different survival times.

The cohort modelled is based on the available trial data. Across all arms of the trials the mean of the median ages is 55 years. However, the median age at onset of disease is older at 70–74 years. This may be a limitation of the model and has been explored in sensitivity analysis. Older patients have poorer prognosis,[3] although more of these patients will also be unsuitable for surgical treatment.

As treatment cannot result in total tumour removal at a microscopic level, the disease could be thought of as always in progression, and this may be defined in a number of ways. The model takes progression to relate to symptomatic, rather than pathological, disease progression. This is appropriate in the model as it allows additional costs and utilities relating to symptoms to be accommodated.

The TMZ trial provides data on the discontinuation of RT due to disease progression and this has been used in the model.[181] As equivalent data are not reported in the BCNU-W trial, rates of drop-out and progression from RT were adopted from the TMZ trial. Average reported drop-out rates were used.

Although repeat surgery and repeat RT are not modelled as separate states in the model, the costs of such second-line treatment are incorporated. In addition, the participants in the trials informing the model were allowed to receive chemotherapy and extra surgery at disease progression and the curves for overall survival therefore already incorporate their impact. It is not known what impact on QoL this may have as patients may have immediate symptom relief through debulking surgery, although adverse effects of surgery and of RT may negatively affect QoL.

A time-dependent utility decrement is used for the 'progressive' disease state giving decreasing QoL as the modelled cohort progress towards death. As some people will have been in the 'progressive' state longer than others, we assumed that they have a lower QoL and should be assigned a lower utility score than those just entering the state. The model tracks how long each patient has been in the state. Details of the data used are described in the section 'Utilities' on p. 65.

To accommodate time dependency, the 'progressive' state is modelled as a series of states. The 'progressive' state shown in the influence diagram in *Figure 13* is actually a succession of substates, each of which represents a sequential worsening of a patient's condition. A patient can enter the 'progressive' state during any cycle after completing the postoperative state. As an example, if a patient enters the 'progressive' state during the model's 10th cycle, then during the 11th cycle they have been in that state for 2 weeks and not 11 weeks.

The number of states collectively labelled 'progressive' was truncated at 120. It was felt that, owing to the very small number of people still alive 120 weeks after entering the 'progressive' state, the amalgamation of weeks 121–260 into one final progressive substate would lead to no significant loss of information. The spreadsheets for each arm of the model therefore have built-in matrices containing information on the lengths of stay in the 'progressive' state, providing useful validation outputs.

Risk of death in the model is time dependent rather than state dependent. The probability of death for a patient is therefore the same at a given time point regardless of the health state they occupy. This may appear counterintuitive, as it would be expected that the probability of dying would increase as a patient physically deteriorated – moving from the 'stable' to the 'progressive' disease state. However, transitions are based on Kaplan–Meier survival curves, so the probability of death increases as time increases and more patients also experience disease progression over time. In a decision model where both effectiveness (QALYs) and nearly all major costs accumulate according to how much time on average patients spend in each disease state, the exact transitions which achieve these average state occupancies are less critical. In other words, it does not matter from which health state those entering the 'death' state are drawn, provided that the resulting overall survival curve and the mean time spent in each state reflect the available empirical evidence. We explore the impact of this assumption in sensitivity analysis.

The only respect in which this time-dependent feature might affect the results is in relation to any costs that are attached to particular transitions to 'death'. For example, in our model, end-of-life palliative care costs (of £3087 per patient in the base case) are attached to all transitions from 'progressive' disease to 'dead'; these might therefore be underestimated if, in reality, a higher proportion of patients would have died when in the 'progressive' disease state. We examined the impact of this assumption through sensitivity analysis.

Sources of estimates used in the PenTAG cost-effectiveness models

Transitions

The probabilities generated are cumulative, since for an individual patient the probability of surviving to the end of a particular period is conditional on them having already survived to the previous period.[213] This, in statistical terms, means that the Kaplan–Meier curve is a graphical representation of the survivor function $S(t)$ for patients in each arm of the trial. To obtain cumulative survival probabilities for individual time intervals, it was necessary to extract points from the curves manually.

The transition probability at any point in time in the multi-state model is equivalent to the standard hazard rate function for a survival time distribution.[215] It was necessary to approximate the Kaplan–Meier curve using a known distribution, in this case a Weibull distribution, which is both versatile and simple to implement. An approximate hazard function for the curve can then be derived. Transition probabilities can then be calculated using standard techniques.[216] Weibull curves were fitted to the overall survival and PFS curves from the main RCT for TMZ.[181] The quality of fit of the Weibull curves to the trial data on overall survival was judged on two criteria:

1. R^2 should be as close to unity as possible.
2. The median survival time predicted should match the trial data as closely as possible.

The Weibull distribution is manipulated by adjusting the two defining curve parameters, the scale parameter (λ) and the shape parameter (γ).

Best fit was used rather than constraining the fit to the trial medians. R^2 values were very high for TMZ and placebo curves (0.9886 and 0.9977) and median survival for the fitted curves was within 3% of the trial data for both curves (0.09 and 3.09%) Further details and examples of the fitted curves are given in Appendix 12. Curves were only fitted to the first 2 years of data in order to help eliminate tail effects for survival curves.[213]

A Weibull curve was fitted to the data extracted from the Kaplan–Meier curves for PFS in the TMZ trial. Initial attempts showed that there was a good fit for the control arm and for the early part of the TMZ curve but not for later stages, where survival was underestimated. We therefore fitted two curves to this data to ensure a better fit. Checking the predicted PFS against trial PFS at specific times points showed that the model now overestimated PFS. We therefore anchored the curves to known data at 3 months using the solver function in Excel. The TMZ arm was also anchored to PFS data at 18 months. See Appendix 12 for details of fitted curves.

No PFS curve is presented in the BCNU-W trial. Transition from the stable to progressive disease state is re-calculated for BCNU-W based on a simple proportional hazards approach. For each model cycle, a constant scaling coefficient is applied to the probability of death to generate the probability of an individual moving from the 'stable disease' state to the 'progressive disease' state. That is, $P_{\text{prog}}(t) = \lambda * P_{\text{death}}(t)$ [$P_{\text{prog}}(t)$ is the probability of transition from stable to progressive at cycle t, $P_{\text{death}}(t)$ is the probability of death at cycle t, and λ is the scaling coefficient]. The probability of death during each cycle is time dependent and modelled using a Weibull function [$P_{\text{death}}(t)$]. For each arm in the model, the Microsoft Excel Solver was used to generate a value of the weighting coefficient λ to maintain the median progression-free survival presented by Westphal and colleagues.[151]

We fitted a Weibull curve to the plotted patient data on overall survival provided by Link Pharmaceuticals.[168] As there was a distinct break in the curves at 21 months, we used a straight line to fit to data after this point as it provided a better fit. This was validated against quartile survival data and produced high R^2 values (see Appendix 12).

By contrast, the PFS curve from the TMZ trial allows this to be modelled as a time-dependent variable in the same way as overall survival.

As data from the TMZ trial start after surgery, the survival curves do not include deaths related to surgery. In order to incorporate this into the model, we used data from a review of perioperative deaths during craniotomy for gliomas.[81] We took a weighted average of the 11 presented perioperative mortality rates (0–3.4%). Perioperative death in that paper[81] relates to deaths in the 3 weeks after surgery, so this overall rate is spread over the first 3 weeks of the model and then the survival curves from the Stupp trial are incorporated from week 4.[181]

Data from Westphal and colleagues' BCNU-W trial show small numbers of perioperative deaths. These are different between the arms, although not statistically significant (1.7 versus 4.2%). There seems little reason to suppose that surgical procedures differ in risk of death between arms. Given this, we have overwritten deaths in the first 3 weeks with data from the same review described above.[81] Survival curves from week 4 of the RCT were then incorporated from week 4.[151] Sensitivity analysis was conducted to explore the effects of differing rates of perioperative death and of differential perioperative death rates between the compared arms.

Fixed transition rates are shown in *Tables 33–36*. Methods of deriving time-dependent transitions based on survival curves are described in Appendix 13. In addition, risk of death was modelled as a time-dependent transition as described in the section 'Model assumptions' on p. 63. The remaining patients remained in their current health state for another cycle. The way in which this rate was calculated is also described in Appendix 13.

The RCTs used in the model quote survival times in terms of months, rather than weeks. As this is likely to be calendar months, this is a potential source of confusion when compared with the results produced by the model, which uses weeks. A calendar correction was therefore applied to the RCT data.

Utilities

Development of the health states for eliciting utility values

Our searches failed to identify any existing sources of utility values that would represent the preferences of the general public in relation to health states associated with high-grade glioma. Estimates of utility were therefore obtained from the NHS Value of Health Panel (VoHP), a pilot project being led by PenTAG in collaboration with

TABLE 33 *Fixed transition probabilities used in modelling BCNU-W treatment*

Transition description	Value	Source
Surgery and postoperative to death	0.0064	Weighted mean of 21-day perioperative mortality reported in the review by Chang *et al.*[81] spread across weeks 1–3
Surgery to postoperative	0.9934	1 – probability of death in week 1
Postoperative to radiotherapy	0.9936	Based on whole cohort moving state in week 3, incorporating weighted mean of 21-day perioperative mortality reported in the review by Chang *et al.*[81] spread across weeks 1–3
Radiotherapy to progressive	0.0093	No intervention-specific data available; rate derived from average numbers discontinuing RT owing to disease progression across both arms of TMZ RCT[181]
Radiotherapy to stable	0.9860	Weibull curve approximation to data presented by Westphal *et al.*[151] Based on the fact that the whole cohort move state in week 9

TABLE 34 *Fixed transition probabilities used in modelling BCNU-W placebo arm*

Transition description	Value	Source
Surgery and postoperative to death	0.0064	Weighted mean of 21-day perioperative mortality reported in the review by Chang *et al.*[81] spread across weeks 1–3
Surgery to postoperative	0.9936	1 – probability of death in week 1
Postoperative to radiotherapy	0.9936	Based on whole cohort moving state in week 3, incorporating weighted mean of 21-day perioperative mortality reported in the review by Chang *et al.*[81] spread across weeks 1–3
Radiotherapy to progressive	0.0093	No intervention-specific data available; rate derived from average numbers discontinuing RT owing to disease progression across both arms of TMZ RCT[181]
Radiotherapy to stable	0.9863	Weibull curve approximation to data presented by Westphal *et al.*[151] Based on whole cohort moving state in week 9

TABLE 35 *Fixed transition probabilities used in modelling TMZ treatment arm*

Transition description	Value	Source
Surgery and postoperative to death	0.0032	Weighted mean of 21-day perioperative mortality reported in the review by Chang *et al.*[81] spread across weeks 1–6
Surgery to postoperative	0.9968	1 – probability of death in week 1
Postoperative to radiotherapy	0.9968	Weibull curve approximation to data presented by Stupp *et al.*[181] Based on whole cohort moving state in week 6
Radiotherapy to progressive	0.0073	Rate derived from numbers discontinuing RT due to disease progression in TMZ arm reported by Stupp *et al.*[181]
Radiotherapy to stable	0.9913	Weibull curve approximation to data presented by Stupp *et al.*[181] Based on whole cohort moving state in week 13

TABLE 36 *Fixed transition probabilities used in modelling TMZ control arm*

Transition description	Value	Source
Surgery and postoperative to death	0.0032	Weighted mean of 21-day perioperative mortality reported in the review by Chang *et al.*[81] spread across weeks 1–6
Surgery to postoperative	0.9968	1 – probability of death in week 1
Postoperative to radiotherapy	0.9968	Weibull curve approximation to data presented by Stupp *et al.*[181] Based on whole cohort moving state in week 6
Radiotherapy to progressive	0.0050	Rate derived from numbers discontinuing RT owing to disease progression in control arm reported by Stupp *et al.*[181]
Radiotherapy to stable	0.9913	Weibull curve approximation to data presented by Stupp *et al.*[181] Based on whole cohort moving state in week 13

the Universities of Southampton and Sheffield. The VoHP currently has 93 members who have been familiarised with the standard gamble method for preference elicitation. It does not reflect, in demographic terms, the general population, but this departure from the NICE reference case is less likely to introduce a bias into the utility values than eliciting utilities from patients or clinicians.

Panel members express their preference using this technique in relation to short descriptions of health states. Data collection is web based. The health state scenarios were developed from disease specific QoL measures. In this report, the health states are described in the section 'Structure of the model' (p. 60). The health state scenarios are shown in Appendix 14. Thirty-six members of the original panel responded rating the glioma health state scenarios.

Scenarios were developed based on the study by Osoba and colleagues[106] described in the section on EORTC (p. 10). This used the EORTC QLQ-30 together with a brain cancer module BC20 to explore QoL in 105 patients with high-grade gliomas. We used mean scores from this study to develop scenarios. We assumed that patients post-surgery were equivalent to our 'stable disease' category, whereas those with recurrence could be considered as the same as those in our 'progressive' state.

Content validity of the health state descriptions was sought using three members of the Expert Advisory Group prior to measuring preferences. They noted that standardising the impact of gliomas was difficult as different tumour locations lead to patients experiencing different symptoms. We tried to accommodate this by designing health states that reflect specific impairments in motor, visual and communication impairment, which have been used in sensitivity analyses, but this remains a limitation of the method.

The health states for which scenarios were developed are shown in *Table 37*. Four 'progressive' disease states were developed. This is because the symptomatic impact of tumour growth is likely to be different depending on tumour location, resulting not in a general deterioration but in specific impairments. The first progression state represents a general deterioration. The following three reflect similar stages of progression but with varying foci. These foci were chosen because they represent functional domains found specifically in the brain cancer questionnaire that seems to reflect a specific brain locus.

Developing the scenarios required the QoL score to be converted into a descriptive account of symptoms or functional loss. However, there are 26 domains across the two questionnaires, which would make the scenarios too complicated. We reduced this to a more manageable nine domains by grouping some similar domains together and excluding some that appeared not relevant to people with high-grade gliomas. Domains used and excluded are shown in Appendix 15.

Differences in scores for the newly diagnosed and recurrent populations are shown in Appendix 16. These scores were translated into scenario descriptions using the severity descriptors above.

The QLQ-C30 core questionnaire has a profile for cancer patients on RT. This was used for the scenarios involving RT by combining it with the BC20 values from the results in the paper and using the same scenario domains with some RT-specific additions.

TABLE 37 *Health states for which utility values were obtained*

Scenario	Details of health state
Stable disease	Patients stable post-surgery, i.e. not getting any worse (and possibly even getting slightly better) without any other treatment such as RT and/or chemotherapy
RT	Patients undergoing RT post-surgery with its associated toxic effects. A full course lasts for 6 weeks
RT and TMZ	Patients undergoing RT post-surgery are also receiving TMZ with its associated toxic effects
RT and BCNU-W	Patients undergoing RT post-surgery, where BCNU-Ws were also implanted.
TMZ	Patients post-surgery and RT receiving ongoing cycles of adjuvant TMZ with its associated toxic effects[a]
Progressive disease	Patients with general symptomatic deterioration
Progressive 1 – motor function impairment	Deterioration with main impairment in motor function
Progressive 2 – visual function impairment	Deterioration with main impairment in visual function
Progressive 3 – communication impairment	Deterioration with main impairment in communication

[a] Since the carmustine in the wafer implants has a delivery duration effect of less than 6 weeks, there is no post-RT chemotherapy scenario for carmustine.[128,153]

For the scenarios of progressive disease with specific foci, the stable scenario was used as a baseline and the relevant domain (visual, motor or communication) was increased to maximum intensity.

The scenarios for the health states involving chemotherapy were more problematic since there was a lack of data on QoL in the trials. The only statistically significantly increased toxic effect in the carmustine wafer trial is raised intracranial pressure.[151] However, the placebo in the carmustine trials is a placebo wafer, which may itself be associated with increased AEs. There is some evidence of an increase in seizures, cerebral abscesses and cerebral bleeds in general in patients receiving implants.[155] We tried to account for this by adding the following additional features to the scenario that had been written for 'post-surgery recovery' as BCNU-W is delivered in a short period: headache, blurred vision and seizures.

The treatment scenarios presented to the VoHP therefore included AEs of treatment. In the model, relevant health states were weighted to account for the proportion of patients experiencing such effects.

For TMZ, data from the trials showed statistically significant increases in toxic effects of nausea/vomiting, fatigue, rash and infection. These were included in the 'radiotherapy' health state description to develop the 'radiotherapy and TMZ' scenario and were added to the 'stable disease' health state description to develop the 'TMZ' scenario.

Utility values obtained

Table 38 shows the results from the VoHP for the relevant glioma scenarios. Mean values were used in the model.

We assumed that patients in the 'progressive' state would experience a constant decline in their QoL, and hence utility value, over time. We modelled this decrement at a rate of 0.5% per model cycle, that is, a 0.5% reduction week on week.

Based on the information from the main RCTs in the systematic review, we assumed that of patients taking TMZ, 18% suffered from nausea and vomiting or infections that might require hospitalisation in the concomitant phase of treatment and 26% in the adjuvant phase of treatment. Of those treated with BCNU-W, we assumed that 19% would be affected by seizures or blurred vision. The scenarios used to elicit utility values about the treatment states described these AEs. Utility values for these states have therefore been weighted accordingly, giving a value for SMG + RT+ TMZ of 0.8091 and for SMG + TMZ of 0.8474. As BCNU-W is thought to be released

TABLE 38 *Utility values obtained from the VoHP*

Scenario	*n*	Mean	Median	Range		Standard deviation
				Lowest	Highest	
SMG	36	0.8872	0.925	0.525	1.0	0.1284
SMG + RT	36	0.8239	0.875	0.425	0.995	0.1502
SMG + RT + TMZ	36	0.7426	0.7875	0.175	0.98	0.2021
SMG + RT + BCNU-W	36	0.7311	0.7625	0.075	0.975	0.2006
SMG + TMZ	36	0.7331	0.775	0.175	0.99	0.1991
PMG	36	0.7314	0.775	0.125	0.995	0.2067

BCNU-W, carmustine wafers; PMG, progressive malignant glioma; RT, radiotherapy; SMG, stable malignant glioma; TMZ, temozolomide.

over 2–3 weeks, the decrement was applied to the surgical and surgical recovery states (totalling 3 weeks) in this arm, giving a value of 0.8572.

Resource use

Estimates of the types and amounts of resources used in each Markov state were derived from typical treatment protocols used in the NHS, as described in the most relevant published papers, or by the review team's Expert Advisory Group of neurosurgeons and clinical oncologists. Where other data were not available, information from the relevant industry submission was used to estimate some resource use parameters. Main resource use assumptions used in the cost-effectiveness model are given in *Table 39*.

Unit costs were derived from the relevant NHS or other UK database of national average unit costs or prices (primarily the 2004 National Schedule of Reference Costs for NHS Trusts,[217] BNF No. 49[218]).

Costs estimated are those for the NHS or Personal Social Services in 2004.

Cost of initial debulking surgery

The main cost of debulking surgery was the cost of the intracranial surgical procedure itself (see *Table 40*), for which we used the national average unit cost for the most relevant Healthcare Resource Group (HRG). It should be noted that, although HRGs are intended to be groupings of clinically similar treatments that consume common levels of healthcare resource use, these particular neurosurgical HRGs contain a highly varied collection of minor and major procedures which would probably have similarly varied resource consumption (see introductory comments in the HRG Definitions Manual, Chapter A – Nervous System[219]).

Although the placement of BCNU-W undoubtedly consumes extra surgeon, theatre staff and operating theatre time, this is estimated (by expert advisers) to only take about an extra 20 minutes. We believe that this would not significantly affect the overall opportunity cost of performing the procedure, that is, no other activities would be foregone or other resources used up by this increased operating time.

In addition to the cost of the surgical procedure itself, an estimated 60% of UK centres perform image-guided surgery, which requires an MRI scan as part of the surgical work-up.

After surgery, all patients are assumed to recover in a high-dependency unit, on average for 1 day. Also, a small proportion (7/240) are estimated to experience cerebrospinal fluid leaks, requiring a mean of an extra four inpatient days, and also re-surgery in a fifth of cases. We have not included the cost of any other AEs related to debulking surgery.

Cost of weeks with radiotherapy

RT for this patient group is usually simple RT (without simulator or hyperfractionation) delivered as 30 × 2-Gy fractions over 6 weeks (five fractions per week). The National Schedule of Reference Costs records the national average unit cost per course of RT treatment. For the weekly cost we therefore used one-sixth of the cost of 'Simple Teletherapy, >12 fractions' (HRG code – w05 = £909).

During RT, it is assumed that some patients may occasionally require hospitalisation. **[Confidential information removed]**, and each of these inpatient stays is assumed to last 2 days. *Table 41* shows the unit costs applied to these resources.

TABLE 39 *Main resource use assumptions used in the cost-effectiveness model*

Assumption	Data	Source	Justification
Proportion of debulking operations in the UK that are image guided (i.e. work-up requiring MRI scan)	60%	Expert opinion	No published data available
Mean number of BCNU-Ws used per operation	6.54	Industry submission (based on T-301 trial reported by Westphal *et al.*[151])	Expert opinion confirmed that spare wafers were likely to be frozen and used later (although their suitability for use later would depend on the length of time between operations)
Proportion of debulking operations that are classified and costed as belonging to *HRG Intracranial Procedures Without Trauma (elective)*, category 3 (= HRG A03)	100%	Matching procedure descriptions within the HRG Definitions Manual (Chapter A – Nervous System)	The Foreword to Chapter A of the Definitions Manual warns that "HRGs A01–A04 do escalate in mean cost, but every HRG in Chapter A contains a mixture of relatively minor and complex major cases that cannot be iso-resource"
Costs attached to extra operating time required to place carmustine implants	None	Expert opinion: placing implants only takes an extra 20 minutes or less	These extra 20 minutes are on top of a mean time in operating theatre 'craniotomy for tumour' of 220 minutes (3 hours 40 minutes), and such operations account for less than 6% of elective neurosurgical procedures (in the NHS)[209]
Proportion of patients who experience CSF leaks post-surgery	2.9%	This is the rate of CSF leaks experienced amongst all patients in the main Gliadel trial	Small numbers in the trial make the differential CSF leak rates in the two arms likely to be due to chance
Mean additional number of hospital inpatient days to treat CSF leak	4	Expert opinion (as low as two days but as long as 2 weeks)	No published data. We used an average of the expert estimates
Percentage of patients with CSF leaks requiring re-operation	20%	Expert opinion	Although AEs, such as CSF leaks and cerebral hypertension, are relatively infrequent, CSF leaks can be expensive to manage if they require another operation
Mean number of days required in a high-dependency unit by each patient	1	Expert opinion	No equivalent data in literature or other UK data sources
TMZ chemotherapy regime (concomitant with RT)	42 days at 75 mg/m^2/day	Schering-Plough Product Information	Prescribed dosage
TMZ chemotherapy regime (adjuvant phase)	Cycle 1: 5 days at 150 mg/m^2 Cycles 2–6: 5 days at 200 mg/m^2 (28-day cycles)	Schering-Plough Product Information	Prescribed dosage
Frequency of hospitalisations for radio- or chemotherapy AEs	**[Confidential information removed]**		No equivalent data in the literature or other UK data sources

continued

TABLE 39 *Main resource use assumptions used in the cost-effectiveness model (cont'd)*

Assumption	Data	Source	Justification
Mean number of days as in inpatient when hospitalised for AEs	2	Expert input	No equivalent data in the literature or other UK data sources
Frequency of CT scans during RT	Once at start for 75% of pts	Expert opinion	No equivalent data in the literature or other UK data sources
Frequency of CT scans after RT and with stable disease	Once at 8 weeks after end of RT	Expert opinion	No equivalent data in the literature or other UK data sources
Frequency of clinical oncology outpatient visits following end of RT and before progression	Quarterly	Expert opinion	No equivalent data in the literature or other UK data sources
Proportion of patients with progressive disease who initially choose second-line (active) treatment (i.e. chemotherapy with or without re-operation)	70%	Expert opinion (based on assumed mean age of patients of 55 years)	No equivalent data in the literature or other UK data sources
Proportion of patients with progressive disease receiving chemotherapy whose regime is PCV	100%	Expert opinion	For simplicity, in the absence of good UK data on the proportions of actively treated patients who receive other chemotherapy regimes (e.g. TMZ)
Proportion of patients with progressive disease who undergo a re-operation	10%	Expert opinion	No published data or authoritative UK data source
Proportion of all days after disease progression spent as a palliative care inpatient	**[Confidential information removed]**		The only source of data on this type of resource (and after disease progression)
Proportion of all days after disease progression spent as an intensive care unit inpatient	**[Confidential information removed]**		The only source of data on this type of resource (and after disease progression)
Proportion of all days after disease progression spent as an oncology inpatient	**[Confidential information removed]**		The only source of data on this type of resource (and after disease progression)
Frequency of CT scans during active treatment for progressive disease	3/4 get a scan (75% CT, 25% MRI) in week of diagnosis; half also get a scan (75% CT, 25% MRI) after 2 cycles of PCV; no scans thereafter		No published data or authoritative UK data source
Proportion of all patients who start second-line chemotherapy (active treatment) who continue PCV until death	100%	Expert opinion – although most would cease chemotherapy 1–2 months prior to death	No equivalent data in the literature or other UK data sources

continued

TABLE 39 *Main resource use assumptions used in the cost-effectiveness model (cont'd)*

Assumption	Data	Source	Justification
Frequency of clinical oncology outpatient visits during active treatment for progressive disease	6-weekly	Expert opinion	No published data or authoritative UK data source
Frequency of clinical oncology outpatient visits during palliative management for progressive disease	**[Confidential information removed]**		No published data or authoritative UK data source
Proportion of patients who choose no active treatment ('palliative management') who have palliative RT	None	Expert opinion – very few patients have palliative RT after tumour recurrence	No equivalent data in the literature or other UK data sources

AE, adverse effect; CSF, cerebrospinal fluid; CT, computed tomography; HRG, Healthcare Resource Group; PCV, procarbazine, carmustine and vincristine combination therapy; RT, radiotherapy.

TABLE 40 *Unit costs for estimating cost of tumour debulking surgery*

Description	Code	Cost (£)	Source	Notes
Main tumour debulking surgery (Intracranial Procedures Except Trauma – Category 3)	HRG – A03	5191	NSRC, 2004[217]	Table – Elective Inpatient Episodes
MRI as part of surgical work-up	RBF1	224	NSRC, 2004[217]	Table – Direct Access Radiology Services
Carmustine implants (per wafer)		688	BNF No. 49[218]	Gliadel® cost per pack = £5500
Inpatient day in high-dependency unit	CC8	584	NSRC, 2004[217]	Table – Critical Care Services
Extra inpatient days due to CSF leaks		257	Industry submission	
Reoperation to resolve CSF leak (Intracranial Procedures Except Trauma – Category 1)	HRG – A01	2347	NSRC, 2004[217]	Table – Elective Inpatient Episodes

CSF, cerebrospinal fluid; HRG, Healthcare Resource Group; NSRC, National Schedule of Reference Costs.

TABLE 41 *Unit costs for estimating cost of weeks in radiotherapy*

Description	Code	Cost (£)	Source	Notes
Simple teletherapy, >12 fractions	HRG – w05	909	NSRC 2004[217]	Table – RT Treatments/Fractions
Inpatient bed-day		200	NSRC 2004[217]	Approximate mean of cost of inpatient bed-days for oncology, neurosurgery, neurology and internal medicine
Clinical oncology outpatient visit	800	93	NSRC 2004217	Table – Outpatient Follow-up Attendance
[Confidential information removed]				

HRG, Healthcare Resource Group; NSRC, National Schedule of Reference Costs.

There are no detailed published data on what supporting medication is typically taken by newly diagnosed glioma patients who are undergoing post-surgical RT without chemotherapy. **[Confidential information removed.]**

Costs of taking temozolomide with radiotherapy (concomitant phase)

For those taking TMZ at the same time as receiving RT, both the cost of TMZ and the cost of higher levels of supporting medication were included. The calculation of the weekly cost of concomitant TMZ is shown in *Table 42*.

[Confidential information removed.]

Supporting medication with carmustine implants

Although BCNU-W might in theory increase the need for supporting medication, there are no robust data on this. Moreover, since the chemotherapeutic effect of the implants lasts only 3 weeks, and is topical rather than systemic in action, in the base-case analysis we assume that patients require the same level of supporting medication as those who have surgery followed by RT only.

Costs of stable disease

The cost to the NHS for post-surgical glioma patients living with stable disease without RT comprises quarterly outpatient visits and a basic level of supporting medication (anti-emetics, anti-convulsants, corticosteroids, antibiotics), of the same types and amounts as patients in the RT only group. Unit costs for estimating the costs of weeks in a stable disease state are given in *Table 43*.

Costs of taking TMZ after radiotherapy (adjuvant phase)

For those taking TMZ after receiving RT, both the cost of TMZ and the higher cost of other supporting medication were included. Adjuvant TMZ is given over 24 weeks, at a lower rate for the initial 28-day cycle (150 mg/m^2/day), and then at 200 mg/m^2/day for the following five 28-day cycles. The calculation of the costs per week is shown in *Table 44*.

TABLE 42 *Cost per cycle of TMZ when concomitant with RT*

Recommended dose (mg/m^2)	Required dose per day (mg)[a]	Obtained from	Cost per day (£)	Days per cycle	Cost per weekly cycle (£)
75	135 mg	1 × 100 mg 7 × 5 mg	93.42	7	654

[a] Assuming a mean body surface area of 1.8 m^2.

TABLE 43 *Unit costs for estimating cost of weeks in stable disease state*

Description	Code	Cost (£)	Source	Notes
Quarterly hospital outpatient visit (clinical oncology)	800	93	NSRC 2004[217]	Table – Outpatient Follow-up Attendance

NSRC, National Schedule of Reference Costs.

TABLE 44 *Cost per cycle of adjuvant TMZ*

	Recommended daily dose (mg/m^2)	Required dose per day (mg)[a]	Obtained from	Cost per day (£)[b,c]	Days per cycle	Weekly cost (£)
Cycle 1 (weeks 1–4)	150	270	2 × 100 mg 3.5 × 20 mg	186.84	5	234
Cycles 2–6 (Weeks 5–24)	200	360	3 × 100 mg 3 × 20 mg	249.12	5	311

[a] Assuming a mean body surface area of 1.8 m^2.
[b] Although the drugs are actually taken in the first 5 days of each 28-day cycle, we allocated the 5-day cost across all four weeks in any cycle.
[c] Source of drug costs: BNF No. 49, March 2005,[218] for Temodal®

Costs with disease progression

When gliomas recur, a range of approaches to management are possible, and there are particular costs which are more likely at the beginning or at the end of disease progression. It is therefore not realistic to assume the same NHS cost of disease progression for all patients, or throughout the time between tumour recurrence and death. In order to generate more plausible cost estimates for this disease state, we therefore made the following key assumptions (mostly based on information from members of the Expert Advisory Group):

1. When disease progression occurs, a proportion of patients (70% in the base case) have further 'active treatment', with the remainder receiving palliative care only, that is, non-curative care to relieve symptoms.
2. Of those who choose active treatment, all receive chemotherapy and a smaller proportion will also have a re-operation. In the base case, the proportion choosing a re-operation is 10% of all glioma patients who reach the 'progressive' disease state. For simplicity, the re-operation is assumed to take place in the first week of the 'progressive' disease state. The cost of this surgery is the same as for first-line treatment.
3. Those receiving chemotherapy in the 'progressive' disease state are assumed to receive standard PCV [which is a combination therapy of procarbazine, lomustine (CCNU) and vincristine]. In the base case, the 70% having active treatment are also assumed to continue chemotherapy until death.
4. It is assumed that all patients with progressive disease (whether in the active treatment or palliative care group) receive some palliative and hospice care over the last month of life.

Blood test costs were not specifically included. However, using resource data from the study by Lamers and colleagues, we used estimates of rates of hospitalisation and rates of use of supporting medication (such as anti-emetics, anti-convulsants and antibiotics) and UK estimates of the frequency of outpatient appointments. The costs per cycle of PVC are shown in *Table 45*.

Cost of death

There is no cost attached to the 'death' state. However, for the practicalities of modelling, the costs of palliative care in the last weeks of life have been attached to the transition from 'progressive' disease to 'death'. They are estimated to be £3087, from the only available published estimates of the cost of palliative care for terminally ill cancer patients in the UK.[220] This cost includes £1885 for hospitalisations, £484 for opioid prescriptions, £231 for GP visits, and £258 for district nurse visits.

Cost of CT and MRI scans

It was clear from discussions with the Expert Advisory Group that clinical practice varies substantially in relation to when this patient group receives scans and what type of scan is used. This is partly because of variations in regional demands on radiology departments and differences in the availability of MRI. For costing purposes in our model, the pattern of scans for this patient group that was thought to represent the current average situation in the NHS is as follows:

- 60% of those having debulking surgery receive an MRI scan to enable stereotactic guided surgery.
- Some patients (75%) receive an RT planning CT scan prior to RT.
- 4–12 weeks after RT (in model, at 8 weeks) all patients are scanned (90% CT, 10% MRI).

TABLE 45 *Costs per cycle of PCV*

	Recommended daily dose (mg/m^2)	Required dose per day (mg)[a]	Obtained from	Cost per day (£)[b]	Days per cycle	Weekly cost (£)
PRO	60	102	2 × 50 mg	1.50	14	20.97
CCNU	110	187	5 × 40 mg	73.30	1	73.30
Vincristine	1.4	2.38	1 × 2 mg	21.17	2	42.34
Total						136.61

CCNU, lomustine; PRO, procarbazine.
[a] Assuming a mean body surface area of 1.75 m^2.
[b] Source of drug costs: BNF No. 49, March 2005.[218]

- Apart from this there are no regular monitoring scans during post-RT stable disease.
- At disease progression (tumour recurrence), 75% have a scan (75% CT, 25% MRI).
- Half of patients on PCV as second-line therapy have a scan after two cycles of chemotherapy (75% CT, 25% MRI).
- It is assumed that there are no further scans thereafter.

The national average unit cost to the NHS of a CT scan is £49 and an MRI scan £224.[217]

Discounting

In accordance with HM Treasury advice, costs are discounted at 1.5% and benefits at 6% with sensitivity analysis at 3.5% for both.

Dealing with uncertainty

One-way sensitivity analysis

Extensive one-way sensitivity analyses were undertaken to explore which of the input parameters, when varied in isolation, have the greatest impact on the incremental cost-effectiveness of chemotherapy. The analysis examined the impact of:

- survival time
- PFS
- type of QoL deterioration
- utility values for disease and treatment states
- costs of RT and surgery, chemotherapy and palliative care.

Inputs used in one-way sensitivity analysis are shown in *Table 46*.

TABLE 46 *Inputs varied in one-way sensitivity analyses*

Variable	Arm(s) affected	Base value	Values used in sensitivity analyses			
			Min.	Max.	Source	Justification
Variables affecting transition probabilities						
Median survival	TMZ	63 wk	57 wk	73 wk	TMZ RCT[181]	95% CI of reported median
Median survival	TMZ control	53 wk	49 wk	57 wk	TMZ RCT[181]	95% CI of reported median
Median survival	BCNU-W	60 wk	53 wk	67 wk	BCNU-W RCT[151]	95% CI of reported median
Median survival	BCNU-W placebo	50 wk	44 wk	55 wk	BCNU-W RCT[151]	95% CI of reported median
Median PFS	TMZ	30 wk	25 wk	36 wk	TMZ RCT[181]	95% CI of reported median
Median PFS	TMZ control	22 wk	18 wk	24 wk	TMZ RCT[181]	95% CI of reported median
Median PFS	BCNU-W	26 wk	19 wk	36 wk	BCNU-W RCT[151]	95% CI of reported median
Median PFS	BCNU-W placebo	26 wk	20 wk	32 wk	BCNU-W RCT[151]	95% CI of reported median
Perioperative death	TMZ + TMZ control	1.5% (≤21 days post-surgery)	0.7%	3.2%	Chang *et al.*[81]	95% CI of reported rate
Perioperative death	BCNU-W	4.2% (≤30 days post-surgery)	1.8%	9.4%	BCNU-W RCT[151] (FDA material[155])	95% CI of reported median
Perioperative death	BCNU-W placebo	1.7% (≤30 days post-surgery)	0.5%	5.9%	BCNU-W RCT[151] (FDA material[155])	95% CI of reported median
Disease progression during RT phase	TMZ	4.9%	2.9%	8.0%	TMZ RCT[181]	95% CI of reported rate
Disease progression during RT phase	TMZ control	5.9%	3.7%	9.3%	TMZ RCT[181]	95% CI of reported median

continued

TABLE 46 *Inputs varied in one-way sensitivity analyses (cont'd)*

Variable	Arm(s) affected	Base value	Values used in sensitivity analyses			
			Min.	Max.	Source	Justification
Disease progression during RT phase	BCNU-W	5.4%	3.3%	15.8%	BCNU-W RCT[151] (FDA material[155])	Min. – number of patients in trial receiving 'non-standard RT' because 'not well enough/ deterioration/ progressive disease' Max. – patients from min. + those who received no RT + those who received non-standard RT for no specified reason
Disease progression during RT phase	BCNU-W placebo	5.4%	2.5%	15%	BCNU-W RCT[151] (FDA material[155])	Min. – number of patients in trial receiving 'non-standard RT' because 'not well enough/ deterioration/ P[rogressive] D[isease]' Max. – patients from min. + those who received no RT + those who received non-standard RT for no specified reason
Variables affecting utility values						
SMG utility value	All	0.8815	0.525	1.0	VoHP	Minimum and maximum values elicited
SMG + RT utility value	All	0.8239	0.425	0.995	VoHP	Minimum and maximum values elicited
SMG + RT + TMZ utility value	TMZ	0.8564	0.175	0.98	VoHP	Minimum and maximum values elicited
SMG + RT + BCNU-W utility value	BCNU-W	0.8526	0.075	0.975	VoHP	Minimum and maximum values elicited
SMG + TMZ utility value	TMZ	0.8432	0.175	0.99	VoHP	Minimum and maximum values elicited
PMG utility value	All	0.7314	0.125	0.995	VoHP	Minimum and maximum values elicited
Post-recurrence utility decrement rate	All	0.5%	0%	1%		
Discount rate for QALYs	All	1.5%	–	3.5%		Forthcoming NICE advice

continued

TABLE 46 *Inputs varied in one-way sensitivity analyses (cont'd)*

Variable	Arm(s) affected	Base value	Values used in sensitivity analyses			
			Min.	Max.	Source	Justification
Variables affecting costs						
Surgery	All	£5191.52	£2080.00	£7926.00	NSRC 2004	Interquartile range of HRG A03 (Intracranial Procedures Except Trauma – Category 3)
Numbers of BCNU implants	BCNU-W	6.54 wafers £4496.25	4 wafers £2750.00	8 wafers £5500.00		Cost of average of 4–8 wafers per operation
Cost of TMZ	TMZ	£6845	–30%	+30%		
Proportion of patients receiving active second-line therapy	All	70%	50%	90%	Expert opinion	
Proportion of patients receiving reoperation	All	10%	5%	20%	BCNU-W RCT151	Proportion of BCNU-W arm who received reoperation
Discount rate for costs	All	6%	3.5%	–		Forthcoming NICE advice

BCNU-W, carmustine wafers; HRG, Healthcare Resource Group; NSRC, National Schedule of Reference Costs; PMG, progressive malignant glioma; RT, radiotherapy; SMG, stable malignant glioma; TMZ, temozolomide; VoHP, Value of Health Panel.

Probabilistic simulation

Probabilistic sensitivity analysis (PSA) was also undertaken. A Monte Carlo simulation was developed to explore the impact of underlying parameter uncertainty on cost-effectiveness. In the stochastic approach, the Markov model was run 1000 times for the hypothetical cohort using key input values randomly drawn from probabilistic density functions in each model run. In these simulations, values were sampled for survival, utilities and costs using the distributions shown in *Table 47* and the ranges shown in *Table 48*.

TABLE 47 *Distributions used in the PSA*

Parameter type	Distribution used	Justification
Fixed transition probabilities	β	Returns values within the accepted [0,1] range
Weibull approximations	Bivariate normal	Curves were fitted using regression analysis so each parameter can be thought of as being drawn from a normal distribution. As the parameters are correlated, the numbers must be sampled simultaneously
Utility values	β	Returns values within the accepted [0,1] range with variances not so high as to produce a distorted (U-shaped) distribution
Utility decrement	Uniform	The original parameter of 0.5% utility decrement per cycle was an assumption as there are no data from which to assess the weekly rate. The distribution reflects the wide variance in uncertainty with no bias in favour of central values when sampling
Number of BCNU-Ws used	Binominal	Number used needs to be an integer and positive in the range 0–8
Proportion of cohort receiving second-line surgery chemotherapy in progressive state	Uniform	Base-case parameter is based on expert opinion, no published data are available. Distribution reflects this wide variance in uncertainty with no bias in favour of central values when sampling
All other cost values	Log-normal	Positively skewed distribution required with values above zero

TABLE 48 *Parameter ranges used in the PSA*

BCNU-W fixed transition probabilities				
Transition	**Arm(s) affected**	**α**	**β**	**Rationale for parameter values**
Surgery to death	Placebo, treatment	15.89	2461.40	Deterministic value derived from 21-day rate quoted in Chang *et al.*[81] and spread over 3 weeks. Standard error values not quoted and so an assumption was made of 1/4 deterministic value
Radiotherapy to progressive	Placebo, treatment	15.08	264.21	Deterministic value derived from aggregating the total number of patients in published TMZ RCT since no value directly available. Standard error values not quoted and so an assumption was made of 1/4 deterministic value
Stable to progressive	Placebo, treatment	116.72	4188.47	Modelling assumption of a constant hazard rate. Transition probability chosen to match median survival value quoted in published RCT. Standard error calculated based on results from same RCT
BCNU-W Weibull approximation to Kaplan–Meier plots				
Transition	**Arm(s) affected**	**λ**	**γ**	**Rationale for parameter values**
All transitions to death from any state except surgery	Placebo	0.00017	2.0784	Kaplan–Meier curve drawn from results in published RCT. Parameter values chosen so as to minimise the residual sum during the regression analysis. Standard errors calculated as part of regression process
All transitions to death from any state except surgery	Treatment	0.00044	1.7946	Kaplan–Meier curve drawn from results in published RCT. Parameter values chosen so as to minimise the residual sum during the regression analysis. Standard errors calculated as part of regression process
BCNU-W utilities				
Transition	**Arm(s) affected**	**α**	**β**	**Rationale for parameter values**
Surgery and post-surgery and stable	Placebo Placebo Placebo, treatment	193.07	21.547	VoHP responses used to calculate mean and standard error
Surgery and post-surgery	Treatment Treatment	205.568	34.245	VoHP responses used to calculate weighted means and standard errors based on the responses to several scenarios
Progressive base value	Placebo, treatment	120.304	44.180	VoHP responses used to calculate mean and standard error
BCNU-W utility decrement				
Transition	**Arm(s) affected**	**Lower bound**	**Upper bound**	**Rationale for parameter values**
Progressive	Placebo, treatment	0.2	0.8	Modelling assumption based on an even spread of values each side as well as the fact that the decrement can realistically never be zero

continued

TABLE 48 *Parameter ranges used in the PSA (cont'd)*

TMZ fixed transition probabilities				
Transition	**Arm(s) affected**	**α**	**β**	**Rationale for parameter values**
Surgery to death	Control, treatment	15.89	2461.40	Deterministic value derived from 21-day rate quoted in Chang *et al.*[81] and spread over 3 weeks. Standard error values not quoted and so an assumption was made of 1/4 deterministic value
Radiotherapy to progressive	Control	14.99	237.19	Deterministic value derived the total number of patients in published TMZ RCT. Standard error values not quoted and so an assumption was made of 1/4 deterministic value
Radiotherapy to progressive	Treatment	15.35	385.11	Deterministic value derived the total number of patients in published TMZ RCT. Standard error values not quoted and so an assumption was made of 1/4 deterministic value
TMZ Weibull approximations to Kaplan–Meier plots				
Transition	**Arm(s) affected**	**λ**	**γ**	**Rationale for parameter values**
All transitions to death from any state except surgery	Control	0.00057	1.7941	Kaplan–Meier curve drawn from results in published RCT. Parameter values chosen so as to minimise the residual sum during the regression analysis. Standard errors calculated as part of regression process
All transitions to death from any state except surgery	Treatment	0.0006	1.6879	Kaplan–Meier curve drawn from results in published RCT. Parameter values chosen so as to minimise the residual sum during the regression analysis. Standard errors calculated as part of regression process
Stable to progressive	Control	0.0134	1.311	Kaplan–Meier curve drawn from results in published RCT. Parameter values chosen so as to minimise the residual sum during the regression analysis. Standard errors calculated as part of regression process
Stable to progressive	Treatment	0.0089	1.2511	Kaplan–Meier curve drawn from results in published RCT. Parameter values chosen so as to minimise the residual sum during the regression analysis. Standard errors calculated as part of regression process
TMZ utilities				
Transition	**Arm(s) affected**	**α**	**β**	**Rationale for parameter values**
Surgery and post-surgery and stable	Control, treatment Control, treatment	193.07	21.547	VoHP responses used to calculate mean and standard error
Radiotherapy	Control	189.827	40.574	VoHP responses used to calculate mean and standard error
Radiotherapy	Treatment	183.664	43.334	VoHP responses used to calculate weighted means and standard errors based on the responses to several scenarios
Stable	Treatment	204.861	36.891	VoHP responses used to calculate weighted means and standard errors based on the responses to several scenarios
Progressive	Control, treatment	120.304	44.180	VoHP responses used to calculate mean and standard error

continued

TABLE 48 *Parameter ranges used in the PSA (cont'd)*

TMZ utility decrement				
Transition	**Arm(s) affected**	**Lower bound**	**Upper bound**	**Rationale for parameter values**
Progressive	Control, treatment	0.2	0.8	Modelling assumption based on an even spread of values each side and also the fact that the decrement can realistically never be zero
Cost values				
Model input	**Arm(s) affected**	**Range for PSA sampling (£)**		**Rationale for parameter values**
Number of BCNU-Ws used	BCNU-W treatment arm only	Absolute range (4–8 wafers)		Max. 8 wafers in pack; no operations use <4 wafers
MRI scan during surgery	All	77.78 372.33		40–80% of operations, and unit cost interquartile range (£194–465)
Cost of resection surgery	All	2080.00 7926.00		Unit cost interquartile range (NSRC 2004[217])
Cost of re-operation due to CSF leak	All	935.00 2723.00		Unit cost interquartile range (NSRC 2004[217])
Cost of post-surgical HDU stay	All	250.56 1111.50		½-day to 1½-day stay in HDU, and unit cost interquartile range (£501–741)
Weekly cost of RT	BCNU-W and TMZ treatment arms only	124.00 333.92		Unit cost interquartile range (NSRC 2004[217])
Outpatient visit during RT	All	58.67 114.49		Unit cost interquartile range (NSRC 2004[217])
One-off cost for pre-RT CT scan	All	42.75 60.75		Unit cost interquartile range (NSRC 2004[217])
One-off cost for post-RT CT scan	All	62.0 128.00		Unit cost interquartile range (NSRC 2004[217])
Other medication during stable disease	All	0 3.00		No cost and double base-case cost
Outpatient visits during stable disease	All	3.67 14.31		4-monthly to 2-monthly visits, and unit cost interquartile range (£58–114)
CT or MRI scan during 1st week in progressive state patients	All	83.00 184.00		Unit cost interquartile range (NSRC 2004[217]) weighted according to CT/MRI split
Oncology outpatient visit during 1st week in progressive state	All	84.97 177.3		Unit cost interquartile range (NSRC 2004[217])
Reoperation during 1st week in progressive state	All	2080.00 7926.00		Unit cost interquartile range (NSRC 2004[217])
Palliative care during progressive disease for patients receiving active therapy	All	16.70 50.10		Palliative care hospital stays half as frequently as and 50% more frequently than base case
ICU bed days during disease for patients receiving active therapy	All	4.63 17.53		ICU hospital stays half as frequently and 50% more frequently than base case
Other hospital days during progressive disease for patients receiving active therapy	All	51.4 154.2		Other hospital stays on 20–60% of days living with progressive disease

continued

TABLE 48 *Parameter ranges used in the PSA (cont'd)*

Cost values (*cont'd*)				
Model input	**Arm(s) affected**	**Range for PSA sampling (£)**		**Rationale for parameter values**
2nd outpatient visit during 1st week with progressive disease for patients receiving active treatment	All	5.81 17.44		2nd outpatient visit half as likely as and 50% more likely than base case
Oncology outpatient visits weeks 2 onwards for patients receiving active care	All	9.78 19.08		Oncology outpatient visits half as frequently and 50% more frequently than base case
Other medicine weeks 2 onwards for patients receiving active care	All	5.00 20.00		Approximately half as costly and twice as costly as base case (£8.57)
Palliative care outpatient visits week 2 onwards for patients receiving palliative care only	All	2.61 22.96		Palliative care outpatient visits half as frequent and 50% more frequent than base case and unit cost interquartile range (NSRC 2004[217])
Cost-associated values				
Model input	**Arm(s) affected**	**Lower bound (£)**	**Upper bound (£)**	**Rationale for parameter values**
One-off cost associated with dying	All	2775.00	3395.00	–10% and +10% of base case value
Proportion of cohorts receiving active treatment during progressive state	All	0.5	0.9	Modelling assumption based on an even spread of values each side of value given by expert opinion
Proportion of the cohorts that receive second-line surgery	All	0	0.2	Modelling assumption based on an even spread of values each side of value given by expert opinion

Cost-effectiveness of carmustine wafers

Baseline results of cost-effectiveness for BCNU-W

Base-case results for the cost-effectiveness of the model are shown in *Table 49*. This table represents the total costs and accumulated QALYs for the modelled cohort of 1000 people over 5 years post-surgery with costs discounted at 6% and QALYs at 1.5%. Treatment using a combination of BCNU-W and RT confers 122 more QALYs to the cohort as a whole for an additional cost of £6,632,856, giving an ICER of £54,501 per QALY.

A breakdown of costs in different states is shown in *Figure 14*. Costs are shown per week, so that although the surgery state is very expensive, this occurs over one cycle only. Additional costs of BCNU-W are front loaded, and there is little difference in costs in the subsequent model states.

Event counts for BCNU-W

At each cycle of the model, a proportion of the patient cohort transfer from one state to another or recycle within their current state. Such transfers can be considered as events. For example, a patient moving from the 'stable' to the 'progressive' disease state is an indication of the

TABLE 49 *Base case cost-effectiveness results for BCNU-W*

	Utilities	**Costs (£)**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY)**
Placebo wafers + RT	789	17,017,936	–	–	–
BCNU wafers + RT	910	23,650,792	6,632,856	122	54,501

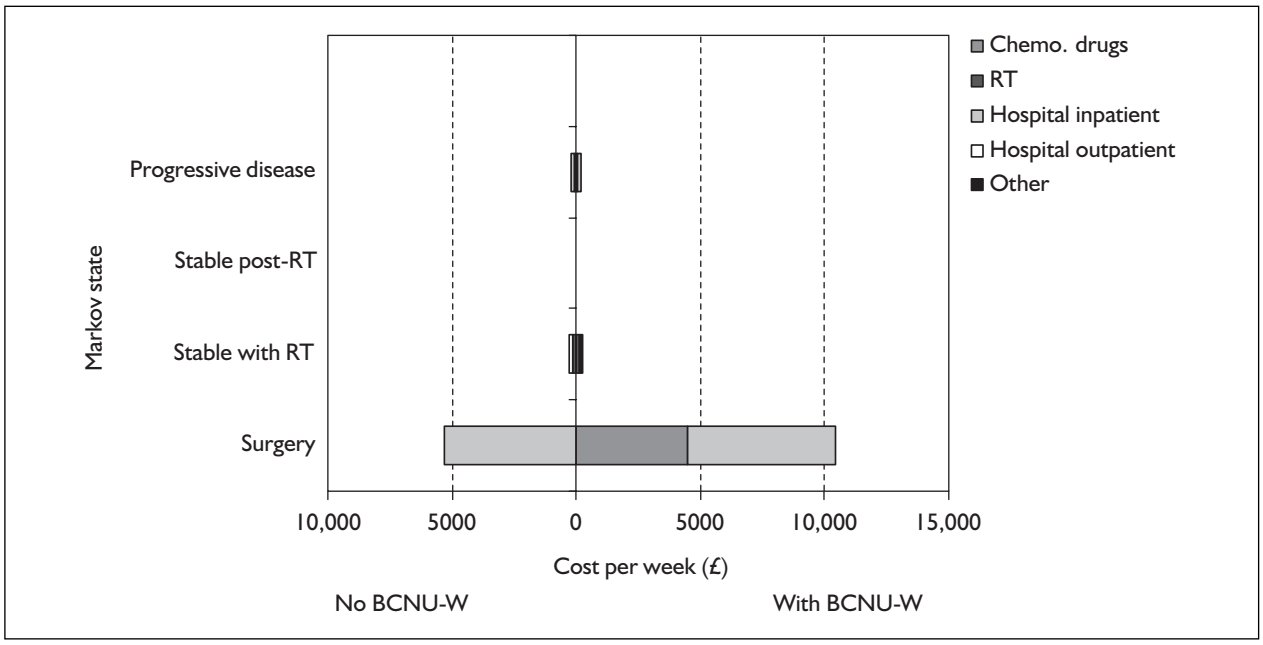

FIGURE 14 *Breakdown of weekly costs in the BCNU-W model*

event of disease recurrence. These events can be aggregated for each modelled arm to provide useful comparative outputs and also a validation tool against clinical data and experience.

Figure 15 shows key event counts from the model between the two arms of the BCNU-W model. It can be seen that assumption leading to death being modelled as time dependent rather than state dependent actually results in few patients dying while in 'stable' disease and this represents a clinically plausible rapid decline for some patients.

The key differences between the two arms of the model for BCNU-W are small disparities in the

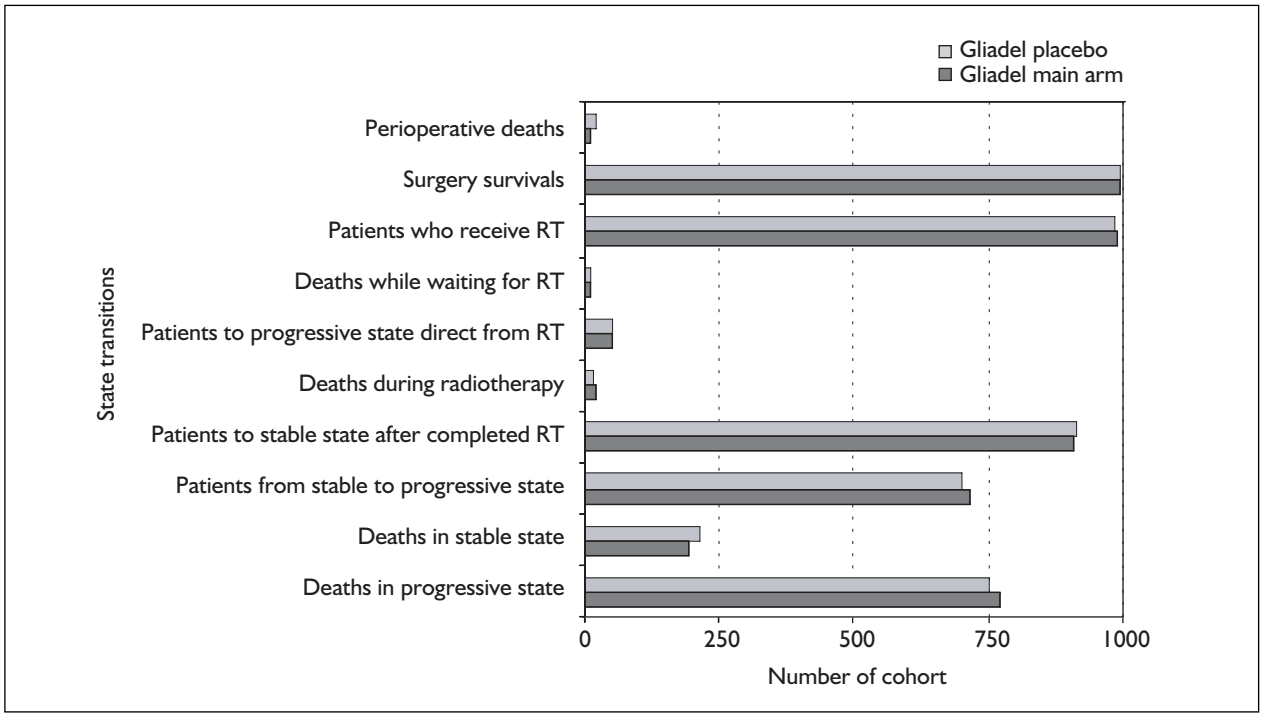

FIGURE 15 *Event counts in the BCNU-W model*

number of deaths within the 'progressive' and 'stable' disease states. This is explained by the differences in survival curves used between the two arms of the model.

State occupancy

State occupancy provides another important output from the model. This represents the aggregated patient populations for each state across all cycles of the model over the modelled time horizon. State occupancy hence shows the relative duration that patients spend in each modelled disease state.

Figure 16 shows the comparative state occupancies for the placebo and BCNU-W arms of the model. We have not included the data for occupancy of the state 'death', as the large numbers distort the graph. The model shows 205,198 cycles spent in the 'death' state in the BCNU-W arm compared with 195,430 in the placebo arm. The slight difference is due to the data from Westphal and colleagues' RCT[151] that was used in our model.

The main differences observed here are in occupancy of the 'stable' and 'progressive' disease states caused by the difference in the survival curves for the two arms of the model. These differences provide the basis for the cost and utility differences between arms of the model.

Sensitivity analyses for carmustine implants

Given the uncertainty in some key parameters for this model, we undertook extensive sensitivity analyses: one-way sensitivity analyses, threshold analyses and probabilistic sensitivity analyses employing Monte Carlo simulation.

One-way sensitivity analyses

Figure 17 shows the effect of changing each parameter individually while the remaining inputs are fixed at their base-case values. The analysis examines the uncertainty associated with individual inputs. Results are shown as the absolute change in the ICER, with the base-case result marked by a dotted line. In this deterministic analysis, the model is particularly sensitive to changes in state transition probabilities, notably differences between the arms in overall survival, differences in time spent in 'stable' disease (PFS) and the risk of death due to surgery. There were no alterations in any of the investigated parameters that brought the cost per QALY below £30,000.

QoL is also important; the model is particularly sensitive to the utility value and decrement in the 'progressive' disease state.

The model is less sensitive to costs. As most costs are similar in the two arms, only the cost of BCNU-W has a notable impact on the ICER.

These parameters were therefore further explored in threshold analysis.

We explored the impact of our assumption that death is time dependent rather than state dependent through extensive sensitivity analysis. The proportion of deaths in the model occurring from the 'stable' and 'progressive' states were varied. This was achieved by recycling proportionately more of the cohort within the

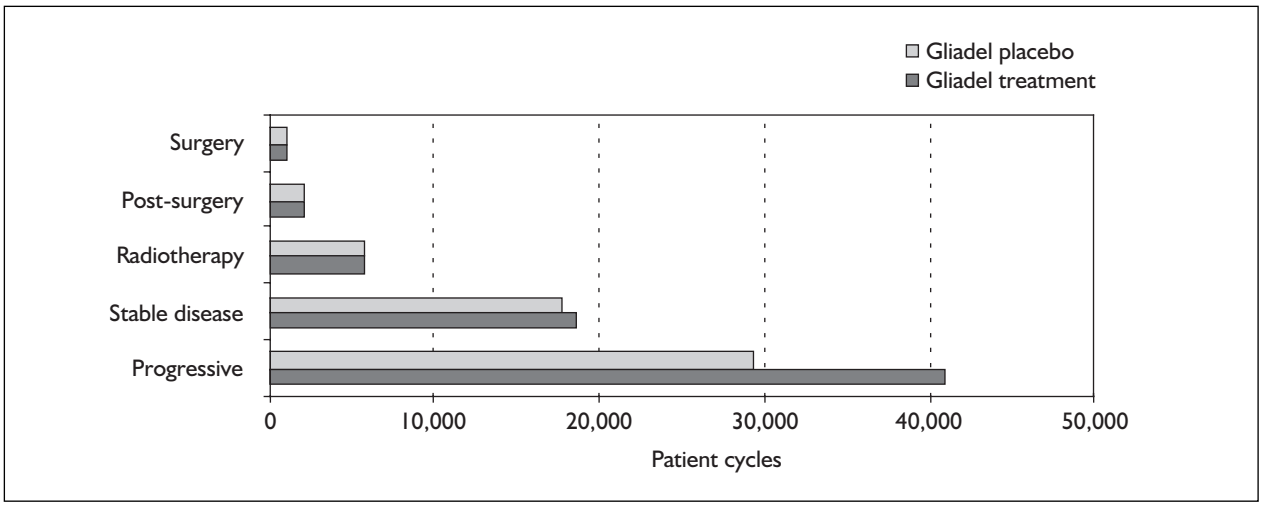

FIGURE 16 *State occupancy for BCNU-W model*

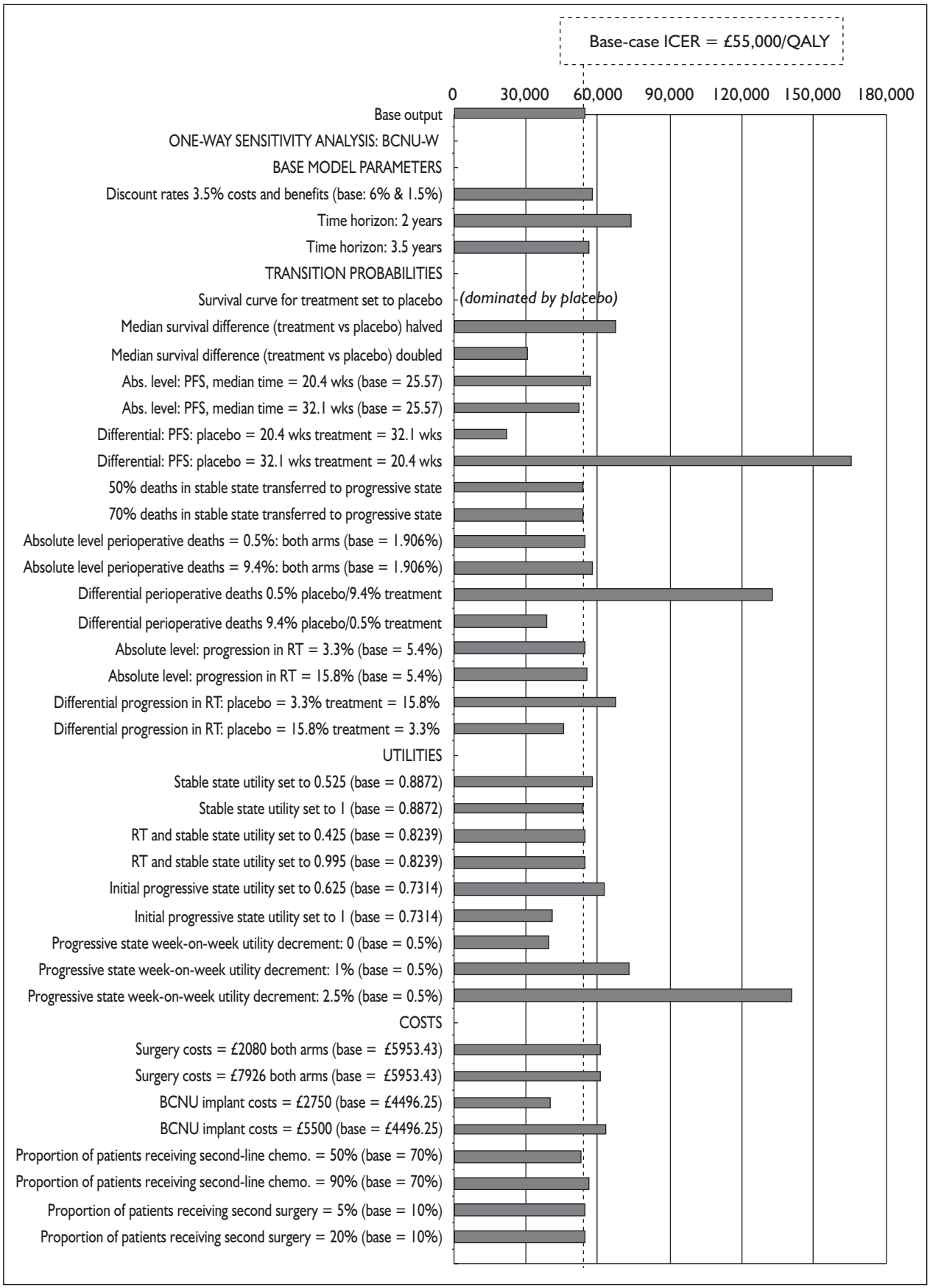

FIGURE 17 *One-way sensitivity analysis: changes in ICERs for BCNU-W versus placebo due to changes in transition probabilities, utility values and costs*

'stable' state and off-setting this number by increasing the death rate from the 'progressive' state. The overall death rate in the model remained the same. *Table 50* shows the impact of transferring different proportions of the deaths occurring from the 'stable' state to the 'progressive' state. There is little change in the ICER even when 75% of the deaths are transferred, showing that the time-dependent assumption has very little impact on model outputs.

Threshold analyses

We used threshold analyses to examine in more detail the level at which specific parameters would result in ICERs that may be considered cost-effective. Again, these are one-way analyses in which the parameter of interest is varied while other values, which may themselves be subject to uncertainty, are held at their base-case values.

Survival advantage with BCNU-W treatment. The model is sensitive to the median survival advantage conferred by BCNU-W compared with placebo. *Figure 18* shows that the ICER falls below £30,000/QALY if BCNU-W confers a median survival advantage of about 18 weeks. Data from Westphal and colleagues' RCT[151] show a non-significant difference of 10.0 weeks (95% CI 8.2 to 11.7).

Progression-free survival advantage with BCNU-W treatment. The model is sensitive to the amount of extra time spent in the 'stable' disease state (PFS) for patients treated with BCNU-W compared with placebo. *Figure 19* shows that the ICER falls below £30,000/QALY if median PFS with BCNU-W were extended by about 8 weeks. Trial data from the main RCT do not show any difference in PFS with BCNU-W compared with placebo (95% CI –1.3 to 3.9).

Quality of life with BCNU-W in the 'stable' disease state. *Figure 20* shows the threshold analysis for changes in the QoL (utility) in the 'stable' disease state for those using BCNU-W. It can be seen that even if this were raised to one (representing full health),

TABLE 50 *Sensitivity analysis assessing the impact of death being a time-dependent variable*

Deaths transferred to 'progressive' state (%)	Placebo		Gliadel		ICER (£/QALY)
	Utilities	Costs (£)	Utilities	Costs (£)	
0 (base case)	789	17,017,936	910	23,650,792	54,501
25	792	16,877,166	914	23,505,981	54,224
50	796	16,722,195	919	23,347,339	53,933
75	800	16,550,489	923	23,172,541	53,629

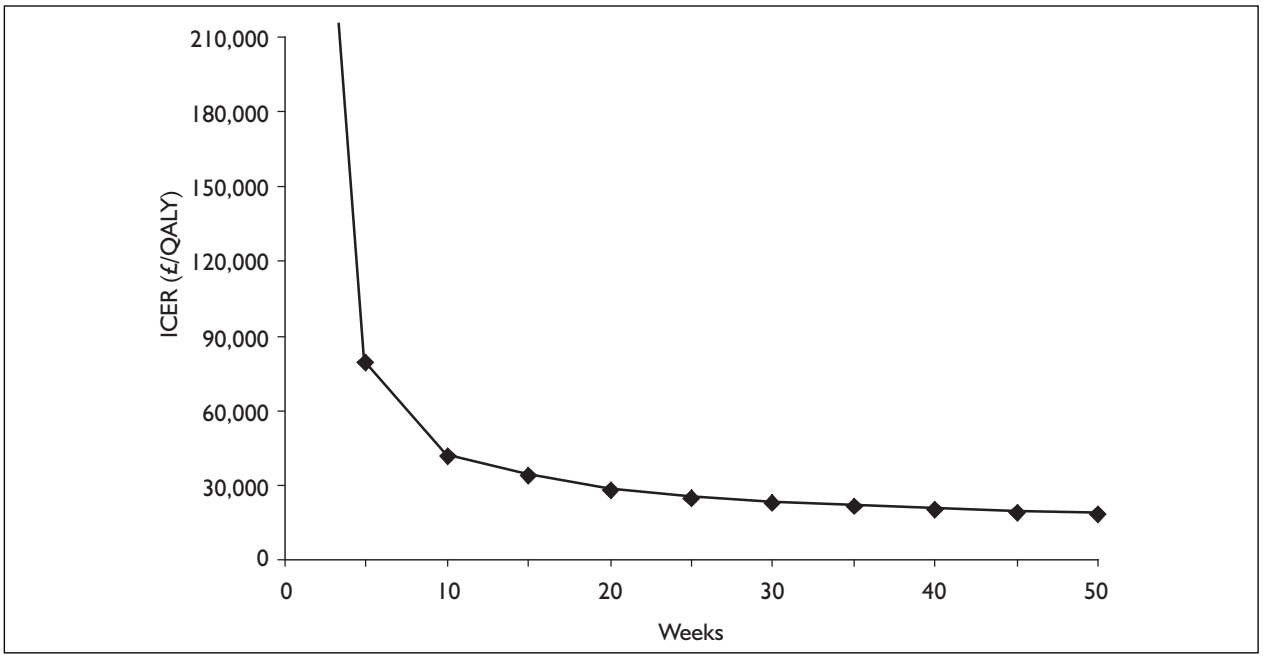

FIGURE 18 *Threshold analysis for changes in median survival advantage with BCNU-W*

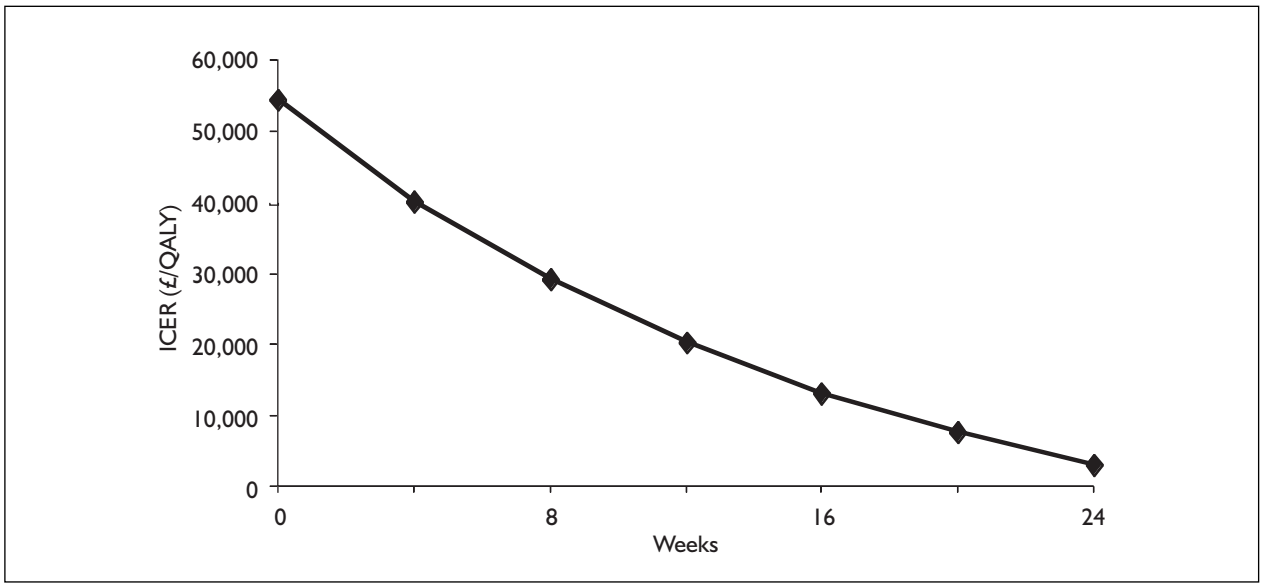

FIGURE 19 *Threshold analysis for changes in median PFS advantage with BCNU-W*

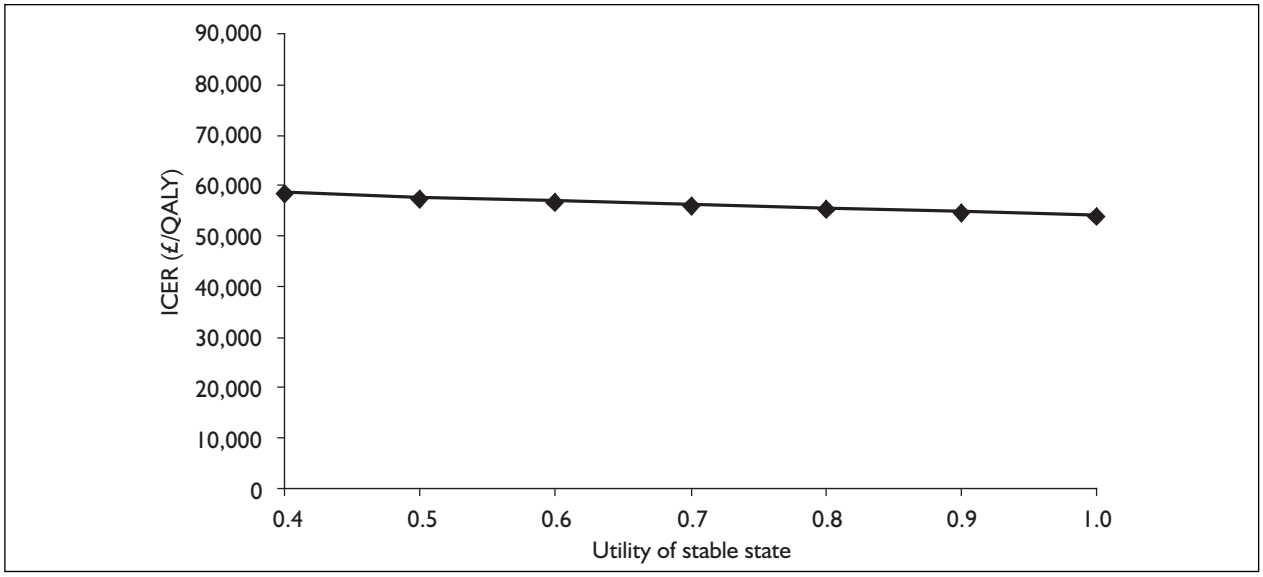

FIGURE 20 *Threshold analysis for changes in QoL in the 'stable' disease state with BCNU-W*

which is unlikely, the ICER does not fall below usually acceptable levels of willingness to pay. Equally, lower utility values in the 'stable' disease state have little effect. This is because there is currently no evidence that BCNU-W extends the time period spent in PFS compared with placebo.

Quality of life with BCNU-W in the 'progressive' disease state. Utility in the 'progressive' state is assessed in *Figure 21*. This was varied through changes in the median utility across the whole time spent in this state and no decrement over time was applied. Usual levels of willingness to pay are only reached if QoL in this state is very high at 0.95 – unlikely in progressive stages of glioma. If quality of life were negatively affected, the ICER rises sharply.

Cost of BCNU-W. *Figure 22* shows the threshold analysis for altering the cost of BCNU-W. This might happen if more or fewer wafers were used or the drug cost or management of adverse effects changed. The ICER falls below £30,000/QALY if BCNU-W costs were reduced to about 35% of current costs (for example, from £687 to £240 per wafer).

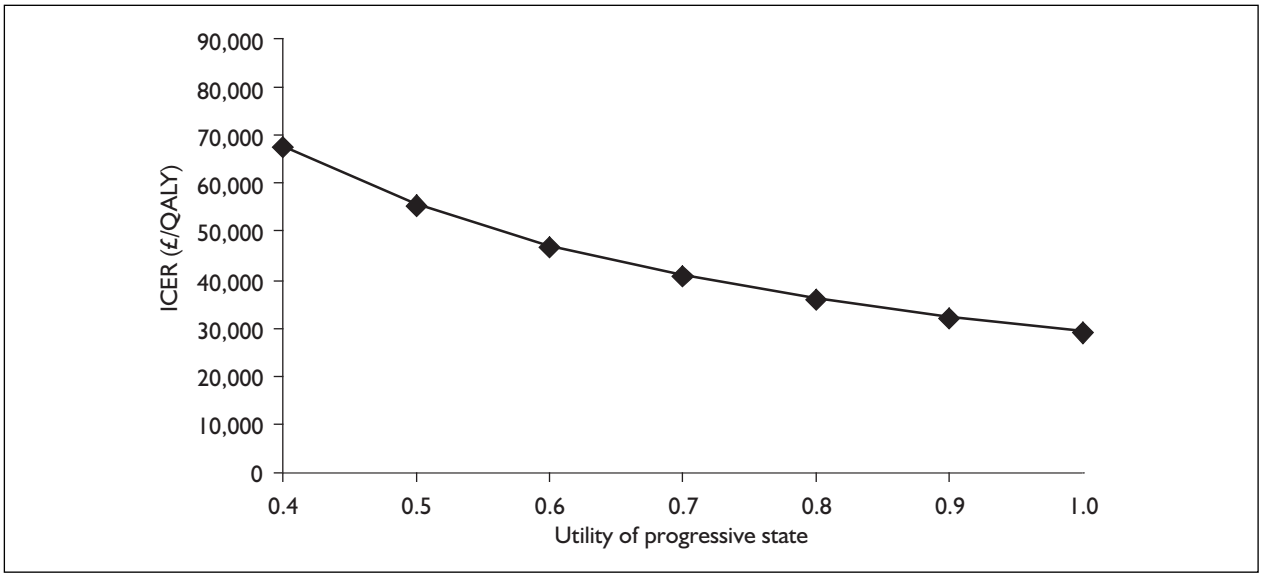

FIGURE 21 *Threshold analysis for changes in QoL in the 'progressive' disease state with BCNU-W*

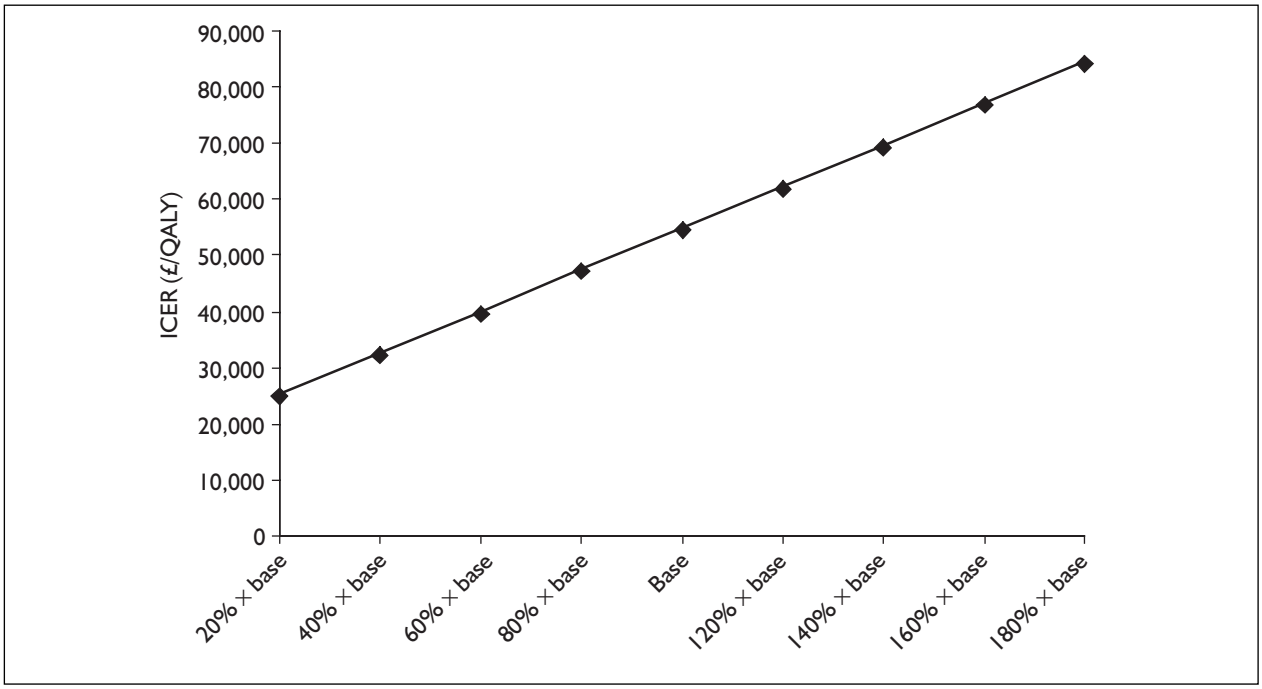

FIGURE 22 *Threshold analysis for the cost of BCNU-W*

Pattern of quality of life decline in the 'progressive' disease state

We were unsure how to model the shape of any decline in QoL (utility value) for people with progressive disease. Our base case used a constant decline of 0.5% per cycle, as this was plausible and the simplest to model. However, expert opinion suggested that QoL decline was likely to be slight in the early stages of progressive disease, with a steeper QoL decline as the patient nears death. This was supported by a paper, available only in abstract form, which used four QoL measures longitudinally in people with terminal cancer[104] (see the section 'Quality of life', on p. 9). We therefore undertook sensitivity analyses by modelling several different patterns of QoL decline. The shape of the utility decline for the cohort is shown in *Figure 23*. This value is derived

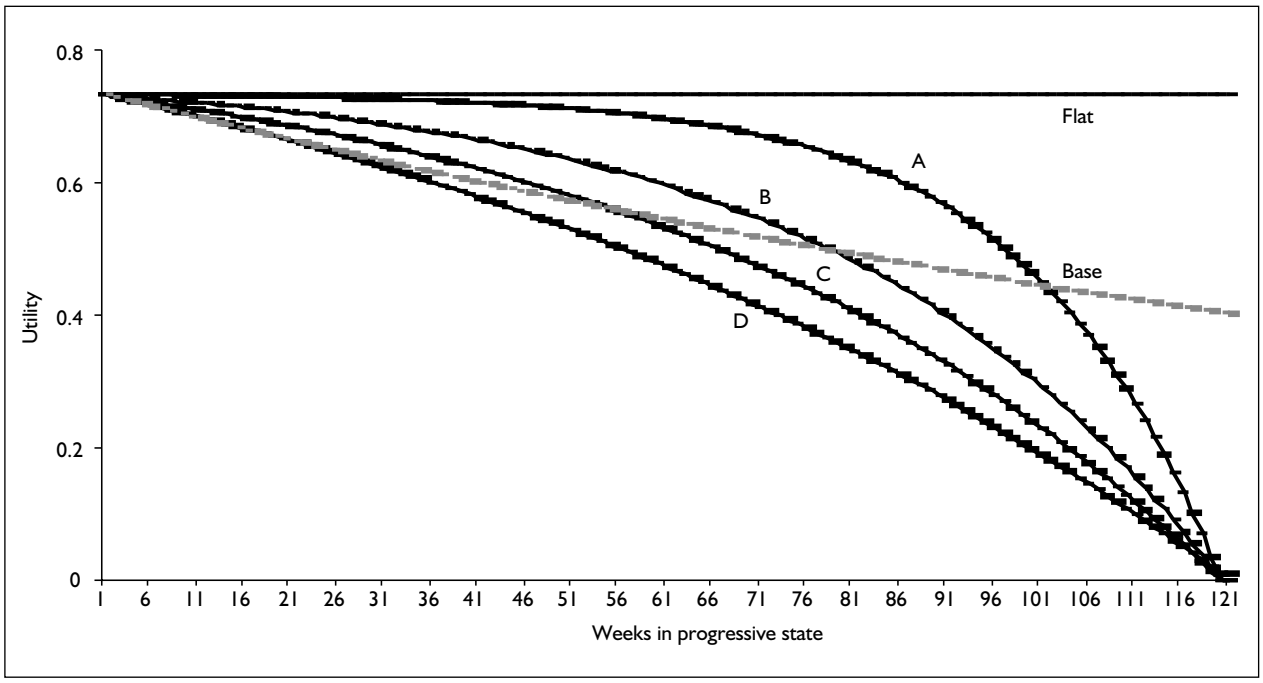

FIGURE 23 *Sensitivity analysis for the pattern of QoL decline with 'progressive' disease*

by sampling from the different shapes and degrees of QoL decline over time for the modelled individuals.

The base-case decline is marked, as is a flat line (which represents no decline in QoL over time). In addition, four curves show different patterns of more or less steep decline in QoL (curves A–D).

The results of this sensitivity analysis for BCNU-W are shown in *Table 51*. In each case, the costs remain the same, but utility values alter based on the shape of QoL decline. Even with no decline in QoL over time with progressive disease, which is unlikely with high-grade glioma, the ICER does not fall below normal levels of willingness to pay. Other shapes show a decline which is slower at the beginning and more rapid towards death (curve A in *Figure 23*) or less delayed and more continuous declines (shown by curves B, C and D in *Figure 23*) which raise the ICER by up to 46%.

Scenario analysis for a patient group with better prognosis

We explored whether a patient group with better prognosis due to being younger, fitter or having a more responsive tumour type might lead to BCNU-W being cost-effective. We therefore created an optimistic patient scenario. This is necessarily exploratory and speculative, as there are no published data specifically relating to such patients.

To create this scenario, changes to various input parameters were made: overall survival time, time

TABLE 51 *Results of one-way sensitivity analyses based on different types of quality of life decline during disease progression with BCNU-W*

BCNU-W	Placebo		Treatment		Difference in utilities	ICER
	Utilities	Costs (£)	Utilities	Costs (£)		
Flat	845	17,017,936	1015	23,650,792	170	39,043
Curve A	822	17,017,936	933	23,650,792	111	59,577
Curve B	798	17,017,936	895	23,650,792	97	68,407
Curve C	782	17,017,936	871	23,650,792	89	74,908
Curve D	768	17,017,936	851	23,650,792	83	79,908
Base case	789	17,017,936	910	23,650,792	122	54,501

spent in the 'stable' disease state (PFS) and secondary treatments following disease progression. These are described in more detail below.

The survival curves were altered significantly by changing the shape coefficient of the Weibull survival curve such that the median time in both placebo and treatment arms was doubled. This was to represent an increase in crude median survival time from 1 year for patients with grade IV tumours, to 2–3 years for those with grade III tumours. The resultant changes to the survival curves are shown in *Figure 24*.

The median time spent in the 'stable' state prior to progression is doubled in both the placebo and treatment arms. For BCNU-W this is achieved by using Microsoft Excel Solver to calculate the relevant scaling in each arm. The two-curve method described above was not used in this analysis due to the lack of data to inform each curve.

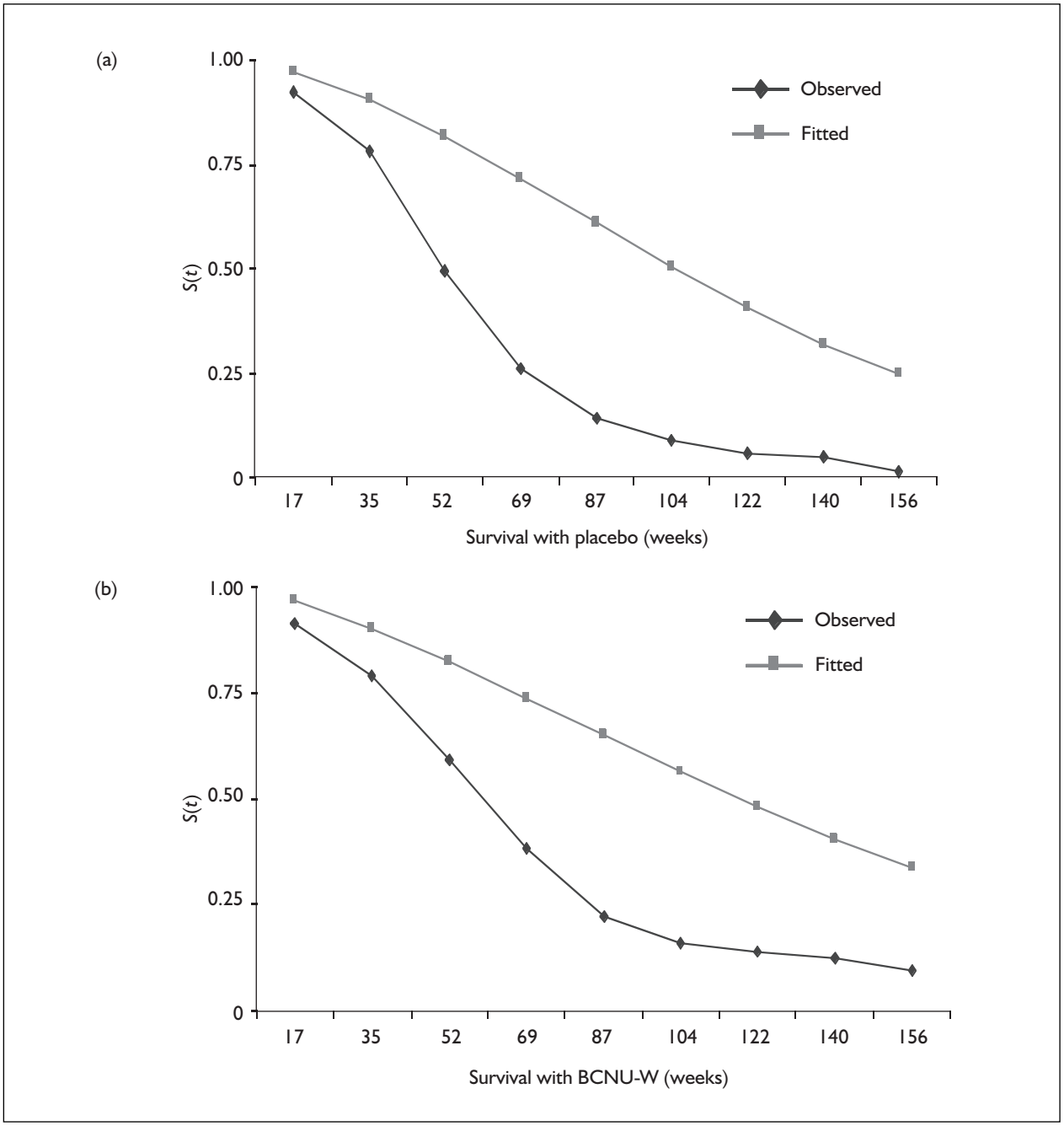

FIGURE 24 *Speculative survival curves used in scenario analysis for patients with good prognosis: (a) with placebo and (b) with BCNU-W*

TABLE 52 *Cost–utility for scenario analysis for patients with good prognosis*

	Utilities (QALYs)	Costs (£)	ICER (£/QALY)
Placebo	1516	23,483,447	–
BCNU-W	1649	29,905,842	–
Increment	132	6,422,395	48,495

The proportion of patients receiving secondary treatment is set to the highest level thought reasonable from expert opinion since it is likely to be much more common for this cohort. The proportion of patients receiving further surgery is increased from 10 to 50%.

The results for this speculative scenario are shown in *Table 52*. The outputs shown reflect the increase in benefits of improved survival and the associated extra costs for the scenario assumptions. The ICER value for this patient population in the model is considerably lower than the base case. However, even with these radically changed input parameters, doubling both the survival and the PFS time, the ICER is still above that generally considered value for money for the NHS.

Probabilistic analyses

Outputs from the Monte Carlo simulation are shown graphically below. For the modelled cohort, these illustrate the ICER values of 1000 simulated trials. A CEAC has also been calculated showing, at different levels of willingness to pay for an additional QALY, the probability that BCNU-W is cost-effective.

The simulation (*Figure 25*) shows that, in most cases, BCNU-W costs more and confers more QALYs than placebo. In 11% of simulations the ICER fell below £30,000 per QALY. In 15% of simulations BCNU-W did more harm than good – costing more while conferring fewer QALYs (i.e. it was dominated by placebo).

The CEAC (*Figure 26*) shows that, given a willingness to pay of £30,000 for an additional QALY, there is about an 11% probability that BCNU-W is cost-effective compared with usual

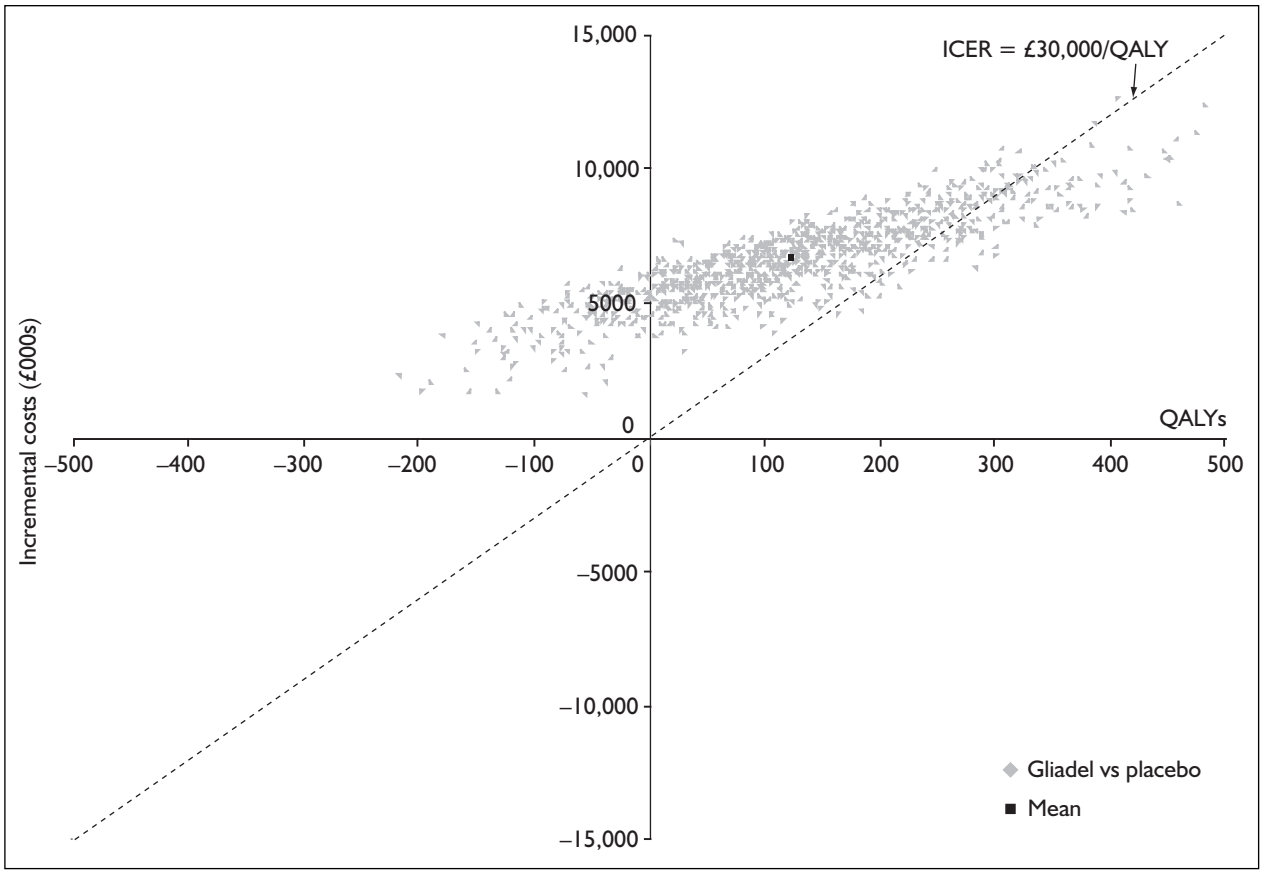

FIGURE 25 *Simulation output (1000 trials) for cost-effectiveness of BCNU-W*

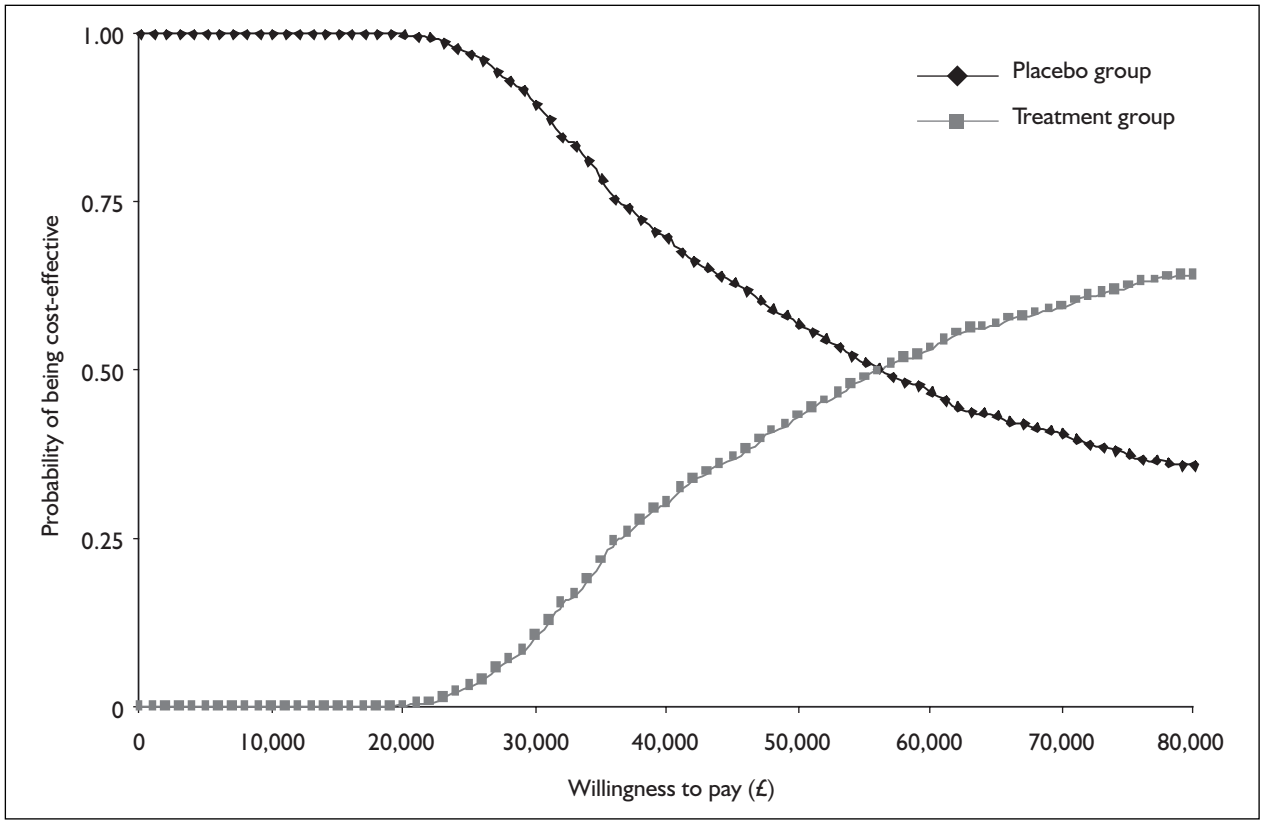

FIGURE 26 *Simulation output (1000 trials) showing the probability that BCNU-W is cost-effective at various levels of willingness to pay: CEAC Gliadel versus RT*

care. It is only above £50,000 per QALY that it becomes likely that BCNU-W is the most cost-effective option.

Cost-effectiveness of temozolomide

Baseline results of cost-effectiveness for temozolomide

Baseline results for the cost-effectiveness of the model are shown in *Table 53*, which represents the total costs (discounted at 6%) and accumulated QALYs (discounted at 1.5%) for the modelled cohort of 1000 people over the 5-year period. Treatment using a combination of TMZ and RT confers 217 more QALYs to the cohort as a whole for an additional cost of £7,788,643, giving an ICER of £35,861 per QALY.

A breakdown of differential costs is shown in *Figure 27*. Note that these are provided as costs per week, so that the cost of surgery is large, but affects only 1 week in the model. The added costs of TMZ are seen in the concomitant and adjuvant treatment phases.

Event counts for temozolomide

At each cycle of the model a proportion of the patient cohort transfer from one state to another or recycle within their current state. These transfers can be considered as events, for example, a patient moving from the 'stable' disease state to the 'progressive' state is an indication of the event of disease recurrence. These events can be aggregated for each modelled arm to provide useful comparative outputs and also as a validation tool against clinical data and experience. *Figure 28* shows key event counts from the model between

TABLE 53 *Baseline cost-effectiveness results for TMZ*

	QALYs	Costs (£)	Incremental costs	Incremental QALYs	ICER (£/QALY)
RT only	889	17,015,357	–	–	–
TMZ + RT	1106	24,804,000	7,788,643	217	35,861

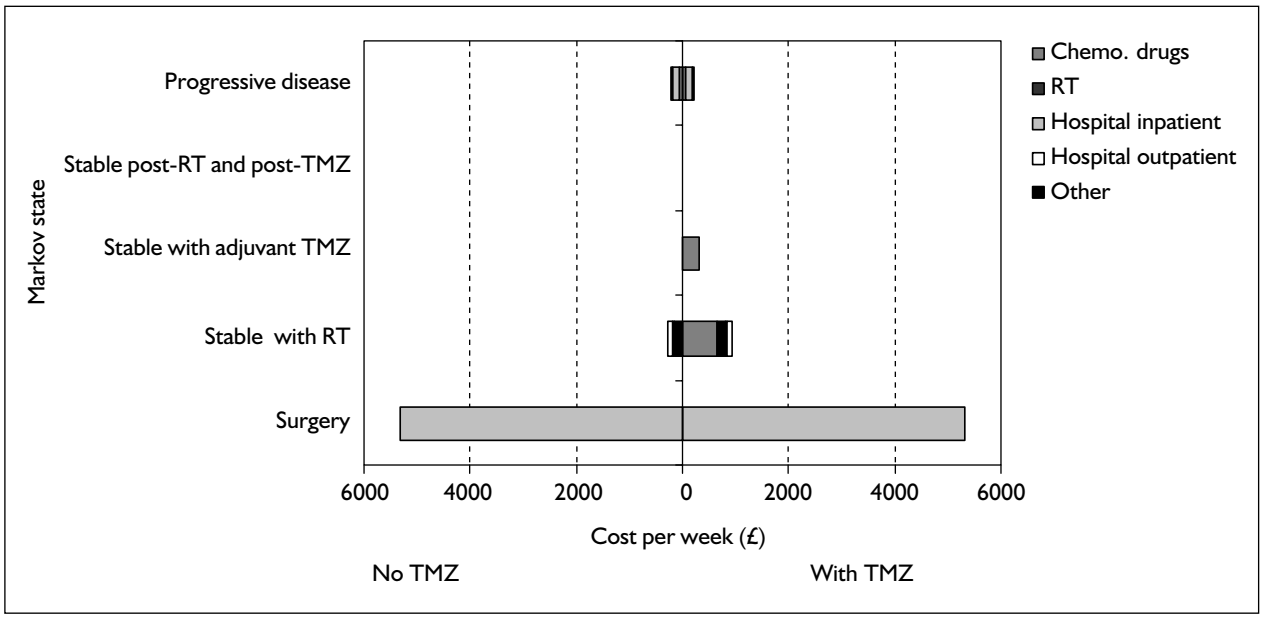

FIGURE 27 *Breakdown of weekly costs in the TMZ model*

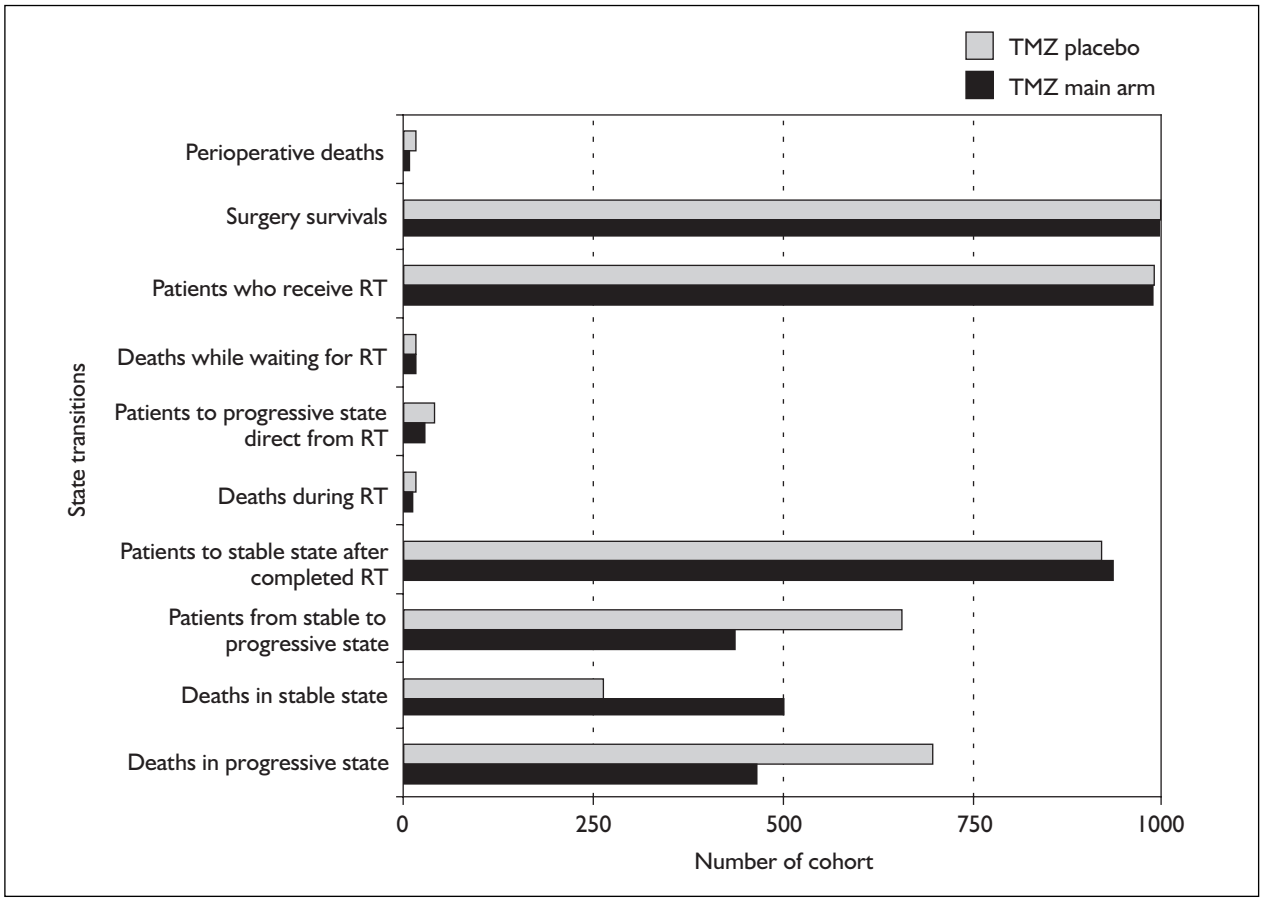

FIGURE 28 *Event counts in the TMZ model*

the two arms of the TMZ model. The main differences are the number of deaths from the 'progressive' and 'stable' disease states. Here the difference between arms in the median time within 'stable' state before progression contributes to the difference between these event counts.

State occupancy

State occupancy provides another important output from the model. This represents the aggregated patient populations for each state across all cycles of the model over the modelled time horizon. State occupancy hence shows the relative durations that the patient cohort spends in each modelled disease state.

Figure 29 shows the comparative state occupancies for placebo and treatment arms of the model. We have not included the state occupancy figures for death as the numbers are large and distort the presentation. For the control arm, 204,028 cycles are spent in the 'death' state compared with 189,091 in the TMZ arm: the lower number a result of longer survival with TMZ. The main differences observed here are in occupancy of the 'stable' and 'progressive' disease states caused by the difference in the survival curves for the two arms of the model. These differences provide the basis for the cost and utility differences between arms of the model.

Sensitivity analyses for temozolomide

One-way sensitivity analyses for temozolomide

One-way sensitivity analyses for a range of transition, cost and utility data inputs were used to examine the uncertainty associated with individual inputs. Results are shown in *Figure 30* as the absolute change in ICER with the base case marked by a dotted line. In this deterministic analysis, the model is particularly sensitive to changes in transitions, notably overall survival, differential time spent in the 'stable' disease state (PFS) and, to a lesser extent, absolute length of time spent with 'progressive' disease.

The model is also sensitive to the utility value in the 'stable' disease state, both the absolute value and the difference between TMZ and control arms.

The model is not very sensitive to costs although the cost of TMZ, as may be influenced by dosage, drug cost or number of cycles taken, has some impact.

Few of these sensitivity analyses reduced the ICER to less than £30,000 per QALY.

These parameters were further explored in threshold analyses.

Threshold analyses

We used threshold analyses to examine in more detail the level at which specific parameters would result in ICERs at which TMZ may be considered cost-effective. Again, this is a one-way analysis in which the parameter of interest is varied while other values, which may themselves be subject to uncertainty, are held at their base-case values.

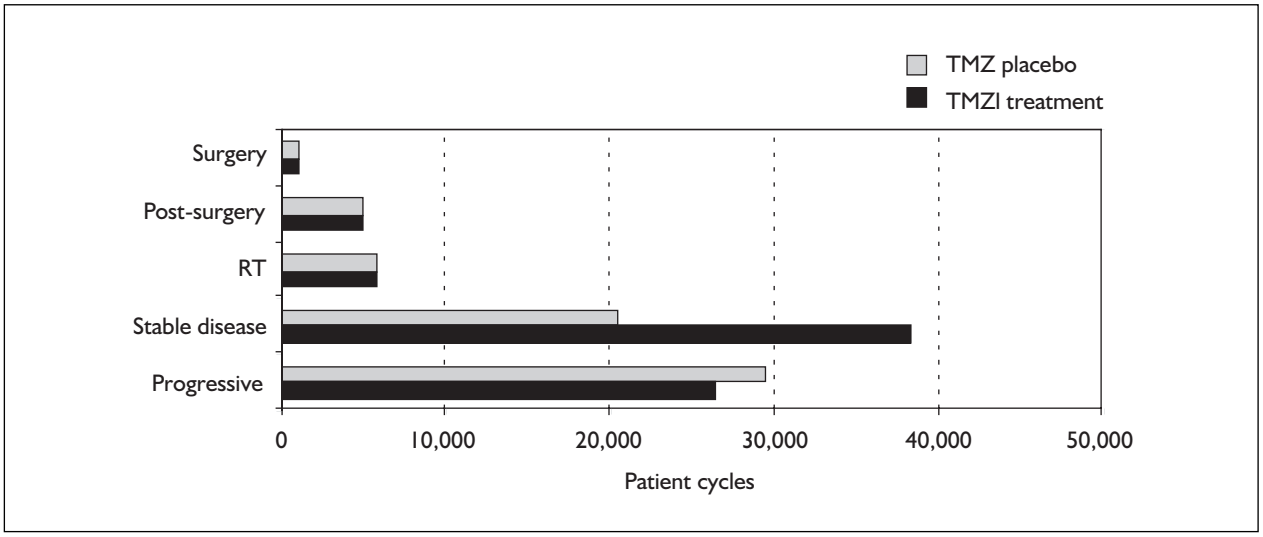

FIGURE 29 *State occupancy in the TMZ model*

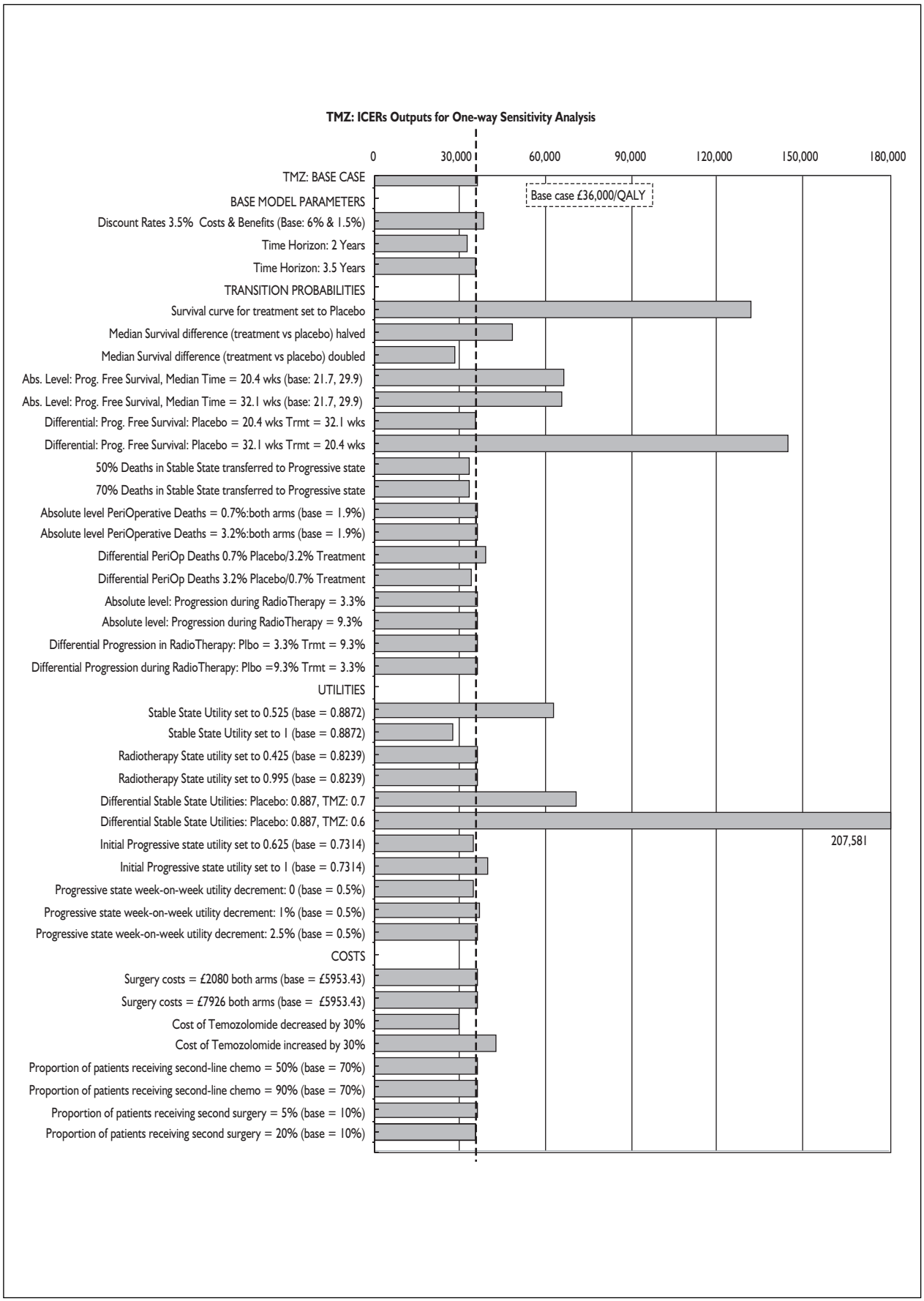

FIGURE 30 *One-way sensitivity analysis: changes in ICERs for TMZ due to changes in transition probabilities, utility values and costs*

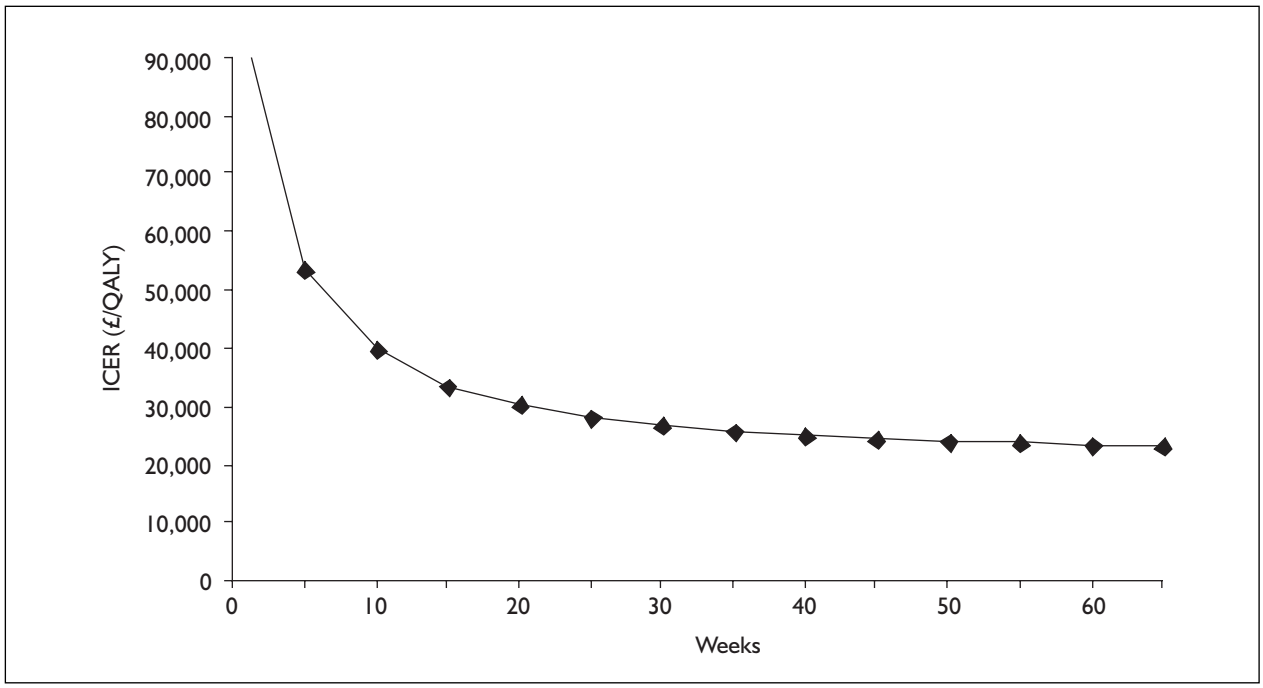

FIGURE 31 *Threshold analysis for changes in median survival advantage with TMZ*

Threshold analysis of median survival advantage with TMZ. *Figure 31* shows that the ICER falls below £30,000 per additional QALY if the overall median survival advantage were at least 22 weeks for patients taking TMZ compared with those receiving usual care. Trial data from the main RCT suggest a difference in median survival of about 11 weeks (95% CI 8.7 to 16.5 weeks).

Threshold analysis of median progression-free survival advantage for TMZ. *Figure 32* shows that the ICER falls below £30,000 per additional QALY if the median time spent in 'stable' disease state (PFS) with TMZ were about 14 weeks longer than with standard treatment. Trial data from the main RCT suggest the difference in median progression-free survival with TMZ is about 8 weeks (95% CI 7.0 to 11.7 weeks).

Threshold analysis for quality of life in the 'stable' disease state with TMZ. *Figure 33* shows that TMZ would be cost-effective at usual levels of

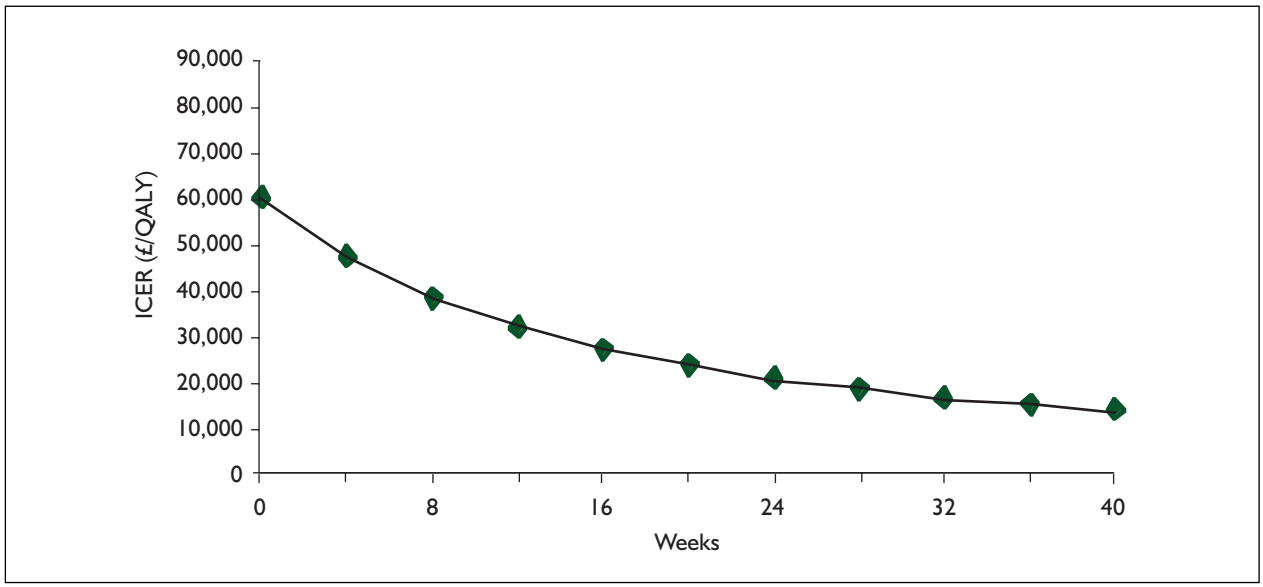

FIGURE 32 *Threshold analysis for changes in median PFS advantage with TMZ*

willingness to pay if the QoL in 'stable' disease state (PFS) were 0.95, which is unlikely in this population. If QoL were lowered, the cost per QALY increases steeply. For example, if the utility value for this state were 0.5, the ICER rises to over £60,000 per QALY. As TMZ is taken as an adjuvant treatment, this analysis also acts as a proxy for investigating the impact of AEs with TMZ. For those with severe AEs, the cost per QALY with TMZ may be high.

Threshold analysis for quality of life in the 'progressive' disease state with TMZ. *Figure 34* also shows that the utility value for the 'progressive' disease state cannot be altered to make TMZ cost-effective at usual levels of willingness to pay. Even in perfect health (utility value = 1.0), the cost per QALY is over £30,000. The line has a very shallow gradient, maybe because the TMZ trials do not show any difference in time spent with progressive disease for those treated with TMZ. Any survival advantage is seen in extending PFS.

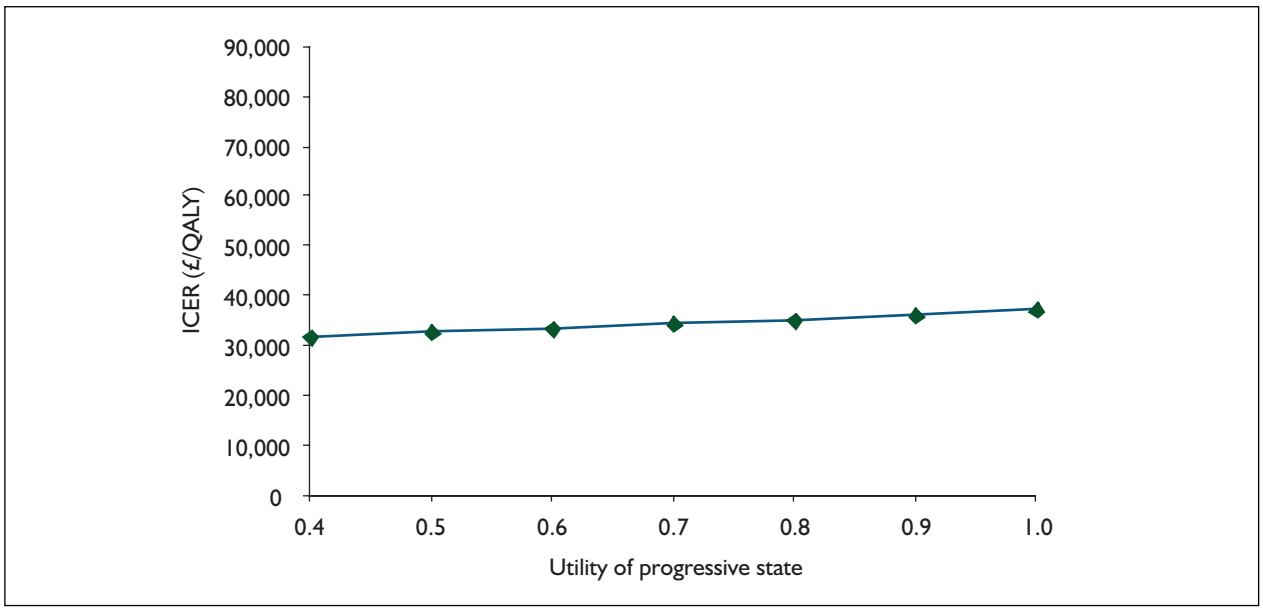

FIGURE 33 *Threshold analysis for QoL with TMZ in the 'stable' disease state*

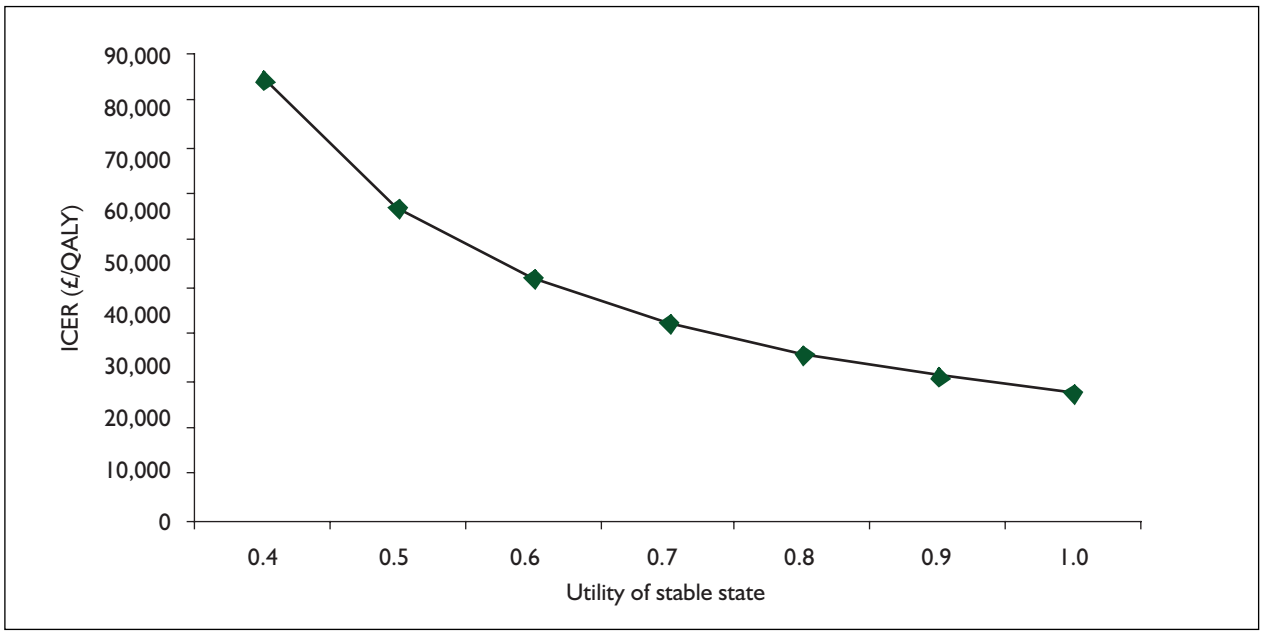

FIGURE 34 *Threshold analysis for utility value in 'progressive' disease state with TMZ*

Threshold analysis for cost of TMZ. *Figure 35* shows that the ICER falls below £30,000 per additional QALY if drug costs were reduced to about 70% of current prices, that is, a reduction in cost per milligram from £0.69 to £0.48 or, for a full completed concomitant and adjuvant course, a reduction from an estimated £11,086 to £7760.

Sensitivity analysis for the pattern of quality of life decline in 'progressive' disease

As with the BCNU-W model, we used sensitivity analysis to assess the impact of different patterns of decline in QoL (utility value) over time for patients with progressive disease. The patterns modelled in the sensitivity analysis are shown in *Figure 36*.

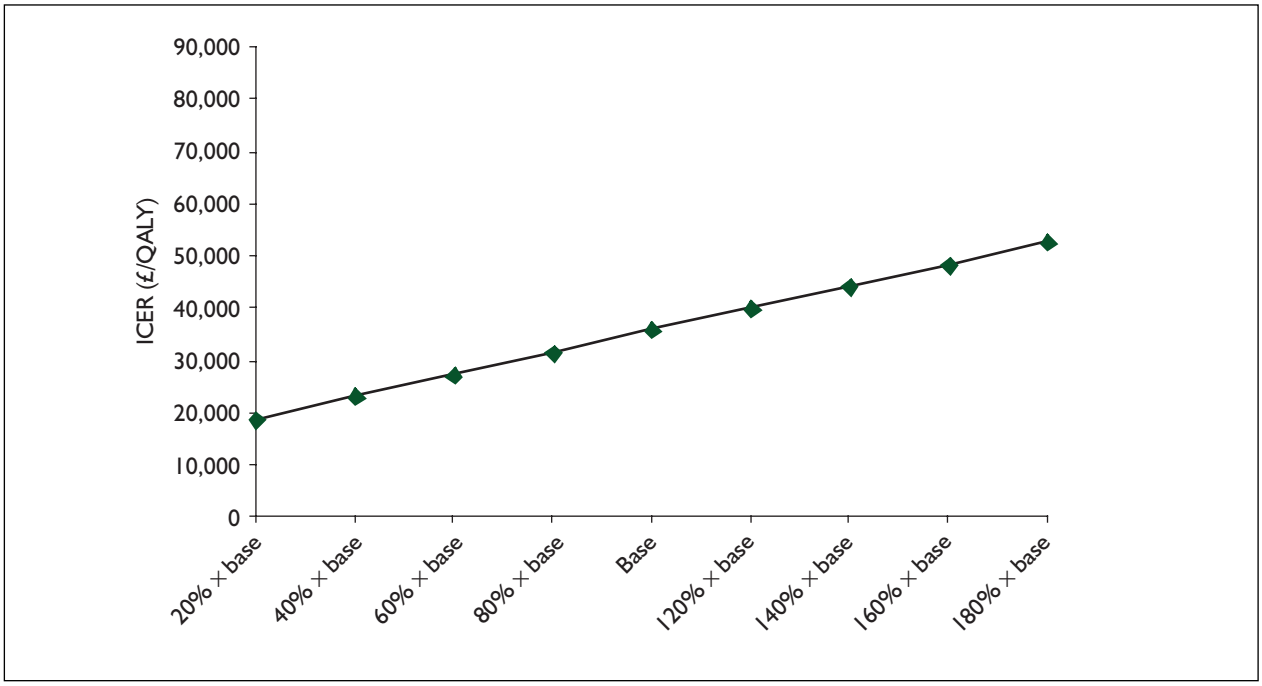

FIGURE 35 *Threshold analysis of the cost of TMZ*

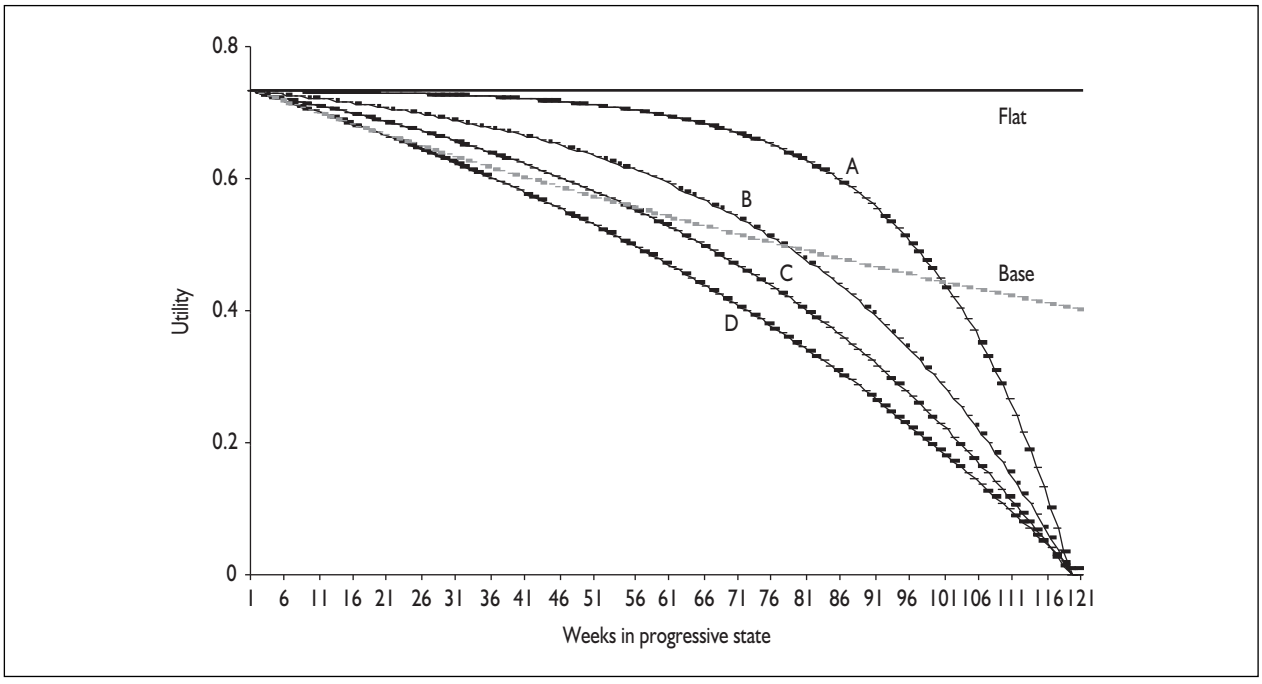

FIGURE 36 *Sensitivity analysis for the pattern of QoL decline with 'progressive' disease*

TABLE 54 *Sensitivity analysis for changes in the pattern of QoL decline with progressive disease*

Pattern of QoL decline	Control		TMZ		QALY difference	ICER (£/QALY)
	Utilities (QALYs)	Costs (£)	Utilities (QALYs)	Costs (£)		
Flat	945	17,015,357	1170	24,804,000	225	34,562
Curve A	928	17,015,357	1134	24,804,000	206	37,786
Curve B	904	17,015,357	1108	24,804,000	204	38,212
Curve C	887	17,015,357	1090	24,804,000	204	38,234
Curve D	869	17,015,357	1073	24,804,000	204	38,142
Base case	889	17,015,357	1106	24,804,000	217	35,861

TABLE 55 *Sensitivity analysis exploring the impact of assuming that death is time dependent*

Deaths transferred from 'stable' to 'progressive' state (%)	Placebo		TMZ		ICER (£/QALY)
	Utilities	Costs (£)	Utilities	Costs (£)	
0 (Base case)	889	17,015,357	1106	24,804,000	35,861
25	889	16,986,789	1111	24,560,658	34,118
50	890	16,958,050	1115	24,423,485	33,250
75	891	16,929,138	1116	24,398,179	33,196

Results are shown in *Table 54*. Even with a flat line for utility values in the 'progressive' disease state, modelling no decline of QoL over time, the ICER value does not fall below usual levels of willingness to pay. If the curve modelled shows a slight initial decline, and then more rapid decline as the patient nears death (curve A in *Figure 36*), the ICER value is slightly increased. More rapid declines (curves B–D in *Figure 36*) in this health state raise the ICER by up to 7%.

Sensitivity analysis for death as time-dependent variable

We explored the impact of our assumption that death is time dependent rather than state dependent through extensive sensitivity analysis. The proportion of deaths in the model occurring from the 'stable' and 'progressive' states were varied. This was achieved by recycling proportionately more of the cohort within the 'stable' state and off-setting this number by increasing the death rate from the 'progressive' state. The overall death rate in the model remained the same. *Table 55* shows the impact of transferring different proportions of the deaths occurring from the 'stable' state to the 'progressive' state. There is little change in the ICER even when 75% of the deaths are transferred, showing that the time-dependent assumption has very little impact on model outputs.

Sensitivity analysis for treatment on disease progression

At disease progression, our base-case analysis models PCV as the second-line chemotherapy for those who receive it, regardless of whether they received TMZ as first-line treatment [see the section 'Costs with disease progression' (p. 74)]. TMZ is not currently recommended as second-line therapy except as a possibility when PCV has failed. However, the Stupp and colleagues' trial data[181] show TMZ being used at recurrence. We investigated the impact of this in sensitivity analysis.

In Stupp and colleagues' trial,[181] those in the control arm were both more likely than those in the TMZ arm to receive chemotherapy at recurrence (72 versus 58%) and were more likely

TABLE 56 *Sensitivity analysis based on Stupp and colleagues' trial data[181] for chemotherapy use at progression*

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
RT only	19,916,431	889			
TMZ + RT	25,404,151	1106	5,487,720	217	25,267

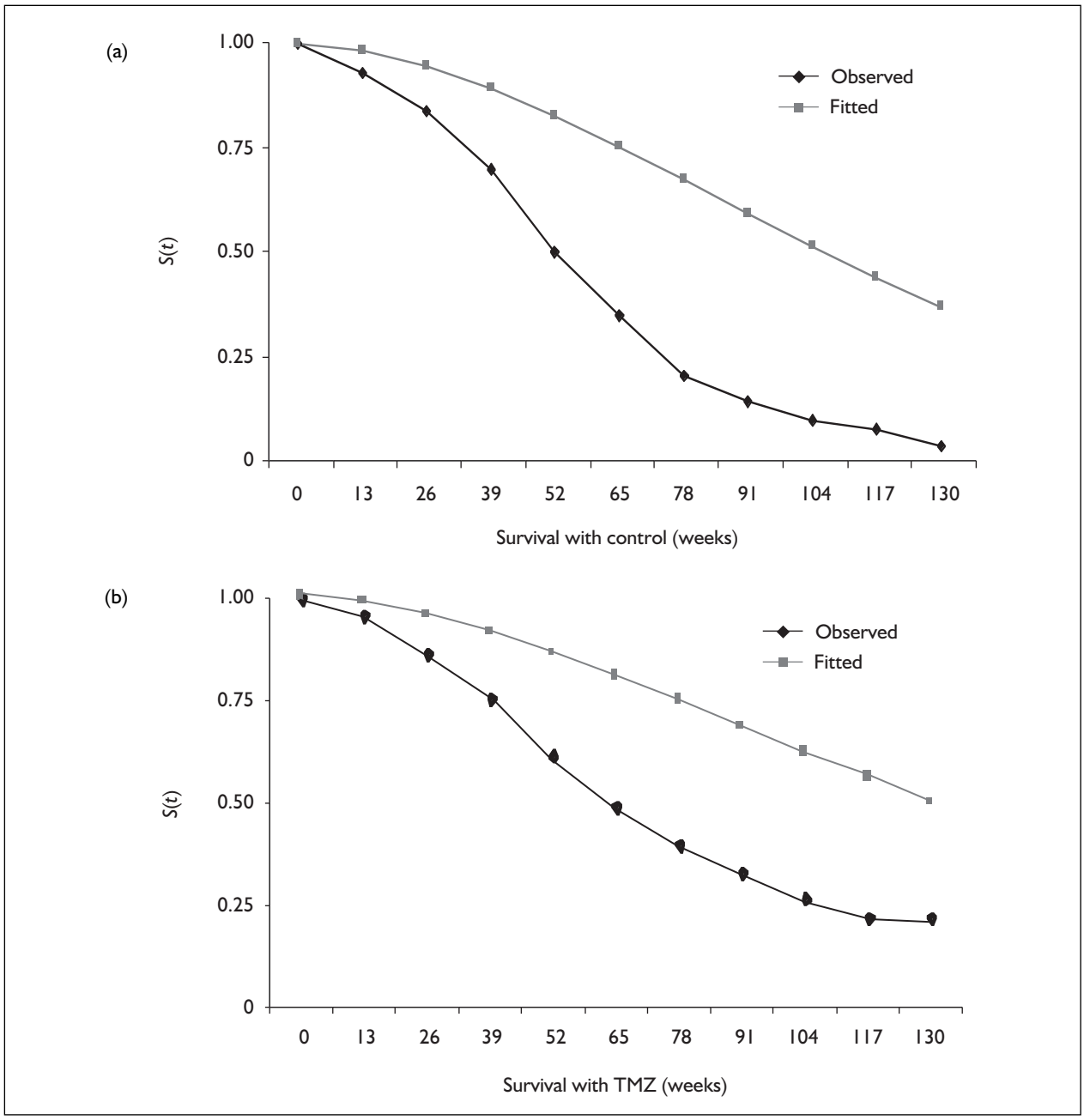

FIGURE 37 *Speculative survival curves used in scenario analysis for patients with good prognosis: (a) survival with control and (b) survival with TMZ*

to receive TMZ (60 versus 25%). When we use these numbers in the model, the incremental costs are reduced as TMZ is much more expensive than PCV. The results of this sensitivity analysis are shown in *Table 56*.

Cost-effectiveness for TMZ in a patient group with good prognosis

As with the BCNU-W analysis, we explored whether TMZ might be cost-effective if used in a patient group with better prognosis owing to being younger, fitter or having a more responsive tumour type. We therefore created an optimistic patient scenario. This is necessarily exploratory and speculative, as there is no published data relating to such patients.

To create this scenario, changes to various input parameters were made: overall survival time, time spent in the 'stable' disease state (PFS) and secondary treatments following disease progression. These are described in more detail below.

The survival curves were altered significantly by changing the shape coefficient of the Weibull survival curve such that the median time in both

control and treatment arms was doubled. This was to represent an increase in crude median survival time from 1 year for patients with grade IV tumours to 2–3 years for those with grade III tumours. The resultant changes to the survival curves are shown in *Figure 37*.

The median time spent in the 'stable' state prior to progression was doubled in both the control and treatment arms. For TMZ, the median survival time for the Kaplan–Meier curve used for this transition has been doubled using the same method described for the survival curves above.

The two-curve method outlined previously was not used here as data to inform each curve are lacking. In addition, the doubling of median overall survival and PFS leads to the point from which the second curve was fitted in the base case no longer being valid.

The proportion of patients who receive secondary treatment is set to the highest level thought reasonable from expert opinion, since secondary treatment is likely to be much more common for this cohort.

TABLE 57 *Cost–utility of TMZ for the scenario for patients with good prognosis*

	Utilities (QALYs)	Costs (£)	ICER (£/QALY)
Control	1607	24,184,064	–
TMZ	1871	33,362,487	–
Increment	264	9,178,422	34,770

The proportion of patients receiving re-surgery is increased from 10 to 50% since this cohort is far more likely to receive further surgery.

Results for this optimistic analysis for patients with good prognosis are shown in *Table 57*. These outputs reflect the increase in benefits of improved survival and the associated extra costs for the scenario assumptions. ICER values for this patient population in the model are lower than base values for TMZ. However, even with these radically changed input parameters, doubling survival time and PFS time, the ICER values are still above £30,000 per QALY.

Probabilistic analyses

Outputs from the Monte Carlo simulation are shown graphically below. For the modelled cohort, these

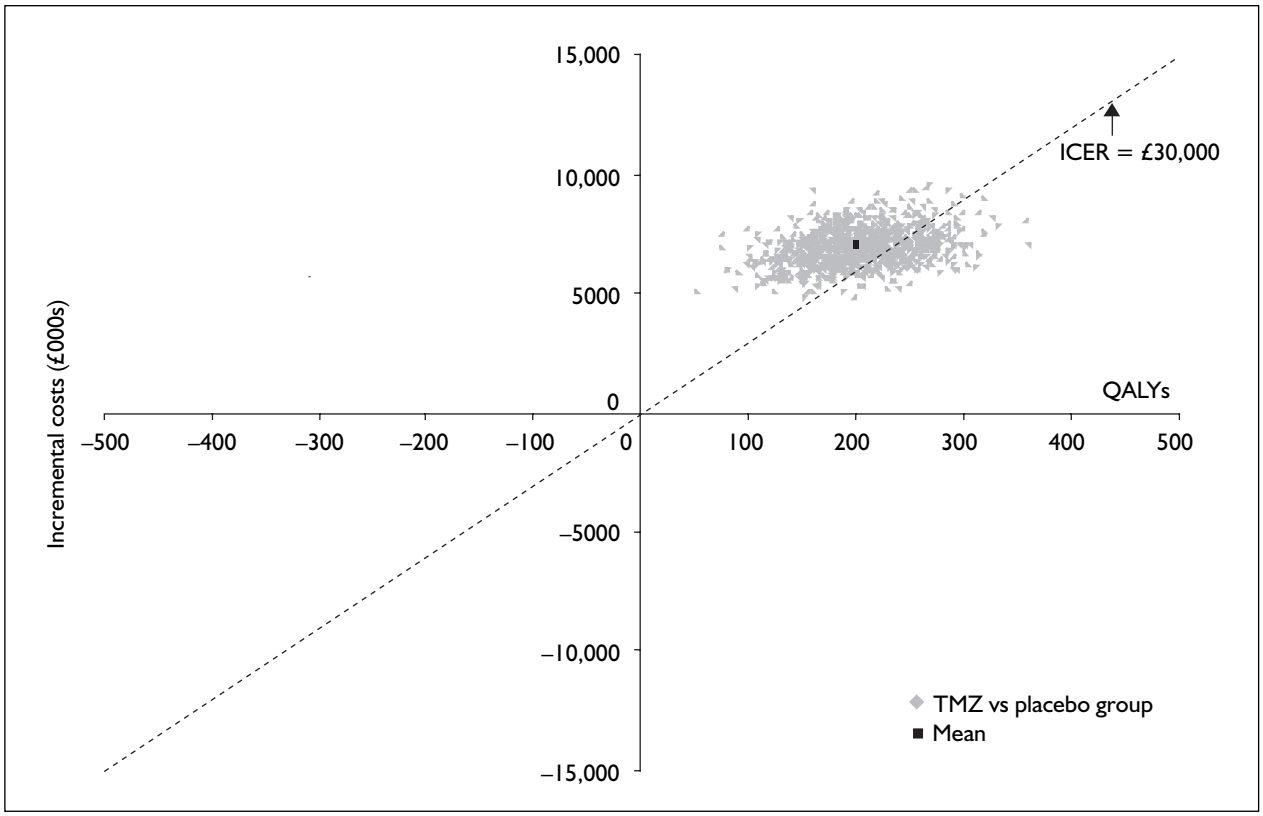

FIGURE 38 *Simulation output (1000 trials) for the cost-effectiveness of TMZ*

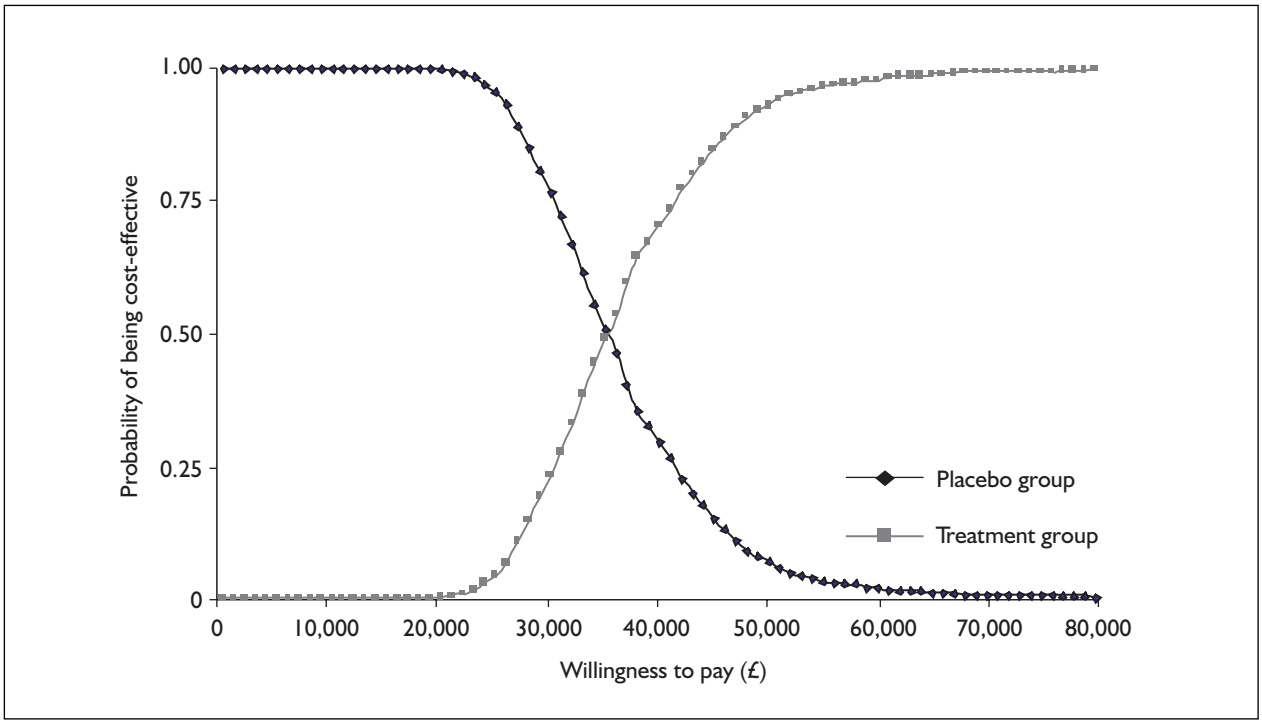

FIGURE 39 *Simulation output (1000 trials) showing the probability that TMZ is cost-effective at various levels of willingness to pay: CEAC for TMZ versus RT*

illustrate the ICER values of 1000 simulated trials. A CEAC has also been calculated showing, at different levels of willingness to pay for an additional QALY, the probability that TMZ is cost-effective.

The simulation (*Figure 38*) shows that, in most cases, TMZ both costs more and confers more QALYs than no treatment. In 23% of simulations the ICER fell below £30,000 per QALY.

The CEAC (*Figure 39*) shows that, at usual levels of willingness to pay, there is a 23% chance TMZ is more cost-effective than usual care. At a willingness to pay level of £35,000 there is a 50% chance that TMZ is the most cost-effective option.

Summary of model uncertainty

A Summary of the model uncertainty is given in *Table 58*.

Model limitations

State transition probabilities are based on the findings of the systematic review described in Chapter 3, which revealed a limited evidence base. Although the trials reported survival values for regular time intervals in tabular form, the length of the chosen intervals was long compared with the median survival times quoted. It was therefore necessary to extract other data points manually from the published Kaplan–Meier curves.

Dependence on a single RCT may introduce an element of inaccuracy into any results produced, as may the process of manual data extraction. The lack of patient-level data also means that it was impossible to know how many patients were classified as either censored or dead in the trials at any one time. This means that the more conventional methods of dealing with survival data (Cox proportional hazard models and log-rank tests) cannot be used. The exclusion of information about covariates from the model may also mean that some bias has been introduced into the results.

In addition, the RCTs are based on populations that are younger and fitter than those seen in normal clinical practice. They therefore probably overestimate the survival seen among those with high-grade glioma generally.

A number of problems were encountered when writing the scenarios for the VoHP which was used to generate the utility estimates for different Markov states. The lack of QoL data in the trials meant that we were very dependent on a single paper.[106] The 'stable disease' and 'progressive' health state descriptions are based on these data and form the basis on which all the other health state descriptions are written. These two scenarios do not look as different from each other as one might have expected from anecdotal clinical

TABLE 58 *Summary of model uncertainty*

Issue	Source of variable	Level of uncertainty in the data	Impact of uncertainty on the model	Overall rating of importance
Transitions				
Median survival advantage	Small evidence base – variable quality RCTs	High	High	Important
Absolute median survival	Small evidence base – variable quality RCTs	High	High	Important
Median PFS advantage	Small evidence base – variety of definitions	High	High	Important
Absolute PFS	Small evidence base – variety of definitions	High	Moderate	Moderately important
Deaths occurring from stable or progressive disease state	Assumption	High	Low	Not important
Perioperative death rate	Review of craniotomy	Moderate	Low	Not important
Utilities				
Stable state utility	VoHP	High	High	Important
Progressive state utility	VoHP	High	High	Important
Progressive state decrement	Expert advice and assumption	Very High	Low	Not important
AEs due to treatment	VoHP, expert opinion and trial data for incidence	High	High	Important
Costs				
Cost of TMZ	Standard sources	Low	Moderate	Not important
Cost of BCNU-W	Standard sources	Low	Moderate	Not important
Cost of recurrent disease treatment	Expert advice and standard sources	Moderate	Very low	Not important
Cost of surgery	Expert advice and standard sources	Moderate	Very low	Not important

evidence. One reason for this may be that the patients in the QoL study are all relatively well, even the recurrent group. This is seen in the baseline characteristics and the fact that only 13 people (12%) were unable to complete the questionnaire at 6–10-week follow-up, only eight of whom were stated to be in poor health. If our estimates for utility are high, we may have overestimated the conferred QALYs and ICERs for the interventions.

Feedback from the Expert Advisory Group suggested that there are no clearly defined patterns of disease progression in malignant glioma, and this complex disease manifests many different symptoms which vary from patient to patient. Patients tend to have symptoms severely in one or two domains but are often free of them in the others. We tried to account for this using three variants on progressive health state descriptions, but the picture is necessarily limited and the results obtained were unclear. The Expert Advisory Group also stressed that steroid and anti-convulsant medication were confounding factors on QoL whose impact has not yet been evaluated.

In the paper by Osoba and colleagues[106] used to write the health state scenarios, some of the patients were already having chemotherapy (46%) and/or RT (10%) at baseline, although we have used these data to indicate the 'stable' disease state. The results from the VoHP to descriptions based on this paper were high, with values similar or higher than general population estimates for the same age group based on the EQ-5D. This does not seem likely for people with terminal cancer. Sensitivity analysis showed that the model was sensitive to reductions in utility value, making the ICER higher.

We did not undertake value of information analysis since a closer level of parameter specification is required than was possible given our project outputs. It is also the case that value of information incorporates a range of assumptions (e.g. uncertainty distributions around parameters, in addition to specific population and time estimates for technology implementation) that in the context of this study are extremely difficult to estimate in order to give meaningful outputs.

Comparison of industry-supplied and PenTAG's economic analyses

Both of the industry-supplied economic evaluations use the same basic division of post-surgical survival into 'stable' and 'progressive' disease phases. However, whereas the industry-submitted economic analysis of BCNU-W uses a simple decision model and defines progression only on the basis of a decline in a number of neuroperformance measures, the industry-submitted economic analysis of TMZ is directly based on particular trial data and defines disease progression as either radiological, neurological or clinical evidence of progression (whichever occurs first).

In order to model different costs, and to reflect possible QoL impacts of undergoing RT or chemotherapy, the PenTAG model divided the 'stable' disease state further into three states: stable pre-RT, stable with RT and stable without RT (*Figure 13*).

Although we criticised the high utility values used in the BCNU-W industry submission, the utility estimates yielded by the VoHP [see the section 'Utilities' (p. 66)] were remarkably similar, at between 0.81 and 0.88 for various stable disease states. These were based on comprehensive descriptions of the symptoms and QoL impacts of post-surgical RT and chemotherapy, living with stable disease or disease progression, and were elicited using a choice-based (standard gamble) method. These data were used in PenTAG's economic analysis. It may be that there are particular problems eliciting meaningful values for terminal illnesses as neither prognosis nor insight into prognosis is taken into consideration by this methodology.

Table 59 shows the other main similarities and differences between the PenTAG and industry-supplied economic analyses.

Table 60 shows a comparison of base-case key assumptions and cost-effectiveness results between the PenTAG and industry-supplied economic analyses.

Explaining the differences in cost-effectiveness between the PenTAG and industry analyses

Comparison of the PenTAG and industry analyses of BCNU-W

Our base-case ICER for BCNU-W compared with surgery and RT only (£54,501/QALY) is over twice that produced by the industry submission (£28,000/QALY). The basic breakdown of this difference is shown in *Table 61*, and it arises from the industry analysis generating both a 36% lower incremental cost and a 33% higher incremental QALY gain than our analysis.

The main reason for the difference in incremental costs is that the industry analysis includes no costs whatsoever after surgery, and therefore omits any additional healthcare costs arising from the longer survival of patients receiving BCNU-W. In contrast, these additional healthcare costs in added months of life are included in the PenTAG analysis, as is recommended in existing guidance on economic evaluations in healthcare.[221,222]

The main reason for the difference in incremental effectiveness is harder to explain fully, because the models have such different structures. The industry model is a relatively simple two-stage model and the PenTAG model is a five-state Markov model. However, in the industry analysis, the 0.16 incremental QALYs arise from assuming that BCNU-W causes an increase in both mean number of progression-free weeks (+8.2 weeks), and mean number of weeks with disease progression (+3.3; see *Table 62*). Multiplying these by the assumed utility weights of progression-free survival (0.8) and survival with disease progression (effectively 0.4, because it is assumed to decline linearly between 0.8 and 0) gives $(8.2 \times 0.8) + (3.3 \times 0.4) = 7.9$ quality-adjusted life-weeks $\approx$ 0.16 incremental QALYs.

In contrast, in our Markov model, the estimated incremental utility of 0.12 QALYs mainly arises from increases in the mean number of weeks that the simulated cohort spends in the 'progressive' disease state (*Table 62*). Our estimates of mean progression-free and overall survival are derived from the area under the extrapolated survival curves (fitted Weibull distributions). The industry's model incorrectly employs median times to neuroperformance decline, and also employs measures of these which do not adjust for declines due to death [see the section 'Overall appraisal' (p. 56)]. Lastly, in relation to overall survival, without access to the patient-level trial data on survival it is impossible to check rigorously the methods used for estimating the area under the Kaplan–Meier curves and thereby their estimate of mean incremental survival. It should also be recognised that our fitting of a smoothed (Weibull) distribution to the actual survival data would introduce further differences in modelled mean survival.

TABLE 59 *Comparison of PenTAG and industry submitted economic analyses*

	PenTAG analysis	**BCNU-W analysis**	**TMZ analysis**
Type of analysis	Model-based	Model-based	Trial-based **[Confidential information removed]**
Type of model	State transition (Markov)	Simple 2-stage (stable, progression) deterministic model	No model **[Confidential information removed]**
Outputs Time horizon	Cost per QALY 5 years	Cost per QALY 16 months (mean survival with treatment)	Cost per life-year 2 years (time horizon of main trial[181]) No time limit **[Confidential information removed]**
Population modelled	Hypothetical cohort of 1000 patients, based on survival curves from Westphal *et al.*'s Phase III trial[151] and Stupp *et al.*'s Phase III trial[181] Mean age 55 years	Implicitly, same population as in Westphal *et al.*'s Phase III trial[151] Mean age 53 (range 21–72 years) 67.7% male	Patient-specific survival (2-year extrapolated) directly from Stupp *et al.*'s Phase III trial[181] Patient-specific costs directly from economic subgroup of this trial **[Confidential information removed]**
Costs included	• Debulking surgery (including work-up) • High-dependency unit bed-days • Gliadel wafers • Concomitant and adjuvant TMZ • RT (30 × 2 Gy fractions) • Supporting medication • Imaging (CT or MRI) • Inpatient hospital stays • Specialist outpatient follow-up appointments • Re-operation on disease progression • Chemotherapy for disease progression (PCV) • End-of-life palliative care (hospital and community-based services)	BCNU wafers only	**[Confidential information removed]**
Source of survival data	The same two Phase III trials upon which the industry analyses are based[151,181]	Westphal *et al.*'s Phase III trial[151]	Patient-specific survival (both 2-year and extrapolated) from Stupp *et al.*'s Phase III trial[181]
Source of resource use data	Expert advisors' accounts of standard care in the UK, industry-recommended drug regimens, and **[Confidential information removed]**	Westphal *et al.*'s Phase III trial data on number of wafers implanted[151]	Patient-specific costs directly from economic subgroup of this trial **[Confidential information removed]**
Source of unit costs	Various, including NSRC 2004, BNF No. 49	UK price of pack of 8 BCNU-W	**[Confidential information removed]**
Source of utility values	VoHP	Approximation, informed by baseline KPS of Westphal *et al.*'s Phase III trial[151] and UK population utility values of 45–54-year-olds of Kind *et al.*[212]	None used
Discount rate used	6% for costs 1.5% for QALYs	Not stated (presumably, therefore, no discounting of costs or QALYs)	**[Confidential information removed]**

TABLE 60 *Comparison of base-case key assumptions and cost-effectiveness results between the PenTAG analysis and the industry-submitted analyses*

	PenTAG analysis	**BCNU-W analysis**	**TMZ analysis**
Cost of treatment with BCNU-W + RT	£23,651 per patient	£4252 per patient	NA
Cost of surgery + RT only (BCNU-W model)	£17,018 per patient	£0 per patient	NA
Cost of treatment with TMZ + RT	£24,804 per patient	NA	**[Confidential information removed]**
Cost of surgery + RT only (TMZ model)	£17,015 per patient	NA	**[Confidential information removed]**
Utility during time with stable disease/before symptom recurrence	• Stable malignant glioma without treatment = 0.86 *or* • with RT only = 0.82 • with RT+TMZ = 0.81 • with BCNU-W = 0.82 • with adjuvant TMZ = 0.85	0.8	NA
Utility during time with disease progression	Time-dependent decline from 0.73, by a factor of 0.005 per week = from 0.73 to 0.65 after 6 months of disease progression	0.4 (mean)	NA
Mean survival with TMZ + RT	NA	NA	1.38 life-years
Mean survival with RT only	NA	NA	1.08 life-years
Mean QALYs per patient with BCNU-W + RT	0.91	0.93	NA
Mean QALYs per patient with RT only	0.79	0.77	NA
Incremental cost	BCNU-W: £6633 TMZ: £7789	£4,252	**[Confidential information removed]**
Incremental effects	BCNU-W: 0.12 QALYs TMZ: 0.22 QALYs	0.16 QALYs	0.3 life-years
ICER (base case)	BCNU-W: £54,501/QALY £28,688/life-year TMZ: £35,861/QALY £27,994/life-year	£28,000/QALY	£19,440/life-year

NA, not applicable.

TABLE 61 *Breakdown of the PenTAG and the industry ICER calculations for BCNU-W*

	PenTAG analysis	**Industry analysis**	**Difference**
Cost with surgery + RT + BCNU-W (£)	23,651	4,252	19,399
Cost with surgery + RT only (£)	17,018	0	17,018
Incremental cost (£)	6,633	4,252	2,381
QALYs with surgery + RT + BCNU-W	0.91	0.93	–0.02
QALYs with surgery + RT only	0.79	0.77	–0.02
Incremental QALYs	0.12	0.16	–0.04
Incremental cost per QALY (ICER)	54,501	28,000	26,501

Our systematic review of the clinical evidence (Chapter 4) has already questioned whether BCNU-W achieves any increase in progression-free survival. Had the industry-submitted economic analysis defined disease progression by either of the other two methods used in their clinical trial (instead of using decline in neurological performance), there would then be no significant increase in progression-free survival – and consequently almost no QALY gains.

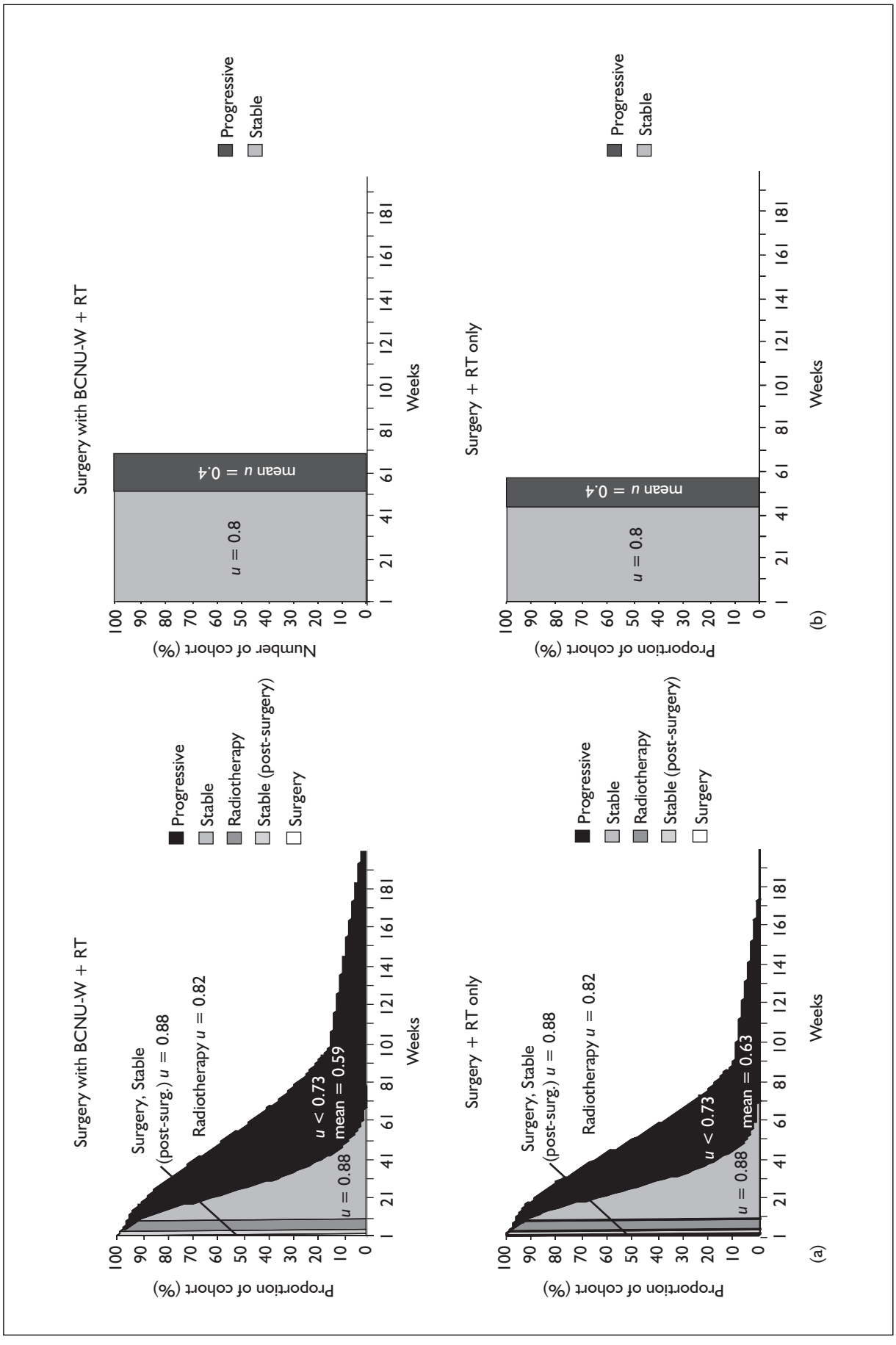

FIGURE 40 *Comparison of survival and time-related utility between (a) the PenTAG and (b) the industry-submitted analyses for BCNU-W*

TABLE 62 *Source of QALY gains with PenTAG and Industry BCNU-W models*

	PenTAG analysis			Industry analysis		
	Mean weeks with stable disease	**Mean weeks in disease progression**	**QALY gain**	**Mean weeks with stable disease**	**Mean weeks in disease progression**	**QALY gain**
Surgery + RT + BCNU-W	27.1	40.9		51.6	17.2	
Surgery + RT only	26.3	29.3		43.4	13.9	
Weeks gained with BCNU-W	0.8	11.6		8.2	3.3	
Mean utility weight of added weeks	0.888[a]	0.506[a]		0.8	0.4	
Quality-adjusted weeks gained	0.75	5.858		6.6	1.3	
Incremental QALYs	0.014	0.113	0.127	0.126	0.026	0.152

[a] Mean utility of being in the progressive disease state is lower in those cohorts which spend more time on average in the progressive disease state (e.g. as in BNCU-W arm).

TABLE 63 *Breakdown of the PenTAG and industry ICER calculations for TMZ*

	PenTAG analysis	Industry analysis	Difference
Cost with surgery + RT + TMZ (£)	24,804	**[Confidential**	6,459
Cost with surgery + RT only (£)	17,015	**information**	4,472
Incremental cost (£)	7,789	**removed]**	1,987
Life-years with surgery + RT + TMZ	1.45	1.38	0.07
Life-years with surgery + RT only	1.17	1.08	0.09
Incremental life-years	0.28	0.30	–0.02
Incremental cost per life-year (ICER)	27,994	19,440	8,554

TABLE 64 *Breakdown of the PenTAG and industry cost calculations (discounted) for TMZ*

	PenTAG analysis (£)	Industry analysis[a] (£)	Difference (£)
Costs during stable disease			
Cost with surgery + RT + TMZ	16,728	**[Confidential**	4,478
Cost with surgery + RT only	7,853	**information**	4,651
Incremental cost	8,874	**removed]**	96
Costs during disease progression			
Cost with surgery + RT + TMZ	9,040	**[Confidential**	2,771
Cost with surgery + RT only	9,844	**information**	614
Incremental cost	–804	**removed]**	2,157
Total costs			
Cost with surgery + RT + TMZ	25,767	**[Confidential**	7,518
Cost with surgery + RT only	17,698	**information**	5,265
Incremental cost	8,070	**removed]**	2,254

[a] Economic subgroup, 2-year restricted. Source: industry submission for TMZ, Table 13, pp. 40–41.

Figure 40 shows a comparison of survival and time-related utility between the PenTAG and industry-submitted analyses for BCNU-W.

Comparison of the PenTAG and industry analyses of TMZ

Table 63 shows the breakdown of the PenTAG and industry ICER calculated for TMZ.

In an important sense, the PenTAG and industry analyses of TMZ are not comparable because different outcomes are used: QALYs and life-years. Therefore, we have also calculated a cost per life-year from the PenTAG model to examine how the difference in incremental cost-effectiveness has arisen.

[Confidential information removed.]

In the PenTAG model, post-progression costs are £804 lower in the TMZ arm. This is because although patients in both arms of the PenTAG model accumulate costs at the same rate (per week spent in the 'progressive' disease state), on average TMZ patients spend less time in the 'progressive' disease state (on average 26.4–29.9 = 3 weeks fewer).

[Confidential information removed.]

[Confidential information removed.]

A summary of the cost-effectiveness of BCNU-Ws and TMZ is given in *Box 11*.

BOX 11 *Summary of cost-effectiveness of BCNU-Ws and TMZ*

- No published cost–utility studies of BCNU-W or TMZ in the relevant population were identified.
- PenTAG designed a Markov model to assess the cost–utility of BCNU-W as concomitant chemotherapy to surgery and RT and of TMZ as a concomitant and adjuvant chemotherapy to surgery and RT compared with surgery and RT alone.
- The base case showed that BCNU-W conferred a small number of additional QALYs (107) and cost an additional £6.1 million, giving an ICER of £57,000/QALY. This is nearly twice the usual willingness-to-pay threshold, suggesting that BCNU-W may not be cost-effective.
- Detailed analysis of the model shows that patients receiving BCNU-W spend a similar amount of time in the 'stable' disease state to those in the comparator group, but more time in the 'progressive' disease state.
- The base case showed that TMZ conferred a small number of additional QALYs (187) and cost an additional £8.6 million, giving an ICER of £46,000/QALY. This is higher than the usual willingness-to-pay threshold, suggesting that TMZ may not be cost-effective.
- Analysis shows that patients receiving TMZ spend a similar amount of time in the 'progressive' disease state to those in the comparator group, but more time in the 'stable' state. Hence their QoL may be better, but they also accrue more costs due to ongoing TMZ treatment.
- The model is sensitive to a number of key variables including survival times, different times spent in 'stable' and 'progressive' disease states and the QoL for people with 'stable' disease, 'progressive' disease and undergoing chemotherapy. Further, data about these parameters must be uncertain given the small evidence base.
- Results from the economic model should be treated with extreme caution given the uncertainty in the model and about key inputs.

Chapter 5
Discussion

Statement of principal findings

The original scope for this report included the clinical and cost-effectiveness of both BCNU-W and TMZ in children with high-grade gliomas. We did not identify any evidence in children and our findings and modelling therefore relate only to adults. The original scope also included grade III and grade IV tumours, but the available data for TMZ are based on trial protocols for patients with grade IV tumours only. Finally, the original scope also included surgery, RT and chemotherapy as a comparator. In all the included RCTs, the comparator is surgery and RT alone compared with surgery and RT with additional BCNU-W or TMZ.

Clinical effectiveness of BCNU-W

Two previous systematic reviews were identified. One used patient-level data from two RCTs to assess the effectiveness of BCNU-W. However, no details of methods used to identify studies or extract data are given, and there was no assessment of study quality. The other was not peer reviewed and gave few details about study quality. We therefore undertook our own systematic review.

Two randomised trials (n = 32 and 240) and two observational studies of BCNU-W were identified. Both trials compared BCNU-W with placebo wafers as adjuvant therapy to surgery and RT for newly diagnosed high-grade glioma. All the studies were in adults and provided data on a total of 193 patients who had received BCNU-W. In both trials the restricted age range is likely to affect generalisibility.

Results from the larger RCT, by Westphal and colleagues,[151] suggest a median survival benefit of 2.3 months for BCNU-W (13.9 versus 11.6 months). This result is not statistically significant using the protocol specified unstratified analysis (p = 0.08). The published analysis stratifies the result by country and is statistically significant (p = 0.03). No improvement in terms of median PFS was shown (5.9 months in both arms). The other, small, RCT appeared consistent with these findings.[152]

Subgroup analysis of patients with GBM in the trial by Westphal and colleagues found no survival advantage with BCNU-W (13.5 versus 11.4 months, p = 0.2).[151]

Although most aspects of the trial methodology appear rigorous, there were concerns about imbalances of baseline characteristics, specifically about numbers of grade III tumours of types that may be more responsive to chemotherapy. PenTAG used the re-analysis of data according to the trial protocol undertaken by the FDA in this report, rather than the published analysis in which a stratified analysis showed a favourable outcome. Long-term follow-up suggests a significant treatment effect for median survival; however, we remain concerned about the internal validity of this trial. 'Tail effects' may come into play with longer term follow-up, that is, a small number of long-term survivors will disproportionately influence survival estimates (see the section 'Progression-free survival', p. 25) and the shape of the survival curve is particularly uncertain in this area.

Inclusion of one small case series[129] (22 patients) with an older population shows a lower median survival than with the younger, fitter populations of the RCTs (9.7 months).

A wide range of AEs is reported, with frequencies of up to 44%. Postoperative complications occur in a small proportion of cases. Only one AE, cranial hypertension, is reported to be significantly more common with BCNU-W than placebo wafer. However, it is unclear whether the implantation of even an inactive wafer may be associated with AEs. In addition, small numbers make it difficult to establish if BCNU-W is associated with rare but serious AEs.

The most common AE reported, aggravation reaction (80%), is not well defined and is only reported by the non-US centres in Westphal and colleagues' RCT.[151] It appears to be related to disease progression. It is also probable that many of the other effects recorded, particularly the neurological ones, are also the result of disease progression.[151] This finding may be further confounded if patients receive additional chemotherapy at progression.

Cost-effectiveness of BCNU-W

NICE received a model-based economic analysis of the cost–utility of BCNU-W from Link Pharmaceuticals. This is not based on a UK perspective and does not include all relevant costs. It also assumes both a progression-free and an overall survival benefit from BCNU-W, assumptions which are questionable according to our assessment of clinical effectiveness. For these reasons, we undertook a separate cost–utility study for this report.

PenTAG's cost–utility model suggests that treatment with BCNU-W conferred a small number of additional QALYs and cost more than placebo wafers, yielding an ICER of £54,500 per QALY. Extensive sensitivity analyses were undertaken, but it was difficult, even with very optimistic values, to demonstrate incremental cost-effectiveness at £30,000 per QALY. The probabilistic sensitivity analysis showed only an 11% probability of BCNU-W being cost-effective at usual levels of willingness to pay. The model is particularly sensitive to changes in

- differences in overall survival
- differences in time spent in 'stable' disease (i.e. PFS)
- quality of life during 'progressive' disease.

Clinical effectiveness of TMZ

There were no previous systematic reviews of TMZ in newly diagnosed high-grade glioma. Two relevant RCTs and two observational studies were included. Evidence from the larger RCT (by Stupp and colleagues[181]) suggests that TMZ confers a small but significant advantage of 2.5 months in overall median survival (14.6 versus 12.1 months, $p < 0.001$) and of 1.9 months in median PFS (6.9 versus 5.0 months, $p < 0.001$). Another smaller RCT supports these findings.[182] Although patient numbers are higher than for BCNU-W ($n = 703$), there are some concerns about the quality of both studies. Neither of the RCTs is placebo controlled and drop-out rates are high. The trial by Stupp and colleagues was formally confined to patients with GBM only, but re-analysis suggested that a significant minority had grade III tumours.[181]

Earlier case series studies report slightly longer median survival.

Haematological toxicity was a concern and led to discontinuation of the drug in 11% of cases in Stupp and colleagues' trial.[181] Other AEs were less severe but common; for example, fatigue was felt by half of the patients.

Cost-effectiveness of TMZ

A trial-based economic analysis was submitted to NICE by Schering-Plough, using data from Stupp and colleagues.[181] However, there is a lack of transparency in the estimation of both costs and effectiveness and cost–utility is not estimated. Results are restricted to cost per life-year gained. For these reasons, we undertook a separate cost–utility study for this report.

PenTAG's cost–utility model suggested that treatment with TMZ conferred a small number of additional QALYs at extra cost, yielding an ICER of £36,000. One-way sensitivity analysis showed that an ICER below £30,000 per QALY is unlikely. The model is particularly sensitive to changes in

- differences in overall survival
- time spent in 'stable' disease (i.e. PFS)
- QoL during 'stable' disease.

Probabilistic analysis showed that TMZ is not likely (23%) to be cost-effective at a willingness to pay threshold of £30,000 per additional QALY.

Indirect comparison of BCNU-W and TMZ

As these two treatments are indicated for the same patient group, but have not been compared directly in a head-to-head trial, the possibility of comparing them indirectly was considered very carefully, particularly in relation to the considerations laid out by Song and colleagues.[200,201] The reasons for not undertaking it are set out in detail on p. 52, but in brief they are as follows:

- The internal validity of the trials, particularly of the TMZ studies with open-label designs, was not adequate to permit a robust indirect comparison.
- The differences in baseline characteristics of the patient groups, including varying proportions of patients with different tumour types, the extent of surgery and the differing times at which randomisation took place in relation to surgery, gave substantial reason to doubt the comparability of the patient cohorts, despite the similar overall survival for BCNU-W and TMZ in the control and no treatment arms

We would therefore strongly caution against any superficial comparison of the effectiveness and cost-effectiveness of the two drugs based on the existing trial data.

Strengths and limitations of the assessment

Strengths

Previous systematic reviews of BCNU-W did not describe their methods fully or rigorously assess the quality of the included studies. There has been no previous systematic review of this TMZ regimen for newly diagnosed high-grade gliomas. Hence the review carried out for this report was able to include studies, both RCTs and observational studies, that may have more relevance in a clinical setting, and to assess their quality in more detail.

No previous cost–utility studies of either drug have been undertaken in a UK setting. Our model included extensive sensitivity analyses to explore the impact of uncertainty in the model and identify parameters to which it was most sensitive.

Limitations

The assessment in this report is limited by the quantity and quality of the available evidence. Data are limited to adult populations only, despite the relative frequency of this cancer in children, and this report cannot comment on the applicability of either of these drugs to this age group.

There are a number of methodological concerns with the trial by Westphal and colleagues.[151] Briefly these are as follows:

- The trial is powered to detect a 20% difference in survival at 12 months. It is therefore underpowered and a Type II error is possible.
- There are differences in the baseline characteristics of the two arms – especially small but potentially significant differences in chemosensitive AO tumours.
- There are more reinterventions at progression in the treatment arm.
- There are differences in the placebo and active wafers sufficient to pose a threat to blinding.
- The main published statistical analysis uses stratification by country (not prespecified), which maximises any apparent difference. Non-stratified analysis indicates non-significant differences between treatment and placebo arms.
- Death was inappropriately treated as an event in the published analyses of KPS decline and time to progression. When recalculated censoring death, the differences were non-significant.

Although lack of power may bias against BCNU-W, all other issues may bias in favour of BCNU-W.

For TMZ, it would have been better for a placebo-controlled trial to have been conducted rather than the open-label ones available. Given the difficulties of defining disease progression, this may lead to differences between the study arms in defining this cut-off point, particularly as this may be linked to post-progression treatment options. In addition, there were high drop-out rates from the TMZ arm.

The exclusion criterion restricting the age of patients recruited into trials means that the results may only be applicable to younger, possibly fitter patients, who comprise only about 40% of the population with these tumours (peak incidence is at ages 70–74 years, see p. 4). Restricting included patients to those who are fit for surgery and have suitably placed and accessible tumours for BCNU-W insertion further reduces generalisability of the trial results, as does the delay in randomisation of the TMZ patients to 6 weeks after surgery.

For both drugs, the results of the trials may be driven by the minority of patients with chemosensitive tumour types. This heterogeneity of response may come from both misclassification of tumours and also lack of knowledge of newly emergent genetic and biomarker subtypes which may respond very differently to chemotherapy. Grade IV (GBM) tumours are the most common type of high-grade tumour (40–45%). The BCNU-W trials showed no difference in survival for patients with GBM treated with the drug compared with those treated with placebo. However, BCNU-W is implanted at the time of initial surgery and there are few UK centres where accurate tumour typing can be done within the time frame of the operation itself. This means that there will be patients who receive unnecessary and expensive chemotherapy, with attendant risk of AEs, and no survival advantage is likely to result.

TMZ is currently only licensed for use with grade IV tumours, but 7–8% of those in the trials were reclassified as having grade III tumours at central analysis. The TMZ trials failed to provide subgroup analysis for those patients with confirmed grade IV tumours. There remains the possibility that the results of this trial are actually driven by chemosensitive tumour types, for whom TMZ may not currently be licensed.

The comparator for both drugs is surgery and RT only. As far as we are aware, RT doses and protocols were the same between control and treatment arms of the trials and similar across

trials. However, we also do not know whether these doses and protocols represent the optimal treatment schedule for these tumours; it is possible that the additional health gain seen from the addition of chemotherapy could have been achieved by optimising the RT element of the trials.

For both sets of trials, the threshold between stable and progressive disease is far from clear, and in the trials patients might be defined as progressive owing to symptoms, size of the tumour on imaging or clinician-defined neurological decline.

The current NICE advice for TMZ is that it may be used at recurrence where standard chemotherapy has failed, but there is local variation in treatment patterns. However, if TMZ and BCNU-W are widely used as first-line treatments, then it is a matter of speculation what treatments will be used on recurrence. Our model base case assumes that those patients who do receive second-line chemotherapy will receive PCV. Although we have explored the impact of a variable proportion of patients receiving TMZ on recurrence, it must be emphasised that these proportions are speculative and cannot reflect current practice.

QoL during 'stable' and 'progressive' disease appears to be rated surprisingly highly for a disease with such a poor prognosis and such a variable effect on performance. The method of eliciting utilities may influence these values; the scenarios used by the PenTAG panel are not explicit about the terminal nature of the disease and are drawn from the only detailed description of the various health states available. The population in the study informing these descriptions was relatively well and able to participate. Given the variable manifestations of the disease, it is possible that further scenarios would elicit different utility values. However, the utilities published in the literature and those obtained for this study are broadly similar, suggesting these estimates may be reasonably accurate. Given the nature of the disease, denial of the prognosis and lack of insight may be prominent features and influence patients' ratings of their QoL. The QoL of carers may be a particular issue in this condition, but current methods do not include carer QoL in cost–utility analyses.

The relationship between QoL and the various performance instruments used to determine progression also remains uncertain. It has been assumed that QoL will decline once 'progressive' disease occurs, but the shape of this decline is again uncertain. Despite these uncertainties, the model is not particularly sensitive to QoL, although if lower values are used, cost-effectiveness declines sharply. The current assumptions in the model about utilities and their rates of decline favour the treatments; revised estimates are therefore more likely to reduce cost-effectiveness than improve it. Nevertheless, we have tried to accommodate changes in QoL from treatment and progression according to current practice.

The model, and published literature, assume that patients receive treatment shortly after diagnosis. In a disease with such a poor prognosis, it is likely that significant delays in patients receiving standard treatment with surgery and RT will adversely affect outcome, in addition to having a detrimental effect on QoL while waiting. PenTAG learnt of routine substantial delays in patients receiving RT in the NHS, of up to 12 weeks, which could alter the effectiveness of both drugs. Some clinicians reported that as a result TMZ may be used outside its licensed indications, being prescribed before surgery and RT.

UK costs identified for this study are 10 years old, and more up-to-date costs are only available for other systems of healthcare. Although our model is not particularly sensitive to costs, costs do account for most of the difference between our model outputs and the two industry submissions. These cost differences arise from the costs attached to treatments used in progressive disease and for palliative care; the industry submissions take no account of the extra costs incurred from treatment by those surviving longer in the treatment arms.

The framework of this assessment makes a clear distinction between first- and second-line treatments used in clearly defined and separate phases, and perhaps does not reflect the underlying disease process accurately or the management of these patients. The impact of chemotherapy combination and order has not been investigated. It may be more helpful to model sequences of treatments used from first line through second line to palliative care.

The tumour classification system requires updating as the emerging data on genetic markers provide better prediction of chemosensitivity than gross tumour type. Targeted use of chemotherapy may provide better outcomes.

Research recommendations

Estimates of the effectiveness and cost-effectiveness of both drugs could be improved substantially by further research. We identified the following areas where further information could materially alter the conclusions of this report. The order is not necessarily an indication of priority.

1. The effectiveness and cost-effectiveness of BCNU-W have not been proven. Further research is needed to investigate this in specific populations.
2. Evidence for effectiveness of TMZ is limited. In particular, it is not known whether patients with confirmed grade IV tumours (the licensed indication) benefit from TMZ. Further research should investigate this.
3. The emerging work on genetic markers suggests that grade III and IV tumours can also be classified according to genetic subtype with strong implications for their responsiveness to chemotherapy. Further research on refining these categories/subtypes, and their measurement, is required, followed by studies that explore the feasibility of using these markers to inform treatment decisions for individual patients in standard clinical settings.
4. Future trials should seek to compare different chemotherapy regimens directly rather than against placebo, and also seek to specify and evaluate sequences of treatment, including second- and third-line treatments, more closely.
5. Future trials should also seek to clarify aspects of QoL that matter most to patients and to characterise the changes in QoL that occur during stable and progressive disease. More explicit consideration of carer views should also be sought.
6. It is important to explore the value that patients put on small absolute survival advantages compared with the disadvantages of treatment requirements; these advantages may be valued differently by those with terminal illness than by others in the population.

Chapter 6
Conclusions

BCNU-W has not been proven to confer a significant advantage in survival for patients with grade III tumours when treated with the drug, compared with placebo. There does not appear to be a survival advantage for patients with grade IV tumours. No increase in PFS has been shown.

Limited evidence suggests a small but significant advantage in both overall survival and PFS with TMZ among a mixed population with grade IV and III (7–8%) tumours. However, it remains unclear whether this is true in grade IV tumours alone.

On the basis of best available evidence, we consider that neither BCNU-W nor TMZ is likely to be considered cost-effective by NHS decision-makers. However, data for the model were drawn from limited evidence of variable quality.

Tumour type is clearly important in assessing patient prognosis with different treatments. Grade IV tumours are commonest and appear to have least chance of response. There were too few grade III tumours included to carry out a formal assessment, but they appear to respond better and drive results for both drugs. Future use of genetic and biomarkers may help identify subtypes which will respond, but current licensing indications do not specify these.

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Contribution of authors

Rob Anderson (Health Economist) obtained costs for the model, contributed to writing the economics chapter and critically assessed published and industry-submitted economic evaluations. Matthew Dyer (Clinical Research Assistant) contributed to writing the report's background and economic sections, designed health state utility scenarios and analysed value of health panel responses. Ruth Garside (Research Fellow) provided overall project management, wrote the protocol, read abstracts for inclusion and exclusion, extracted and checked data and contributed to writing and editing the report. Stuart Mealing (Research Assistant) assisted in the design and execution of the economic model and contributed to writing the economics chapter. Martin Pitt (Research Fellow) designed and ran the economic model and also contributed to, and commented on, the economics chapter. Alison Price (Information Scientist) undertook literature searches for the project and commented on drafts of the protocol and the TAR. Gabriel Rogers (Research Assistant) read abstracts for inclusion and exclusion, extracted and checked data, produced meta-analyses and contributed to writing the report's systematic review sections. Margaret Somerville (Director of Public Health Learning and Principal Lecturer) read and commented on the protocol and contributed to writing the report's discussion chapter. Ken Stein (Senior Lecturer in Public Health) read and commented on the protocol and the report, contributed to the design of the model and supervised the utility value elicitation process.

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Appendix 1

EORTC questionnaires: QLQ-C30

Multi-item scales: functional

Physical function (5–10)

Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? (1/2)
Do you have any trouble taking a long walk? (1/2)
Do you have any trouble taking a short walk outside of the house? (1/2)
Do you have to stay in a bed or a chair for most of the day? (1/2)
Do you need help with eating, dressing, washing yourself or using the toilet? (1/2)

Role function (2–4)

Are you limited in any way in doing either your work or doing household jobs? (1/2)
Are you completely unable to work at a job or to do household jobs? (1/2)

Cognitive function (2–8)

Have you had difficulty in concentrating on things, like reading a newspaper or watching television? (1–4)
Have you had difficulty remembering things? (1–4)

Emotional function (4–16)

Did you feel tense? (1–4)
Did you worry? (1–4)
Did you feel irritable? (1–4)
Did you feel depressed? (1–4)

Social function (2–8)

Has your physical condition or medical treatment interfered with your family life? (1–4)
Has your physical condition or medical treatment interfered with your social activities? (1–4)

Symptoms

Fatigue (3–12)
Did you need to rest? (1–4)
Have you felt weak? (1–4)
Were you tired? (1–4)
Pain (2–8)
Have you had pain? (1–4)
Did pain interfere with your daily activities? (1–4)
Nausea/vomiting (2–8)
Have you felt nauseated? (1–4)
Have you vomited? (1–4)

Global health status/QoL (2–14)

How would you rate your overall physical condition during the past week? (1–7)
How would you rate your overall quality of life during the past week? (1–7)

Single-item scales

Dyspnoea

Were you short of breath? (1–4)

Insomnia

Have you had trouble sleeping? (1–4)

Appetite loss

Have you lacked appetite? (1–4)

Constipation

Have you been constipated? (1–4)

Diarrhoea

Have you had diarrhoea? (1–4)

Financial difficulties

Has your physical condition or medical treatment caused you financial difficulties? (1–4)

EORTC QLQ-C30 BN20 brain cancer supplement questionnaire

Multi-item scales

Future uncertainty

Did you feel uncertain about the future?
Did you feel you had setbacks in your condition?
Were you concerned about disruption of family life?
Did your outlook on the future worsen?

Visual disorder

Did you have double vision?
Was your vision blurred?
Did you have difficulty reading because of your vision?

Motor dysfunction

Did you have weakness on one side of your body?
Did you have trouble with your coordination?
Did you feel unsteady on your feet?

Communication deficit
Did you have trouble finding the right words to express yourself?
Did you have difficulty speaking?
Did you have trouble communicating your thoughts?

Single-item scales

Headaches
Did you have headaches?

Seizures
Did you have seizures?

Drowsiness
Did you feel drowsy during the daytime?

Hair loss
Did hair loss bother you?

Itching
Did itching of your skin bother you?

Weak legs
Did you have weakness of both legs?

Bladder control
Did you have trouble controlling your bladder?

Appendix 2

Expert Advisory Group

Members of the Expert Advisory Group were Professor Michael Brada, Professor of Clinical Oncology, The Royal Marsden Hospital, Surrey, Dr Robin Grant, Consultant Neurologist, Western General Hospital, Edinburgh, Mr James Palmer, Consultant Neurosurgeon, Derriford Hospital, Plymouth, and Mr Vakis Papanastassiou, Senior Lecturer in Neurosurgery, Southern General Hospital, Glasgow.

Appendix 3

Project protocol

The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma

Details of the research team

The research team consisted of Ruth Garside, Research Fellow, Peninsula Technology Assessment Group, Dean Clarke House, Southernhay East, Exeter EX1 1PQ (author for correspondence; telephone 01392 207818; email ruth.garside@pentag.nhs.uk); Dr Margaret Somerville, Director of Public Health Learning and Principal Lecturer, Peninsula Medical School; Dr Martin Pitt, Research Fellow, Peninsula Technology Assessment Group; Gabriel Rogers, Research Assistant, Peninsula Technology Assessment Group; Dr Matthew Dyer, SHO in Public Health, Peninsula Technology Assessment Group; Dr Rob Anderson, Senior Lecturer in Health Economics, Peninsula Technology Assessment Group; Stuart Mealing, Research Assistant, Peninsula Technology Assessment Group; Alison Price, Information Scientist, Southampton Health Technology Assessment Group; and Dr Ken Stein, Senior Lecturer in Public Health, Peninsula Technology Assessment Group.

Full title of research questions

- Compared with current standard treatment, what are the clinical effectiveness and cost-effectiveness of carmustine implants (BCNU-W) as adjunct treatment to surgery and radiation therapy to treat newly diagnosed high grade glioma?
- Compared with current standard treatment, what are the clinical effectiveness and cost-effectiveness of temozolomide (TMZ) as concomitant and adjunct treatment to surgery and radiation therapy to treat newly diagnosed high-grade glioma?

Clarification of research questions and scope

Malignant brain tumours are not common, accounting for about 1.6% of all primary cancers, but have very poor prognosis. Most originate in the glial (supportive) tissue of the brain and are known as gliomas. Brain tumours are graded according to the speed at which they grow, with grade I the slowest growing and grade IV the most rapidly growing, aggressive tumours. Grades III and IV are considered high-grade tumours and no cure is available. Incidence of high-grade gliomas in England and Wales is 4/100,000 and about 2100 new cases are diagnosed each year.[2]

There are several types of glioma. The most common are astrocytomas, which develop from astrocytes (star-shaped glial cells). Grade III tumours are called anaplastic astrocytoma (AA), and have a mean age at onset of 40 years. The average life expectancy for a patient with AA is 2–3 years.[12] Such tumours often progress to grade IV tumours called glioblastoma multiforme (GBM) although these also present *de novo*. Average age at onset is 53 years.[12] The estimated 1-year survival rate with GBM is 30%.

Signs and symptoms vary with the position and size of the tumour, but include changes in mental function, headaches, seizures, focal neurological signs and symptoms of raised intracranial pressure.

Currently, the primary therapy for gliomas is surgery which aims to remove the tumour. However, given the nature of these tumours, total resection is impossible without considerable damage to surrounding brain tissue. The impact of surgery on survival is yet to be confirmed.[12] The object is therefore to debulk the tumour to relieve symptoms, rather than achieve complete resection. Surgery is usually followed by radiation therapy aiming to stop growth among remaining cancer cells. Radiation in addition to surgery is associated with a 3–4-month survival advantage compared with chemotherapy or supportive care alone.[84]

Chemotherapy, using agents singly or in combination, may also be employed, especially at recurrence. However, poor penetration of the blood–brain barrier of most agents and their associated adverse effects mean that these are not widely accepted.[223] A recent meta-analysis found an increase of 2 months in median survival with chemotherapy.[91] However, this analysis combined data from a variety of chemotherapy regimens and most were conducted in the 1970s.

Steroids are frequently used to reduce tissue oedema as part of a palliative strategy.[224]

Scope

This technology assessment will estimate the clinical and cost-effectiveness of BCNU-W and of TMZ as adjunct therapy to surgical and radiation treatment for newly diagnosed, primary high-grade (grade III or IV) gliomas. The effectiveness of these two drugs will be assessed individually. It is not expected that a head-to-head comparison will be possible but may be examined if appropriate data are available. For both drugs, adult and child populations will be assessed. Specific subgroups, such as those defined according to the extent of surgery (biopsy, partial resection or complete resection) or by grade of tumour (for example, GBM or AA) will be assessed if the evidence allows.

All RCTs in newly diagnosed high-grade gliomas will be included when they are of BCNU-W adjunct to surgery with standard RT and/or chemotherapy compared with placebo implants adjunct to surgery with or without standard RT, or to surgery with or without standard RT and chemotherapy with antineoplastic agents (excluding those listed in the intervention, for example nitrosourea-based regimens such as PCV).

All RCTs in newly diagnosed high-grade gliomas will be included when they are of TMZ as an adjunct to surgery and concomitant with standard RT and adjunct to it compared with surgery with or without standard RT or surgery with or without standard RT and chemotherapy with antineoplastic agents (excluding those listed in the intervention, for example nitrosourea-based regimens such as PCV).

A cost–utility analysis will be carried out if sufficient data are available from the literature or other sources. If a well-designed cost–utility analysis is already available and required data are available, this will form the basis for the assessment of cost-effectiveness.

Intervention 1

Intervention 1 consists of carmustine implants (Gliadel® wafers, Link Pharmaceuticals, distributor for Guilford Pharmaceuticals) as an adjunct treatment to surgery with or without RT for newly diagnosed grade III or IV primary gliomas. It has recently received UK approval for use in newly diagnosed high-grade gliomas through the EU mutual recognition scheme in addition to recurrent disease.

The implants are made from biodegradable polyanhydride polymer impregnated with carmustine that can deliver up to 7.7 mg directly into the brain when inserted perioperatively in the resection site of a glioma. Up to eight wafers can be implanted at any time. Carmustine is released to the tumour site over the next 2–3 weeks.[88]

Comparators

- Surgery with or without radiation treatment.
- Surgery with or without RT and chemotherapy with antineoplastic agents (excluding those listed in the intervention, for example nitrosourea-based regimens such as PCV).

Intervention 2

Temozolomide (Temodar®, Schering Plough) is an adjunct treatment to surgery and radiation for newly diagnosed grade III or IV primary gliomas. Currently licensed for use in recurrent tumours, a licence for use as concomitant with, and adjuvant after, radiation treatment in newly diagnosed high-grade primary gliomas is pending.

TMZ is given as an oral tablet for five consecutive days, repeated every 28 days. Dosage for adults is 150–200 mg/m^2/day or a total dose of 750–1000 mg/m^2/cycle. For children, the dose is 60–100 mg/day or a total dose of 900–1075 mg/cycle.

Comparators

- Surgery and RT.
- Surgery and RT with chemotherapy with antineoplastic agents (excluding those listed in the intervention, for example nitrosourea-based regimens such as PCV).

Populations of interest

For both drugs, the populations of interest are adult and paediatric patients with newly diagnosed grade III or IV primary gliomas who are suitable for surgery.

Inclusion criteria
Participants with a new, primary diagnosis of grade III or IV glioma will be eligible for inclusion.

Exclusion criteria
Studies will be excluded if patients with the following characteristics are not reported separately:

- other grades of glioma
- treatment with carmustine other than as wafers at the time of surgery with or without RT
- use of TMZ other than as concomitant and adjunct to surgery and RT.

Outcomes
The review will focus on patient-centred outcomes:

- mortality (survival, PFS, quality-adjusted survival)
- adverse effects (including convulsions, weakness, low platelet count, high blood sugar, alopecia, nausea, vomiting, headache, rash, fatigue, constipation, myelosuppression and elevated liver function tests)
- QoL
- cost-effectiveness (from cost-effectiveness analyses only).

Patient preferences
Where available, information on the treatment preferences of patients and caregivers will be extracted from included trials.

Time perspective
Follow-up should be at least 6 months to allow meaningful analysis of survival.

Review and report methods

Search strategy
A search strategy will be developed for the electronic databases shown below. For the question of effectiveness, publications that describe trials described below will be included.

The search will be performed in:

- electronic databases, including MEDLINE PubMed, EMBASE, The Cochrane Library [including Cochrane Systematic Reviews Database and the Cochrane Central Register of Controlled Trials (CENTRAL)], Science Citation Index, Web of Science Proceedings, DARE, NHS EED and HTA databases
- trial registers in the UK (National Research Register), Current Controlled Trials, USA (Clinical Trials.gov) and Canada
- bibliographies
- by contacting research groups and industry.

Two researchers will independently assess the relevance of the abstracts retrieved and full texts of these papers will be obtained. Two researchers will then independently assess whether these trials fulfil the inclusion criteria.

Inclusion
- All systematic reviews and RCTs in newly diagnosed high-grade gliomas in adults or children will be included when they are of carmustine implants adjunct to surgery with standard RT and/or chemotherapy compared with placebo implants adjunct to surgery with or without standard RT, or to surgery with or without standard RT and chemotherapy with antineoplastic agents (excluding those listed in the intervention, for example nitrosourea-based regimens such as PCV).
- All systematic reviews and RCTs in newly diagnosed high-grade gliomas in adults or children will be included when they are of TMZ as an adjunct to surgery and concomitant with standard RT and adjunct to it compared with surgery with or without standard RT or surgery with or without standard RT and chemotherapy with antineoplastic agents (excluding those listed in the intervention, for example nitrosourea-based regimens such as PCV).

Non-randomised evidence may be considered if it gives the best estimates of a required parameter (for example, AEs or patient preferences) or where RCT data are scanty or uninformative.

The economic evaluation will consider cost-effectiveness, cost–utility and cost–benefit studies of BCNU-W compared with placebo or current standard treatment for treatment of newly diagnosed high-grade glioma, and of TMZ compared with placebo or current standard treatment for treatment of newly diagnosed high-grade glioma.

Exclusion
- Systematic reviews included in or superseded by more recent reviews.
- Studies only available as abstracts or conference presentations, where insufficient detail are given to allow study quality to be assessed.
- Animal models.
- Preclinical and biological experimentation *in vitro* or on humans.

- Studies not reporting patient relevant outcomes.
- Studies not available in English.

Data extraction
Data will be extracted by one researcher and checked by a second researcher, with differences resolved by consensus.

Quality assessment
The methodological quality of included RCTs and systematic reviews will be assessed using the criteria reported in the NHS CRD Report No. 4. Cost-effectiveness and cost–utility studies will be assessed following the methodology reported by Sculpher and colleagues.[211]

Methods of analysis/synthesis
Meta-analysis will be performed if sufficient, appropriate randomised evidence is located. Otherwise, a tabulated description of the available evidence will be presented and discussed.

The meta-analysis will use a fixed-effects method if data are homogeneous. Analyses will be based on ITT data. Sources of heterogeneity will be identified and their impact explored. Subgroup analyses will be specified prior to meta-analysis, based on further examination of the papers to be included. Such analyses may be related to patient, intervention or methodological factors.

Estimation of effectiveness, quality of life, costs and cost-effectiveness or cost–utility
Cost data will be extracted from published work, NHS costs and industry submissions as appropriate. If insufficient data are retrieved from published sources, costs will be derived from individual Trusts or groups of Trusts. In the base case, costs will be discounted at 6% and benefits at 1.5%, and these will be explored in sensitivity analysis.

If possible, independent cost–utility models will be developed to determine cost-effectiveness and cost–utility of treatment with BCNU-W compared with surgery with RT, with or without standard chemotherapy, and of TMZ compared with surgery with RT, with or without standard chemotherapy.

Uncertainty in the model will be examined by sensitivity analyses. One-way sensitivity analysis will examine the impact of individual parameters in the model. Probabilistic sensitivity analysis will be used to investigate the combined effect of uncertainty across all the parameters.

Handling industry submission

Information provided by the industry will be included in the report when meeting our inclusion criteria (RCTs) and for information on costs.

A critique of any economic evaluations, including models, submitted by industry will be undertaken using the framework outlined by Sculpher and colleagues.[211]

Any 'commercial-in-confidence' data taken from the industry submissions will be underlined and the source identified in the assessment report.

Project management

Timetable
- initial draft protocol: 14 March 2005
- final draft protocol: 4 April 2005
- progress report: 10 June 2005
- complete and near final draft report to peer review: 1 August 2005 (to be confirmed)
- final draft report: 5 September 2005.

Competing interests
None.

External reviewers
The Technology Assessment Report (TAR) will be subject to external review by at least two experts acting on behalf of the NHS R&D HTA Programme. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that the NICE secretariat and Appraisal Committee will undertake methodological review. In addition, an external methodological referee will be asked to review the report on behalf of the NHS R&D HTA Programme. Referees will review a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. Referees will be required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking, which we will hold on file. Comments from referees and the Technical lead, together with our responses, will be made available to NCCHTA in strict confidence for editorial review and approval.

Appendix 4

Search strategies

Clinical searches

Databases and years searched	Search files	No. of hits
Cochrane Library (CDSR) Issue 1/2005 Searched 1 March 2005	MEDLINE search strategy run as below	1 BCNU-W
Cochrane Library (CENTRAL) Issue 1/2005	As below	67 BCNU-W 8 TMZ
MEDLINE (OVID) 1966 to February week 3 2005 Searched 1 March 2005	1 exp glioma/ or exp astrocytoma/ or ependymoma/ or oligodendroglioma/ (34588) 2 exp Glioblastoma/ (7348) 3 (glioblastoma mulitforme or GBM).tw. (2517) 4 ((grade$ 4 or four or IV) adj3 (glioma$ or astrocytoma$ or AA)).tw. (1157) 5 ((grade$ 3 or three or III) adj3 (glioma$ or astrocytoma$ or AA)).tw. (1745) 6 1 or 2 or 3 or 4 or 5 (37381) 7 (carmustine adj10 implant$).mp. (45) 8 Gliadel$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (17) 9 exp Carmustine/ (3069) 10 exp Absorbable Implants/ (1524) 11 exp Drug Implants/ (5227) 12 10 or 11 (6711) 13 9 and (10 or 11) (46) 14 7 or 8 or 12 or 13 (6726) 15 6 and 14 (64) 16 temozolomide.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (529) 17 temoda$.mp. (27) 18 Dacarbazine/ad, ae, aa, pd, tu (2362) 19 16 or 17 or 18 (2456) 20 6 and 19 (229) 21 15 (64) 22 limit 21 to (humans and english language) (41) 23 20 (229) 24 limit 23 to (humans and english language) (217)	41 BCNU-W 217 TMZ
PREMEDLINE In-process and other non-indexed citations Searched 28 February 2005	1 (glioma or astrocytoma or ependymoma or oligodendroglioma).tw. (444) 2 (glioblastoma mulitforme or GBM).tw. (59) 3 ((grade$ 4 or four or IV) adj3 (glioma$ or astrocytoma$ or AA)).tw. (25) 4 ((grade$ 3 or three or III) adj3 (glioma$ or astrocytoma$ or AA)).tw. (48) 5 1 or 2 or 3 or 4 (521) 6 (carmustine adj10 implant$).mp. (1) 7 Gliadel$.mp. [mp=title, original title, abstract, name of substance word] (1) 8 6 or 7 (2) 9 5 and 8 (2)	1 BCNU-W 10 TMZ

continued

Databases and years searched	Search files	No. of hits
	10 temozolomide.mp. [mp=title, original title, abstract, name of substance word] (35) 11 temoda$.mp. (0) 12 10 or 11 (35) 13 5 and 12 (14) 14 from 9 keep 1 (1) 15 from 13 keep 3-12 (10)	
EMBASE (OVID) 1980 to 2005 week 09 Searched 1 March 2005	1 exp glioma/ or exp astrocytoma/ or ependymoma/ or oligodendroglioma/ (27235) 2 exp Glioblastoma/ (7920) 3 (glioblastoma mulitforme or GBM).tw. (2191) 4 ((grade$ 4 or four or IV) adj3 (glioma$ or astrocytoma$ or AA)).tw. (1038) 5 ((grade$ 3 or three or III) adj3 (glioma$ or astrocytoma$ or AA)).tw. (1583) 6 1 or 2 or 3 or 4 or 5 (29652) 7 (carmustine adj10 implant$).mp. (62) 8 Gliadel$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (94) 9 exp Carmustine/ (9393) 10 exp biodegradable implant/ (692) 11 exp Drug Implant/ (842) 12 10 or 11 (1521) 13 9 and (10 or 11) (28) 14 7 or 8 or 12 or 13 (1646) 15 6 and 14 (96) 16 temozolomide.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (1296) 17 temoda$.mp. (154) 18 exp Temozolomide/ (1280) 19 16 or 17 or 18 (1297) 20 6 and 19 (528) 21 15 (96) 22 limit 21 to (human and english language) (66) 23 20 (528) 24 limit 23 to (human and english language) (447)	66 BCNU-W 447 TMZ
DARE Searched 1 March 2005	As MEDLINE	1 TMZ
NHS EED (in Cochrane Library) Searched 1 March 2005	As MEDLINE	1 BCNU-W 1 TMZ
HTA database (in Cochrane Library)	As MEDLINE	2 BCNU-W 3 TMZ
	Total refs sent in first batch 1 March 2005 Total Gliadel refs Total Temozolomide refs (11 refs keyworded both terms)	638 Total 148 BCNUW 501 TMZ
ISI Web of Science SCI 1981–present Limited to English Searched 31 March 2005	#1 TS=(carmustine SAME implant*) 23 #2 TS=(carmustine) 878 #3 TS=(gliadel) 23 #4 TS=(implant* or wafer*) 100,000 #5 #2 and #4 39 #6 #1 or #3 or #5 59 #7 TS=(glioma* or glioblastoma* or GBM or astrocytoma*) 29,875 #8 #7 and #6 43 #9 TS=(temozolomide or temoda*) 711 #10 #11 and #13 310	43 BCNU-W 310 TMZ

continued

Databases and years searched	Search files	No. of hits
ISI Proceedings 1990–2005 Limited to English	Above strategy run	5 BCNU-W 53 TMZ
Total refs – clinical effectiveness = 799 **Of which carmustine implants = 173** **Temozolomide = 639** **(13 refs keyworded both carmustine implants and temozolomide)**		
NRR 2005/Issue 1 Searched 31 March 2005	#1 gliadel 0 #2 (implant* or wafer*) 1234 #3 carmustine 12 #4 glioma* or glioblastoma* or GBM or astrocytoma* 297 #5 #2 and #3 3 #6 #5 and #4 3 #7 temozolomide or temoda* 121 #8 #7 and #4 66	3 BCNU-W 66 TMZ

Quality of life searches for glioma

Databases and years searched		Search files	No. of hits
MEDLINE (Ovid) 1966 to March week 4 2005 Searched 6 April 2005 Update searches 25 August 2005	1	value of life/	4400
	2	quality adjusted life year/	2081
	3	quality adjusted life.ti,ab.	1435
	4	(qaly$ or qald$ or qale$ or qtime$).ti,ab.	1114
	5	disability adjusted life.ti,ab.	247
	6	daly$.ti,ab.	324
	7	health status indicators/	8958
	8	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.	4169
	9	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.	608
	10	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.	467
	11	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.	21
	12	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab.	249
	13	(euroqol or euro qol or eq5d or eq 5d).ti,ab.	563
	14	(hql or hqol or h qol or hrqol or hr qol).ti,ab.	1322
	15	(hye or hyes).ti,ab.	44
	16	health$ year$ equivalent$.ti,ab.	30
	17	health utilit$.ab.	263
	18	(hui or hui1 or hui2 or hui3).ti,ab.	294
	19	disutil$.ti,ab.	52
	20	rosser.ti,ab.	53
	21	quality of well being.ti,ab.	495
	22	quality of wellbeing.ti,ab.	2
	23	qwb.ti,ab.	94
	24	willingness to pay.ti,ab.	558
	25	standard gamble$.ti,ab.	336
	26	time trade off.ti,ab.	287
	27	time tradeoff.ti,ab.	104
	28	tto.ti,ab.	187
	29	(index adj2 well being).mp.	1296

continued

Database and years searched	Search files	No. of hits
	30 (quality adj2 well being).mp.	2537
	31 (health adj3 utilit$ ind$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	191
	32 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	125
	33 quality adjusted life year$.mp.	2699
	34 (15D or 15 dimension$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	386
	35 (12D or 12 dimension$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	163
	36 rating scale$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	43228
	37 linear scal$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	237
	38 linear analog$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	604
	39 visual analog$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	11132
	40 (categor$ adj2 scal$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	767
	41 or/1-40	80570
	42 (letter or editorial or comment).pt.	726307
	43 41 not 42	78150
	44 exp glioma/ or exp astrocytoma/ or ependymoma/ or oligodendroglioma/	34869
	45 exp Glioblastoma/	7426
	46 (glioblastoma mulitforme or GBM).tw.	2544
	47 ((grade$ 4 or four or IV) adj3 (glioma$ or astrocytoma$ or AA)).tw.	1169
	48 ((grade$ 3 or three or III) adj3 (glioma$ or astrocytoma$ or AA)).tw.	1762
	49 44 or 45 or 46 or 47 or 48	37686
	50 49 and 43	49
	51 limit 50 to english language	44
EMBASE 1980 to 2005 week 14 Searched 6 April 2005	1 quality adjusted life year/	1864
	2 quality adjusted life.ti,ab.	1402
	3 (qaly$ or qald$ or qale$ or qtime$).ti,ab.	1052
	4 disability adjusted life.ti,ab.	230
	5 daly$.ti,ab.	272
	6 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.	4090
	7 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.	711
	8 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.	452
	9 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.	22
	10 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab.	168
	11 (euroqol or euro qol or eq5d or eq 5d).ti,ab.	567
	12 (hql or hqol or h qol or hrqol or hr qol).ti,ab.	1287
	13 (hye or hyes).ti,ab.	25
	14 health$ year$ equivalent$.ti,ab.	21
	15 health utilit$.ab.	250
	16 (hui or hui1 or hui2 or hui3).ti,ab.	218
	17 disutil$.ti,ab.	57
	18 rosser.ti,ab.	43
	19 quality of well being.ti,ab.	459

continued

Database and years searched	Search files	No. of hits
	20 quality of wellbeing.ti,ab.	5
	21 qwb.ti,ab.	83
	22 willingness to pay.ti,ab.	556
	23 standard gamble$.ti,ab.	312
	24 time trade off.ti,ab.	282
	25 time tradeoff.ti,ab.	99
	26 tto.ti,ab.	199
	27 (index adj2 well being).mp.	1193
	28 (quality adj2 well being).mp.	2362
	29 (health adj3 utilit$ ind$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]	184
	30 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]	122
	31 quality adjusted life year$.mp.	2391
	32 (15D or 15 dimension$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]	416
	33 (12D or 12 dimension$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]	153
	34 rating scale$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]	39919
	35 linear scal$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]	217
	36 linear analog$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]	597
	37 visual analog$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]	12473
	38 (categor$ adj2 scal$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]	688
	39 or/1-38	64407
	40 (letter or editorial or comment).pt.	421224
	41 39 not 40	62938
	42 (cost$ adj2 effective$).ti,ab.	30903
	43 (cost$ adj2 benefit$).ti,ab.	7728
	44 cost effectiveness analysis/	37315
	45 cost benefit analysis/	20211
	46 budget$.ti,ab.	6692
	47 cost$.ti.	29289
	48 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.	34609
	49 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti.	11341
	50 (price$ or pricing$).ti,ab. (8304	
	51 (financial or finance or finances or financed).ti,ab.	17194
	52 (fee or fees).ti,ab.	4045
	53 cost/	17295
	54 cost minimization analysis/	774
	55 cost of illness/	2407
	56 cost utility analysis/	1288
	57 drug cost/	23100
	58 health care cost/	40670
	59 health economics/	7336
	60 economic evaluation/	2421
	61 economics/	4588
	62 pharmacoeconomics/	828
	63 budget/	5706
	64 economic burden.ti,ab.	975

continued

Database and years searched	Search files		No. of hits
	65	"resource use".ti,ab.	16316
	66	or/42-65	186180
	67	(editorial or letter).pt.	421224
	68	66 not 67	168102
	69	exp glioma/ or exp astrocytoma/ or ependymoma/ or oligodendroglioma/	27431
	70	exp Glioblastoma/	7990
	71	(glioblastoma mulitforme or GBM).tw.	2199
	72	((grade$ 4 or four or IV) adj3 (glioma$ or astrocytoma$ or AA)).tw.	1044
	73	((grade$ 3 or three or III) adj3 (glioma$ or astrocytoma$ or AA)).tw.	1594
	74	69 or 70 or 71 or 72 or 73	29860
	75	74 and 68	140
	76	limit 75 to english language	131
PREMEDLINE (Ovid) MEDLINE in-process and other non-indexed citations to April, 2005 Searched 6 April 2005	1	(glioma$ or astrocytoma$ or glioblastoma$).mp. [mp=title, original title, abstract, name of substance word]	547
	2	quality adjusted life.ti,ab.	71
	3	(qaly$ or qald$ or qale$ or qtime$).ti,ab.	65
	4	disability adjusted life.ti,ab.	17
	5	daly$.ti,ab.	16
	6	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.	281
	7	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.	38
	8	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.	42
	9	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.	1
	10	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab.	4
	11	(euroqol or euro qol or eq5d or eq 5d).ti,ab.	52
	12	(hql or hqol or h qol or hrqol or hr qol).ti,ab.	103
	13	(hye or hyes).ti,ab.	0
	14	health$ year$ equivalent$.ti,ab.	0
	15	health utilit$.ab.	14
	16	(hui or hui1 or hui2 or hui3).ti,ab.	19
	17	disutil$.ti,ab.	0
	18	rosser.ti,ab.	1
	19	quality of well being.ti,ab.	22
	20	quality of wellbeing.ti,ab.	0
	21	qwb.ti,ab.	1
	22	willingness to pay.ti,ab.	43
	23	standard gamble$.ti,ab.	19
	24	time trade off.ti,ab.	9
	25	time tradeoff.ti,ab.	5
	26	tto.ti,ab.	10
	27	(index adj2 well being).mp.	42
	28	(quality adj2 well being).mp.	118
	29	(health adj3 utilit$ ind$).mp. [mp=title, original title, abstract, name of substance word]	13
	30	((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. [mp=title, original title, abstract, name of substance word]	2
	31	quality adjusted life year$.mp.	68
	32	(15D or 15 dimension$).mp. [mp=title, original title, abstract, name of substance word]	32
	33	(12D or 12 dimension$).mp. [mp=title, original title, abstract, name of substance word]	10

continued

Database and years searched	Search files	No. of hits
	34 rating scale$.mp. [mp=title, original title, abstract, name of substance word]	460
	35 linear scal$.mp. [mp=title, original title, abstract, name of substance word]	64
	36 linear analog$.mp. [mp=title, original title, abstract, name of substance word]	16
	37 visual analog$.mp. [mp=title, original title, abstract, name of substance word]	513
	38 (categor$ adj2 scal$).mp. [mp=title, original title, abstract, name of substance word]	36
	39 or/2-38	1823
	40 (letter or editorial or comment).pt.	15754
	41 39 not 40	1812
	42 41 and 1	1

Cost-effectiveness searches

Databases and years searched	Search files	No. of hits
MEDLINE (Ovid) 1966 to March week 4 2005 Saved as med-glioma-costs Searched 1 April 2005	Above MEDLINE strategy run with cost-effectiveness filter 25 exp ECONOMICS/ (330031) 26 exp ECONOMICS, HOSPITAL/ (13193) 27 exp ECONOMICS, PHARMACEUTICAL/ (1442) 28 exp ECONOMICS, NURSING/ (3633) 29 exp ECONOMICS, DENTAL/ (3254) 30 exp ECONOMICS, MEDICAL/ (9597) 31 exp "Costs and Cost Analysis"/ (114053) 32 VALUE OF LIFE/ (4400) 33 exp MODELS, ECONOMIC/ (4087) 34 exp FEES/ and CHARGES/ (6592) 35 exp BUDGETS/ (8674) 36 (economic$ or price$ or pricing or pharmacoeconomic$ or pharma economic$).tw. (71633) 37 (cost$ or costly or costing$ or costed).tw. (157200) 38 (cost$ adj2 (benefit$ or utilit$ or minim$)).tw. (11450) 39 (expenditure$ not energy).tw. (8773) 40 (value adj2 (money or monetary)).tw. (507) 41 budget$.tw. (9087) 42 (economic adj2 burden).tw. (1036) 43 "resource use".ti,ab. (20338) 44 or/25-43 (481027) 45 letter.pt. (522379) 46 editorial.pt. (170387) 47 comment.pt. (266642) 48 or/45-47 (726307) 49 44 not 48 (451051) 50 49 and 22 (0) GLIADEL 51 49 and 24 (8) 52 from 51 keep 1-8 (8) TEMOZOLOMIDE	8 TMZ
EMBASE 1980 to 2005 week 13 Searched 1 April 2005 Saved as emb-glioma-costs	1 (cost$ adj2 effective$).ti,ab. (30874) 2 (cost$ adj2 benefit$).ti,ab. (7725) 3 cost-effectiveness analysis/ (37265) 4 cost benefit analysis/ (20188) 5 budget$.ti,ab. (6688)	1 Gliadel 17 TMZ

continued

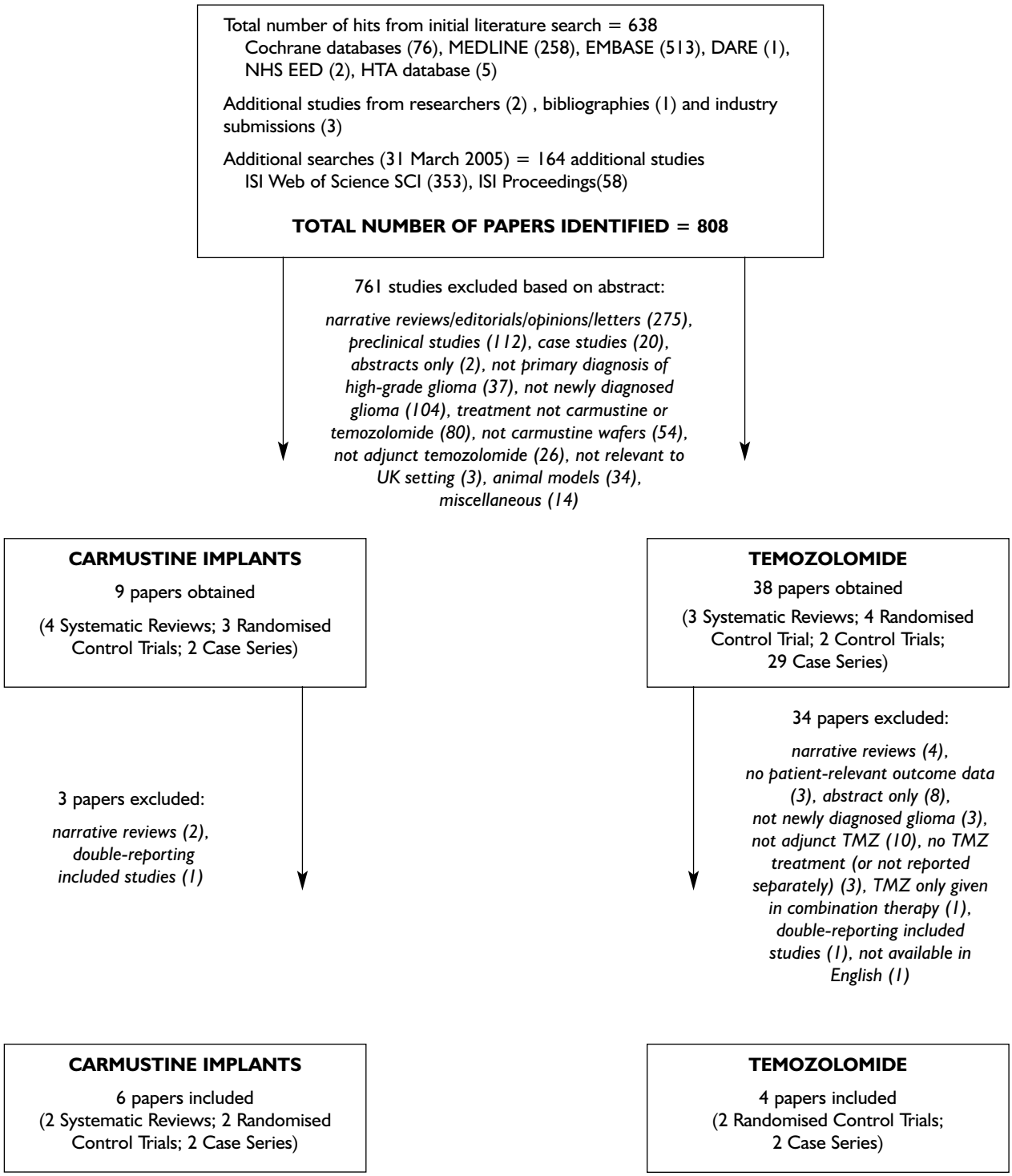
Databases and years searched	Search files	No. of hits
	6 cost$.ti. (29268) 7 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab. (34581) 8 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti. (11337) 9 (price$ or pricing$).ti,ab. (8297) 10 (financial or finance or finances or financed).ti,ab. (17184) 11 (fee or fees).ti,ab. (4039) 12 cost/ (17291) 13 cost minimization analysis/ (772) 14 cost of illness/ (2403) 15 cost utility analysis/ (1287) 16 drug cost/ (23072) 17 health care cost/ (40615) 18 health economics/ (7323) 19 economic evaluation/ (2417) 20 economics/ (4585) 21 pharmacoeconomics/ (828) 22 budget/ (5693) 23 economic burden.ti,ab. (973) 24 "resource use".ti,ab. (16297) 25 or/1-24 (185994) 26 (editorial or letter).pt. (420726) 27 25 not 26 (167940) Run with Embase search for clinical effectiveness 48 42 and 27 (1) 49 47 and 27 (21) 50 limit 49 to english language (17) 51 from 48 keep 1 (1) 52 from 50 keep 1-17 (17)	
PREMEDLINE	1 (economic$ or price$ or pricing or pharmacoeconomic$ or pharma economic$).tw. (2482) 2 (cost$ or costly or costing$ or costed).tw. (4889) 3 (cost$ adj2 (benefit$ or utilit$ or minim$)).tw. (342) 4 (expenditure$ not energy).tw. (218) 5 (value adj2 (money or monetary)).tw. (16) 6 budget$.tw. (317) 7 (economic adj2 burden).tw. (75) 8 "resource use".ti,ab. (1002) 9 letter.pt. (7539) 10 editorial.pt. (4280) 11 comment.pt. (7907) 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (7827) 13 or/9-11 (15754) 14 12 not 13 (7671) 15 (glioma$ or astrocytoma$ or glioblastoma$).mp. [mp=title, original title, abstract, name of substance word] (547) 16 (glioblastoma mulitforme or GBM).tw. (47) 17 ((grade$ 4 or four or IV) adj3 (glioma$ or astrocytoma$ or AA)).tw. (26) 18 ((grade$ 3 or three or III) adj3 (glioma$ or astrocytoma$ or AA)).tw. (48) 19 15 or 16 or 17 or 18 (596) 20 (carmustine adj10 implant$).mp. (1) 21 Gliadel$.mp. [mp=title, original title, abstract, name of substance word] (0) 22 20 or 21 (1) 23 19 and 22 (1) 24 14 and 23 (0)	0 Gliadel 0 TMZ

continued

Databases and years searched	Search files	No. of hits
	25 temozolomide.mp. [mp=title, original title, abstract, name of substance word] (34) 26 temoda$.mp. (0) 27 25 or 26 (34) 28 19 and 27 and 14 (0)	
Cochrane Library 2005/Issue 1	MEDLINE search strategy run	2 Gliadel Central 1 TMZ Central 1 TMZ DARE 2 TMZ HTA 2 Gliadel HTA 1 Gliadel NHS EED 1 TMZ NHS EED
EconLIT	(glioma* or astrocytoma* or glioblastoma*) and gliadel or carmustine implant* glioma* or astrocytoma* or glioblastoma*) and temozolomide	0
Total glioma costs database keyworded cost-effectiveness		27

Appendix 5

Identification, retrieval and inclusion/exclusion of studies



Appendix 6

Studies excluded at full-text stage

Temozolomide

Reference	(Type)	Abstract	Reason for exclusion
Athanassiou H, Synodinou M, Maragoudakis E, Paraskevaidis M, Verigos C, Misailidou D, *et al.* Combination of temozolomide (TMZ) and radiotherapy (RT) versus radiotherapy (RT) alone in newly diagnosed glioblastoma multiforme (GBM) – A randomized phase II study. *Int J Radiat Oncol Biol Phys* 2004;**60**:56	(RCT)	–	Abstract only
Brandes AA, Vastola F, Basso U, Berti F, Pinna G, Rotilio A, *et al.* A prospective study on glioblastoma in the elderly. *Cancer* 2003;**97**:657–62	(CT)	BACKGROUND – Elderly patients (age >65 years) with GBM frequently are excluded from clinical studies and prospective trials for patients with this age group do not exist to date. METHODS – The authors conducted a prospective trial in 79 consecutive elderly patients with glioblastoma who underwent surgery and received RT (59.44 Gy in 33 fractions; Group A; $n = 24$ patients) or received the same RT plus adjuvant chemotherapy with PCV (lomustine 110 mg/m^2 on day 1, procarbazine 60 mg/m^2 on days 8–21 and vincristine 1.4 mg/m^2 on days 8 and 29 every 42 days; Group B; $n = 32$ patients), or received the same RT plus adjuvant TMZ (150 mg/m^2 for 5 days every 28 days; Group C; $n = 22$ patients). RESULTS – The median time to disease progression (TTP) and median survival (MST) were 7.2 months (95% CI 6.34 to 8.64) and 12.5 months (95% CI, 11.6 to 14.8), respectively. The TTP was significantly better for Group C than Groups A and B (10.7 versus 5.3 and 6.9 months, respectively; $p = 0.0002$). KPS ($p < 0.001$) and TMZ ($p < 0.001$) were the only independent prognostic factors. Overall survival was better in Group C than Group A (14.9 versus 11.2 months; $p = 0.002$), but there were no statistical differences found between Groups A and B or between Groups B and C. Only KPS ($p < 0.001$) was predictive of overall survival, even if TMZ chemotherapy was very close to the significance level ($p = 0.058$). Hematological grade 3–4 toxicity was higher with the PCV than the TMZ chemotherapy regimen. CONCLUSIONS – Age alone should not preclude appropriate treatment in elderly patients with good performance status, for whom definitive RT and adjuvant chemotherapy with TMZ is advised. Copyright 2003 American Cancer Society	TMZ not given as an adjunct to RT (only given as adjuvant treatment)

continued

Reference	(Type)	Abstract	Reason for exclusion
Broniscer A, Iacono L, Chintagumpala M, Fouladi M, Wallace D, Bowers DC, *et al.* Role of temozolomide after radiotherapy for newly diagnosed diffuse brainstem glioma in children – results of a multiinstitutional study (SJHG-98). *Cancer* 2005;**103**:133–39	(CS)	BACKGROUND – The role of chemotherapy in the treatment of children with newly diagnosed diffuse brainstem glioma is uncertain. The authors tested the efficacy of TMZ treatment after RT in this setting. METHODS – Patients ages 3–21 years were eligible for the current multi-institutional study. An optional window therapy regimen consisting of 2 cycles of intravenous irinotecan (10 doses of 20 mg/m^2 per day separated by 2 days of rest per cycle) was delivered over 6 weeks and was followed by conventionally fractionated RT. The 5-day schedule of TMZ (200 mg/m^2 per day) was initiated 4 weeks after RT and was continued for a total of 6 cycles. The pharmacokinetics of TMZ and its active metabolite, 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC), were analysed during cycles 1 and 3. RESULTS – 33 patients (median age at diagnosis, 6.4 years) were enrolled. Of the 16 patients who received window therapy, 6 had irinotecan treatment discontinued owing to clinical progression (n = 5) or toxicity (n = 1); the remaining 10 experienced disease stabilisation after 2 cycles. All patients completed RT (median dose, 55.8 Gy). 29 patients received a combined total of 125 cycles of TMZ. Grade III/IV neutropenia and thrombocytopenia occurred in 33 and 29% of all TMZ cycles, respectively. In approximately one-third of the cycles, dose reduction was required owing to myelosuppression. No correlation was demonstrated between TMZ/MTIC exposure and myelosuppression at the conclusion of cycle 1. All patients died of disease progression (median survival, 12 months). The estimated 1-year survival rate was 48% (standard error, 8%). CONCLUSIONS – The administration of TMZ after RT did not alter the poor prognosis associated with newly diagnosed diffuse brainstem glioma in children	TMZ not given as an adjunct to surgery (no surgery in most cases) and RT (only given as adjuvant treatment following RT)
Bucci MK, Maity A, Janss AJ, Belasco JB, Fisher MJ, Tochner ZA, *et al.* Near complete surgical resection predicts a favorable outcome in pediatric patients with nonbrainstem, malignant gliomas – results from a single center in the magnetic resonance imaging era. *Cancer* 2004;**101**:817–24	(CS)	BACKGROUND – Because few reports on outcome in patients with paediatric malignant gliomas during the MRI era were available, the authors studied the outcomes of children with these tumours at their institution. METHODS – The medical records of 39 patients with non-brainstem malignant gliomas who were treated at the Hospital of the University of Pennsylvania/Children's Hospital of Philadelphia between 1 February 1989 and 31 December, 2000 were reviewed retrospectively. MRI was used to assess tumors at presentation and at follow-up. PFS and overall survival (OS) were determined using the Kaplan–Meier method. Univariate and multivariate analyses were performed using a Cox proportional hazards model. RESULTS – The median follow-up for the 14 surviving patients was 47.6 months. The median PFS for all patients was 12.2 months and the median OS for all patients was 21.3 months. The extent of surgery was the strongest prognostic factor for predicting outcomes in these patients, with a median survival of 122.2 months in patients who underwent macroscopic total resection compared with 14.1 months in patients who had significant residual disease after surgery. In univariate analyses, other than the extent of surgery, only the absence of visual symptoms at diagnosis significantly predicted improved OS. Local control was improved for patients who underwent better resection and had smaller tumors. In multivariate analyses, although the extent of surgery continued to predict outcomes significantly, histological grade, which was not significant in the univariate analysis, also was significant. CONCLUSIONS – Children with malignant gliomas appeared to fare better than their adult counterparts. Because the extent of resection was one of the strongest predictors of outcome, the authors concluded that the optimal therapy for these patients would include the maximal possible resection. Copyright 2004 American Cancer Society	Data for patients who received TMZ not reported separately

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Reference	(Type)	Abstract	Reason for exclusion
Chang SM, Lamborn KR, Malec M, Larson D, Wara W, Sneed P, *et al.* Phase II study of temozolomide and thalidomide with radiation therapy for newly diagnosed glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 2004;**60**:353–7	(CS)	PURPOSE – The chemotherapeutic agent TMZ and the antiangiogenic agent thalidomide have both demonstrated antitumour activity in patients with recurrent malignant glioma. The objectives of this study were to determine if the combined strategy of these oral agents with RT is associated with an improved median survival of patients with newly diagnosed GBM and to evaluate toxicity. METHODS AND MATERIALS – 67 patients were enrolled in this trial. RT parameters were a total dose of 60 Gy delivered in 2-Gy fractions over 6 weeks. TMZ was administered starting the first day of RT at 150 mg/m^2 daily for 5 days every 4 weeks for the first cycle and escalated to a maximum dose of 200 mg/m^2. Thalidomide was started on day 7 of RT at 200 mg and escalated by 100–200 mg every 1–2 weeks depending on patient tolerance, to a maximum of 1200 mg daily. RESULTS – 61 patients progressed, with a median time to progression of 22 weeks. 56 patients died, and the median survival was 73 weeks. CONCLUSIONS – This strategy of combination TMZ, thalidomide and RT was relatively well tolerated with favourable survival outcome for patients with GM when compared with patients not treated with adjuvant chemotherapy and similar to those who received nitrosourea adjuvant chemotherapy. It is unclear the added advantage thalidomide has in combination with TMZ for this patient population	TMZ only administered in combination therapy
Chang SM, Seiferheld W, Curran W, Share R, Atkins J, Choucair A, *et al.* Phase I study pilot arms of radiotherapy and carmustine with temozolomide for anaplastic astrocytoma (Radiation Therapy Oncology Group 9813) – implications for studies testing initial treatment of brain tumors. *Int J Radiat Oncol Biol Phys* 2004;**59**:1122–6	(CS)	PURPOSE – To determine the safety and toxicity of carmustine (BCNU) and TMZ with RT in newly diagnosed AA. METHODS AND MATERIALS – Patients >18 years old with AA, a KPS score of ⩾60, and adequate pulmonary function were eligible. All patients provided informed consent. Standard RT started within 5 weeks of diagnosis. In both arms, 150 mg/m^2 of TMZ were given on days 1–5 of RT. In Arm 1, 200 mg/m^2 of BCNU were given on day 1 of RT. In Arm 2, 150 mg/m^2 of BCNU were given on day 5 of RT. After RT, TMZ and BCNU were repeated for a total of six cycles. RESULTS – A total of 15 and 14 patients were enrolled in the two pilot arms. Because of hematological and pulmonary toxicities, dose reductions by the second cycle of therapy occurred in >70% of the patients in Arm 1 and >50% in Arm 2 despite a reduction in the BCNU dose. CONCLUSION – The results of these pilot studies have implications for the design of studies testing the initial treatment of brain tumors. Because of the poor tolerance of the combination, the multicooperative group Phase 3 study consists of two randomized arms of single-agent BCNU vs single-agent TMZ	No relevant outcome data reported

continued

Reference	(Type)	Abstract	Reason for exclusion
Chibbaro S, Benvenuti L, Caprio A, Carnesecchi S, Pulera F, Faggionato F, *et al.* Temozolomide as first-line agent in treating high-grade gliomas – phase II study. *J Neurooncol* 2004;**67**:77–81	(CS)	TMZ, a recent, oral, second-generation alkylating agent, is a chemotherapeutic with demonstrated efficacy for the treatment of high-grade gliomas; its efficacy has been demonstrated in both preclinical and Phase 1 and 2 studies. The goal of this study is to determine the activity and safety of TMZ in improving overall survival (OS), PFS and health-related quality of life (HRQoL) in patients with malignant gliomas. 42 patients with newly diagnosed glioblastoma, AA and AO were studied. The mean follow-up period was 12 months. The overall response rate (only responsive patient) for all histological groups was 40%, 10 patients (24%) showed a stabilisation of disease. The median PFS and OS was respectively 8.35 and 14.1 months – time to progression was 34 weeks, ranging from 21 to 47 weeks. In all patients, treatment with TMZ was associated with improvement of performance status including the patient showing disease progression – KPS improved in all patients by a minimum of 10, with a median of 20 at 6 months. No patient stopped the treatment owing to side-effects; no major adverse events were recorded. CONCLUSION – TMZ appears to be an ideal, first-line, single agent, with a safe profile and demonstrated HRQoL benefits in patients with high-grade gliomas	Outcomes not reported separately for patients who had radiotherapy
Combs SE, Gutwein S, Schulz-Ertner D, Van Kampen M, Wannenmacher M, Thilmann C, *et al.* Phase I/II-study of temozolomide combined with radiation as postoperative treatment in primary glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 2004;**60**:1003	(CS)	–	Abstract only
Connolly ES. Prospective controlled trial of temozolomide and PCV in the elderly with glioblastoma. *Neurosurgery* 2003;**52**:U19	(CT)	–	News item; no original information

continued

Reference	(Type)	Abstract	Reason for exclusion
Corsa P. A preliminary retrospective study with temozolomide and radiotherapy versus radiotherapy alone for the treatment of high-grade gliomas. *Int J Radiat Oncol Biol Phys* 2003;**57**:S378	(CS)	–	Abstract only; outcomes for patients who underwent both concomitant and adjuvant TMZ not reported separately; insufficient detail to appraise quality of study
Engelhard HH, Stelea A, Mundt A. Oligodendroglioma and anaplastic oligodendroglioma – clinical features, treatment, and prognosis. [Review; 111 refs]. *Surg Neurol* 2003;**60**:443–56	(SR)	BACKGROUND – Recent advances that have been made in diagnostic imaging, surgical technique, chemotherapy, molecular biology and prediction of therapeutic response could have potential impact on the optimal diagnosis and treatment of patients with brain tumours, especially those with oligodendrogliomas. The topic of oligodendroglioma and AO is reviewed, highlighting the new clinical developments. METHODS – Information for this review was obtained by performing a MEDLINE search for recent references using the term 'oligodendroglioma'. The bibliographies of papers obtained also were checked for articles that could provide additional understanding of this disease and its current treatment. RESULTS – The incidence of oligodendroglioma is increasing, most likely owing to its improved recognition. Seizures and/or headaches are still common presenting features and surgery continues to be the primary treatment. Positron emission tomography (PET) and molecular analysis of the surgical specimen are emerging as important diagnostic tools. Patients having either oligodendroglioma or AO are likely to respond to chemotherapy. This has had an impact upon the timing of RT. Survival times are increasing and patients can now be divided into prognostic subgroups based on the molecular features of their tumours. While PCV chemotherapy has been the standard, other agents, notably TMZ, are currently being tested. CONCLUSIONS – The algorithm for diagnosing and treating patients with oligodendrogliomas has changed. Neurosurgeons need to be aware of the new developments so they can offer sound advice to their patients	Insufficient reporting of review methods, and superseded by more recent publications

continued

Reference	(Type)	Abstract	Reason for exclusion
Fazeny-Dorner B, Gyries A, Rossler K, Ungersbock K, Czech T, Budinsky A, *et al.* Survival improvement in patients with glioblastoma multiforme during the last 20 years in a single tertiary-care center. *Wien Klin Wochenschr* 2003;**115**:389–97	(CS)	METHODOLOGY – The survival of 357 consecutive patients with newly diagnosed GBM in three treatment groups reflecting different periods of diagnosis (A, 1982–4; B, 1994–5; C, 1996–8) was analysed to assess the impact and the potential improvement of changing treatment strategies in our tertiary-care center. PATIENTS AND METHODS – Group A (n = 100) included all consecutive patients diagnosed from 1982 to 1984 and served as the historical control. Group B (n = 93) included all consecutive patients diagnosed in 1994/1995 and group C (n = 164) those diagnosed from 1996 to 1998. Survival in the three treatment groups (A vs B vs C) was analysed according to treatment given after neurosurgical intervention (i.e. no specific therapy versus RT versus combined RT/chemotherapy), and according to first-line chemotherapy, age (<40, 40–60, >60), sex and tumour location (hemispheric versus bilateral or multifocal tumours, and tumours involving eloquent brain areas). Survival was analysed using Kaplan–Meier's non-parametric method. A p-value <0.05 was considered statistically significant. RESULTS – Patients in groups A and B received RT and/or chemotherapy to a varying extent (RT, group A 22%, group B 62%; chemotherapy, group A 6%, group B 33%). Chemotherapy was administered after termination of RT in both groups. In group C, 96% of patients received combined RT/chemotherapy, which was administered concomitantly and started within 3 weeks after surgery. Median survival was 5.2 months in group A, 5.1 months in group B and 14.5 months in C ($p < 0.0001$). Nine patients in group A (9%), 9 in group B (10%) and 40 in group C (25%) survived more than 18 months ($p < 0.05$). CONCLUSIONS – Survival improvement in group C might be attributable to the early start of combined RT/chemotherapy. Therapy was administered on a complete outpatient basis, enabled by a dedicated interdisciplinary neuro-oncological team caring for group C. Toxicity was mild and patients' acceptance excellent	TMZ not given as first-line chemotherapy (only given as second-line treatment in patients with progressive disease)
Friedman HS, McLendon RE, Kerby T, Dugan M, Bigner SH, Henry AJ, *et al.* DNA mismatch repair and O^6-alkylguanine-DNA alkyltransferase analysis and response to Temodal in newly diagnosed malignant glioma. *J Clin Oncol* 1998;**16**:3851–7	(CS)	PURPOSE – We evaluated the response to Temodal (Schering-Plough Research Institute, Kenilworth, NJ) of patients with newly diagnosed malignant glioma, as well as the predictive value of quantifying tumour DNA mismatch repair activity and O^6-alkylguanine-DNA alkyltransferase (AGT). PATIENTS AND METHODS – 33 patients with newly diagnosed GBM and five patients with newly diagnosed AA were treated with Temodal at a starting dose of 200 mg/m^2 daily for 5 consecutive days with repeat dosing every 28 days after the first daily dose. Immunochemistry for the detection of the human DNA mismatch repair proteins MSH2 and MLH1 and the DNA repair protein AGT was performed with monoclonal antibodies and characterised with respect to percent positive staining. RESULTS – Of the 33 patients with GBM, complete responses (CRs) occurred in 3, partial responses (PRs) in 14, stable disease (SD) in 4, and progressive disease (PD) in 12 patients. Toxicity included infrequent grades 3 and 4 myelosuppression, constipation, nausea and headache. 30 tumors showed >60% cells that stained for MSH2 and MLH1, with 3 CRs, 12 PRs, 3 SDs, and 12 PDs. Eight tumors showed ⩽60% cells that stained with antibodies to MSH2 and/or MLH1, with 3 PRs, 3 SDs and 2 PDs. 11 tumours showed ⩾20% cells that stained with an antibody to AGT, with 1 PR, 2 SDs and 8 PDs. 25 tumours showed <20% cells that stained for AGT, with 3 CRs, 12 PRs, 4 SDs and 6 PDs. CONCLUSION – These results suggest that Temodal has activity against newly diagnosed GBM and AA and warrants continued evaluation of this agent. Furthermore, pretherapy analysis of tumour DNA mismatch repair and, particularly, AGT protein expression may identify patients in whom tumours are resistant to Temodal	No relevant outcomes reported

continued

Reference	(Type)	Abstract	Reason for exclusion
Jakacki R, Prados M, Yates A, Timmerman R, Krailo M, Qu WC, *et al.* A phase I trial of temozolomide and CCNU in pediatric patients with newly diagnosed incompletely resected nonbrainstem high-grade gliomas (HGG) – A children's oncology group study. *Neuro-oncol* 2004;**6**:459	(CS)	–	Abstract only
Loh KC, Willert J, Meltzer H, Roberts W, Kerlin B, Spear MA, *et al.* Temozolomide and radiation for aggressive pediatric central nervous system malignancies. *J Pediatr Hematol Oncol* 2005;**27**:254–8	(CS)	This study describes the outcomes of children treated with combinations of TMZ and RT for various aggressive central nervous system malignancies. Their age at diagnosis ranged from 1 to 15 years. Patients with focal disease were treated with concomitant TMZ (daily 75 mg/m^2) and three-dimensional conformal radiotherapy in a dose that ranged from 50 to 54 Gy, followed by TMZ (200 mg/m^2/d $\times$ 5 days/month in three patients, 150 mg/m^2 $\times$ 5 days/month in one patient). Patients with disseminated disease were treated with craniospinal radiation (39.6 Gy) before conformal boost. One patient received temozolomide (200 mg/m^2 $\times$ 5 days/month) before craniospinal radiation, and one patient received temozolomide (daily 95 mg/m^2) concomitant with craniospinal radiation and a radiosurgical boost, followed by TMZ (200 mg/m^2 $\times$ 5 days/month). Three patients achieved a partial response during treatment, with two of these patients dying of progressive disease after treatment. One patient has no evidence of disease. Three patients achieved stable disease, with one of these patients dying of progressive disease after treatment. Toxicities observed included low-grade neutropenia, thrombocytopenia and lymphopenia. The combination of TMZ and RT appears to be well tolerated in a variety of treatment schemas for aggressive paediatric central nervous system malignancies. This information is of particular use in designing future studies, given the recent positive results in a randomised study examining the use of TMZ concomitant with radiation in the treatment of adult glioblastoma	Case series featuring only one child with pathology under review
Mahaley MS Jr, Whaley RA, Krigman MR, Bouldin TW, Bertsch L, Cush S. Randomized phase III trial of single versus multiple chemotherapeutic treatment following surgery and during radiotherapy for patients with anaplastic gliomas. *Surg Neurol* 1987;**27**:430–2	(CS)	In 81 patients with anaplastic supratentorial gliomas, single versus multiple chemotherapeutic agents were selected for treatment following surgery and during RT in a prospective randomised study. Time to treatment failure and survival were not significantly enhanced by multiple agent chemotherapy, as administered in this study	TMZ not used

continued

Reference	(Type)	Abstract	Reason for exclusion
Micke O, Schafer U, Schuller P, Schul C, Willich N. Temozolomide and concurrent radiotherapy in patients with glioblastoma multiforme – First results of a phase II trial. *Strahlenther Onkol* 2004;**180**:36	(CS)	–	Not available in English
Mirimanoff R, Mason W, Kortmann R, Van den Bent M, Fisher B, Taphoorn M, *et al.* Radiotherapy (RT) and concomitant and adjuvant temozolomide (TMZ) versus radiotherapy alone for newly diagnosed glioblastoma (GBM) – Overall results and recursive partitioning analysis (RPA) of a phase III randomized trial of the EORTC brain tumor and radiotherapy groups and the NCIC clinical trial group. *Int J Radiat Oncol Biol Phys* 2004;**60**:55	(RCT)	This reports data from the same trial as the included paper by Stupp *et al.*	Abstract only
Newlands ES, Blackledge GR, Slack JA, Rustin GJ, Smith DB, Stuart NS, *et al.* Phase I trial of temozolomide (CCRG 81045 – M&B 39831 – NSC 362856). *Br J Cancer* 1992;**65**:287–91	(CS)	TMZ (CCRG 81045 – M&B 39831 – NSC 362856) is an analogue of mitozolomide displaying similar broad-spectrum activity in mouse tumours, but showing considerably less myelosuppression in the toxicology screen. TMZ was initially studied intravenously at doses between 50 and 200 mg m^{-2} and subsequently was given orally up to 1200 mg m^{-2}. A total of 51 patients were entered on the single dose schedule. TMZ exhibited linear pharmacokinetics with increasing dose. Myelotoxicity was dose limiting. Experimentally, TMZ activity was schedule dependent and therefore oral administration was studied as a daily ×5 schedule between total doses of 750 and 1200 mg m^{-2} in 42 patients. Myelosuppression was again dose limiting. The recommended dose for Phase 2 trials is 150 mg m^{-2} po for 5 days (total dose 750 mg m^{-2}) for the first course, and if no major myelosuppression is detected on day 22 of the 4-week cycle, the subsequent courses can be given at 200 mg m^{-2} for 5 days (total dose 1 g m^{-2}) on a 4-week cycle. Mild to moderate nausea and vomiting were dose related but readily controlled with antiemetics. Clinical activity was detected using the 5-day schedule in four (2 CR, 2 PR; 17%) out of 23 patients with melanoma and in one patient with mycosis fungoides (CR lasting 7 months). Two patients with recurrent high-grade gliomas also had partial responses. TMZ is easy to use clinically and generally well tolerated. In the extended Phase 1 trial TMZ only occasionally exhibited the unpredictable myelosuppression seen with mitozolomide	Not newly diagnosed glioma

continued

Reference	(Type)	Abstract	Reason for exclusion
Newlands ES, Foster T, Zaknoen S. Phase I study of temozolamide (TMZ) combined with procarbazine (PCB) in patients with gliomas. *Br J Cancer* 2003;**89**:248–51	(CS)	TMZ is an oral alkylating agent with a good safety profile and proven efficacy in the treatment of malignant glioma. Procarbazine (PCB) has been used for treating gliomas for many years and here both agents were combined in the treatment. This Phase I study was designed to evaluate the efficacy and safety of TMZ alone (course 1) and TMZ in combination with PCB in subsequent courses in chemotherapy-naive patients with malignant glioma. Patients with AA, GBM and low-grade glioma were treated with TMZ 200 mg m^{-2} on days 1–5 on a 28-day cycle for course 1. Beginning with course 2, cohorts of patients received TMZ at full dose with escalating doses of PCB (50/75/100/125 mg m^{-2} days 1–5 given 1 h prior to TMZ). A total of 28 patients were enrolled with three patients each at dose levels 1 and 2, 16 patients at dose level 3 and six patients at dose level 4 received 182+ cycles of treatment and were included in this analysis. In all, 16 patients had GBM, seven patients had AA, five had grade 1 or 2 glioma and the median age was 47 years. The patients had received prior surgery and RT. Responses were seen at all dose levels. Overall, there were 10 (36%) responses lasting from 2 to 17+ months. Treatment was generally well tolerated with few grade 3 or 4 toxicities, except at dose level 4, where four patients had grade 3/4 thrombocytopenia at this dose and several patients had moderate-to-severe lethargy. TMZ 200 mg m^{-2} and PCB 100 mg m^{-2} were well tolerated on a daily 5× and 4-weekly cycle in patients with malignant glioma and clearly had antitumour activity	Not newly diagnosed glioma
NHS Northern and Yorkshire Regional Drug and Therapeutics Centre. The use of temozolomide in the management of high grade gliomas. 2000 (unpublished)	(SR)	High-grade gliomas are relatively rare, aggressive neurological tumours. They include GBM (grade IV astrocytoma) and AA (grade III astrocytoma). In newly diagnosed patients, surgical resection or biopsy followed by RT is the treatment of choice in patients with a reasonable performance status. Standard treatment for recurrent tumour is chemotherapy with either lomustine alone or in combination with procarbazine and vincristine. TMZ is licensed for the treatment of GBM and AA showing recurrence or progression after standard therapy. In patients with recurrent AA an open trial of TMZ showed median PFS to be 5.4 months. Only one comparative trial has been performed in patients with recurrent GBM and is currently unpublished. This demonstrated a marginal benefit over high-dose procarbazine with median PFS extended by 1.01 months to 2.89 months. The commonest AEs experienced with TMZ are nausea (42%), vomiting (35%), thrombocytopenia (19%) and neutropenia (17%).The cost of a 5-day cycle of TMZ in a 70-kg patient is between £1000 and £1250. An estimated 146 patients in the Northern and Yorkshire region may present each year with high-grade gliomas. However, it is likely that a significant proportion of these patients would not be well enough to receive chemotherapy after recurrence. If 50% of patients receive TMZ on recurrence for between three and six cycles the cost would be £205,000–£546,000. Until further comparative trials are published, the use of TMZ cannot be recommended over conventional chemotherapy regimes. If TMZ is used it should only be prescribed in hospital units with particular expertise in the management of high-grade gliomas and within the confines of locally agreed protocols. NICE will produce guidance on the use of TMZ in brain tumours early in 2001. The conclusions of this report will be superseded by the NICE appraisal decision	Not a systematic review

continued

Reference	(Type)	Abstract	Reason for exclusion
O'Reilly SM, Newlands ES, Glaser MG, Brampton M, Rice-Edwards JM, Illingworth RD, *et al*. Temozolomide – a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumours [published erratum appears in *Eur J Cancer* 1993;**29A**:1500]. *Eur J Cancer* 1993;**29A**:940–2	(CS)	TMZ, a new oral cytotoxic agent, has been given to 28 patients with primary brain tumours. Treatment was given at a dose of 150 mg/m^2/day for 5 days (i.e. total dose 750 mg/m^2) escalating, if no significant myelosuppression was noted on day 22, to 200 mg/m^2/day for 5 days (i.e. total dose 1000 mg/m^2) for subsequent courses at 4-week intervals. A major improvement in CT scan was noted in 5/10 patients with astrocytomas recurrent after RT, with a major clinical improvement but minor improvement on CT scan in one further patient. Reduction in the size of the CT lesion was also observed in 4/7 patients with newly diagnosed high-grade astrocytomas given 2–3 courses of TMZ prior to irradiation. One patient with recurrent medulloblastoma had a clinical response in bone metastases. TMZ was well tolerated with little subjective toxicity and usually predictable myelosuppression and is a promising new drug in the treatment of primary brain tumours	No relevant outcomes reported
Ostermann S, Csajka C, Buclin T, Leyvraz S, Lejeune F, Decosterd LA, *et al*. Plasma and cerebrospinal fluid population pharmacokinetics of temozolomide in malignant glioma patients. *Clin Cancer Res* 2004;**10**:3728–36	(CS)	PURPOSE – Scarce information is available on the brain penetration of TMZ, although this novel methylating agent is mainly used for the treatment of malignant brain tumours. The purpose was to assess TMZ pharmacokinetics in plasma and cerebrospinal fluid (CSF) along with its inter-individual variability, to characterize covariates and to explore relationships between systemic or cerebral drug exposure and clinical outcomes. EXPERIMENTAL DESIGN – TMZ levels were measured by high-performance liquid chromatography in plasma and CSF samples from 35 patients with newly diagnosed or recurrent malignant gliomas. The population pharmacokinetic analysis was performed with nonlinear mixed-effect modelling software. Drug exposure, defined by the area under the concentration–time curve (AUC) in plasma and CSF, was estimated for each patient and correlated with toxicity, survival and PFS. RESULTS – A three-compartment model with first-order absorption and transfer rates between plasma and CSF described the data appropriately. Oral clearance was 10 l/h; volume of distribution [*V*(D)], 30.3 litres; absorption constant rate, 5.8 h^{-1}; elimination half-time, 2.1 hours; transfer rate from plasma to CSF [*K*(plasma $\rightarrow$ CSF)], 7.2 $\times$ 10^{-4}h^{-1}; and backwards rate, 0.76 h^{-1}. Body surface area significantly influenced both clearance and *V*(D), and clearance was sex dependent. The AUC(CSF) corresponded to 20% of the AUC(plasma). A trend toward an increased *K*(plasma $\rightarrow$ CSF) of 15% was observed in case of concomitant radiochemotherapy. No significant correlations between AUC in plasma or CSF and toxicity, survival or PFS were apparent after deduction of dose–effect. CONCLUSIONS – This is the first human pharmacokinetic study on TMZ to quantify CSF penetration. The AUC(CSF)/AUC(plasma) ratio was 20%. Systemic or cerebral exposures are not better predictors than the cumulative dose alone for both efficacy and safety	No relevant outcome data reported

continued

Reference	(Type)	Abstract	Reason for exclusion
Parney IF, Chang SM. Current chemotherapy for glioblastoma. [Review; 81 refs]. *Cancer J* 2003;**9**:149–56	(SR)	INTRODUCTION – GBM continues to be associated with a dismal prognosis, despite aggressive therapy. What limited therapeutic impact that has been made has come via multimodality treatment in which chemotherapy plays an important role. This paper reviews current chemotherapy options for glioblastomas. METHODS – The current literature concerning GBM chemotherapy was reviewed. In addition to a review of landmark references, a MEDLINE search of the literature published from January 2000 to November 2002 was performed using the keywords 'chemotherapy AND malignant glioma' and limiting responses to clinical trials. RESULTS – Several cytotoxic chemotherapeutic agents that are efficacious in treating glioblastoma are in common clinical use. These can be classified as first- or second-line agents, depending on their efficacy. In addition, cytostatic chemotherapy agents are beginning to play a role in glioblastoma treatment. Finally, new methods to deliver high chemotherapy doses to brain tumours hold promise for future therapies. CONCLUSIONS – Despite the overall poor prognosis of patients with GBM, multimodality treatment and chemotherapy in particular improve outcome, and chemotherapeutic options are beginning to have an increased impact. Strategies currently in clinical trials may improve this impact more in the future	Not a systematic review and superseded by more recent publications
Patwardhan RV, Shorter C, Willis BK, Reddy P, Smith D, Caldito GC, *et al*. Survival trends in elderly patients with glioblastoma multiforme – Resective surgery, radiation, and chemotherapy. *Surg Neurol* 2004;**62**:207–13	(CS)	BACKGROUND – It is appropriate to investigate and to determine survival trends following GBM treatment using resective surgery, RT and/or chemotherapy in patients aged 59 years and higher. METHODS – We retrospectively reviewed 30 elderly patients (⩾59 years old) who were treated for histopathologically confirmed GBM at our tertiary care institution from 1990 through 2002. All patients were treated with steroids. In addition, 22 patients underwent resective surgery (RS), 17 underwent RT and 10 underwent chemotherapy (C). Many patients underwent these treatments in various combinations: 6 underwent biopsy only, 7 RS only, 6 RS + RT only and 9 RS + RT + C. For each case, pretreatment KPS, tumour location, presenting symptoms and signs, associated surgical morbidity and pre-existing medical conditions were also recorded. Patients were categorised into one of four treatment subgroups: biopsy only, RS only, RS + RT, and RT + RS + C. For each of these subgroups, pretreatment KPS and post-treatment survival were compared. RESULTS – Post-treatment survival following biopsy only was 3.2 ± 0.8 months (mean ± SE); RS 2.2 ± 0.5; RS + RT 5.5 ± 1.2; RS + RT + C 13.6 ± 2.1. A longer survival trend was noted for the RS + RT versus RS group (two-tailed unpaired *t*-test, $p = 0.02$;), and also the RS + RT + C group, which showed consistently higher survival in comparison to most of the other groups ($p = 0.0021$, 0.00039, 0.013 vs the biopsy only RS only and RS + RT groups, respectively). No significant difference was found in KPS, comparing all individual groups versus each other ($p \geqslant 0.06$). Remarkably, 6 patients survived over 14 months (range, 14.1–22.7 months), all of whom received RS + RT + C. CONCLUSIONS – This study suggests a significant improvement in elderly patients treated with the combination of resective surgery, RT, and chemotherapy, rather than either treatment alone or other combination. This significant improvement does not appear to be biased by pretreatment KPS, as mean KPS values did not significantly differ between any of these groups. However, a greater number of patients in each group must be considered to achieve the power to make more definitive treatment guidelines	TMZ not given as first-line chemotherapy (only given as second-line treatment in patients who did not tolerate BCNU)

continued

Reference	(Type)	Abstract	Reason for exclusion
Paz MF, Yaya-Tur R, Rojas-Marcos I, Reynes G, Pollan M, Guirre-Cruz L, *et al.* CpG island hypermethylation of the DNA repair enzyme methyltransferase predicts response to temozolomide in primary gliomas. *Clin Cancer Res* 2004;**10**:4933–8	(CS)	PURPOSE – The DNA repair enzyme O^6-methylguanine DNA methyltransferase (MGMT) inhibits the killing of tumour cells by alkylating agents, and its loss in cancer cells is associated with hypermethylation of the MGMT CpG island. Thus, methylation of MGMT has been correlated with the clinical response to 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) in primary gliomas. Here, we investigated whether the presence of MGMT methylation in gliomas is also a good predictor of response to another emergent alkylating agent, TMZ. EXPERIMENTAL DESIGN – Using a methylation-specific PCR approach, we assessed the methylation status of the CpG island of MGMT in 92 glioma patients who received TMZ as first-line chemotherapy or as treatment for relapses. RESULTS – Methylation of the MGMT promoter positively correlated with the clinical response in the glioma patients receiving TMZ as first-line chemotherapy ($n = 40$). Eight of 12 patients with MGMT-methylated tumours (66.7%) had a partial or complete response, compared with 7 of 28 patients with unmethylated tumours (25.0%; $p = 0.030$). We also found a positive association between MGMT methylation and clinical response in those patients receiving BCNU ($n = 35$, $p = 0.041$) of procarbazine/1-(2-chloroethyl)-3- cyclohexyl-1-nitrosourea ($n = 17$, $p = 0.043$) as first-line chemotherapy. Overall, if we analyse the clinical response of all of the first-line chemotherapy treatments with TMZ, BCNU and procarbazine/1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea as a group in relation to the MGMT methylation status, MGMT hypermethylation was strongly associated with the presence of partial or complete clinical response ($p < 0.001$). Finally, the MGMT methylation status determined in the initial glioma tumour did not correlate with the clinical response to TMZ when this drug was administered as treatment for relapses ($p = 0.729$). CONCLUSIONS – MGMT methylation predicts the clinical response of primary gliomas to first-line chemotherapy with the alkylating agent TMZ. These results may open up possibilities for more customised treatments of human brain tumours	No relevant outcome data reported
Pearson A, Estlin E, Lashford L, Ablett S, Dugan M, *et al.* Phase I study of temozolomide in pediatric patients with advanced cancer. *Proc Am Soc Clin Oncol* 1996;**15**:490		–	Abstract only; reported outcomes not relevant to review

continued

Reference	(Type)	Abstract	Reason for exclusion
Raizer JJ, Malkin MG, Kleber M, Abrey LE. Phase 1 study of 28-day, low-dose temozolomide and BCNU in the treatment of malignant gliomas after radiation therapy. *Neuro-oncol* 2004;**6**:247–52	(CS)	We conducted a study to determine the dose-limiting toxicity of an extended dosing schedule of TMZ when used with a fixed dose of BCNU or 1,3-bis(2-chloroethyl)-1-nitrosourea (carmustine), taking advantage of TMZ's ability to deplete O^6-alkylguanine-DNA-alkyltransferase and the synergistic activity of these two agents. Patients with malignant gliomas who had undergone RT were eligible. Patients were treated with TMZ for 28 days, followed by a 28-day rest (1 cycle). The TMZ was started at 50 mg/m^2 and increased in 10-mg/m^2 increments; a fixed dose of BCNU (150 mg/m^2) was given within 72 hours of starting TMZ. A standard Phase 1 dose-escalation scheme was used with 3 patients per cohort. Fourteen glioblastoma patients and 10 anaplastic astrocytoma patients were treated. The dose-limiting toxicity was myelosuppression at 90 mg/m^2 of TMZ. The total number of cycles given was 73 (median 2). Six patients (25%) required a dose reduction in BCNU and six were removed from study for hematological toxicity after cycle 1; three patients overlapped. The median time to progression and overall survival were, respectively, 82 and 132 weeks for AA and 14 and 69 weeks for glioblastomas. We conclude that the combination of BCNU and the extended dosing schedule of TMZ is feasible and that the maximal tolerated dose of a 28-day course of TMZ is 80 mg/m^2 when combined with a fixed dose of BCNU at 150 mg/m^2. This is the recommended dose for Phase 2, but myelosuppression after cycle 1 suggests that long-term treatment may be difficult	TMZ not given as an adjunct to radiotherapy (only given as adjuvant treatment)
Salvati M, Piccirilli M, Caroli E, Brogna C, Artizzu S, Frati A. Treatment of glioblastoma multiforme in the elderly in functionally non-critical areas. Clinical remarks on 22 patients. *J Exp Clin Cancer Res* 2003;**22**:395–8	(CS)	The aim of this study was to evaluate the efficacy of multimodality treatment of GBM in the elderly. Although several studies report a poor outcome in elderly patients with glioblastoma, in the light of our experience, treatment of elderly patients with glioblastoma in non-critical areas and KPS >60 should be just as aggressive as in younger patients	Only 2 patients received TMZ concomitantly and adjuvantly with RT and outcome data were not reported separately
Scapati A, Barbara R, Giovannini P, Pecchia R, Ascarelli AA. Health related quality of life in 10 patients with anaplastic gliomas treated with temozolomide and radiation therapy. *Tumori* 2001;**87**:S154–5	(CS)	–	Abstract only

continued

Reference	(Type)	Abstract	Reason for exclusion
Slack JA, Stevens MFG, Quarterman CP, Newlands ES, Blackledge GRP. The phase I clinical trial and pharmacokinetics of temozolomide. *J Pharma Pharmacol Suppl* 1991;**43**(pp. 22)	(CS)	–	Abstract only
Stark AM, Nabavi A, Mehdorn HM, Blomer U. Glioblastoma multiforme-report of 267 cases treated at a single institution. *Surg Neurol* 2005;**63**:162–9	(CS)	GBM is the most common and most malignant primary brain tumour in adults. We present 267 cases treated at a single institution and discuss clinical characteristics and prognostic factors with regard to the neurosurgical literature. Included in this study were 267 patients who underwent craniotomy for newly diagnosed GBM between 1990 and 2001 at our department. Clinical charts and radiographic images were reviewed. Association to patient survival was estimated using log-rank test. Median patient age was 61 years (mean, 59.5; range, 22–86 years), the male–female ratio was 1.2:1. In 35 cases (13.1%) the tumour was multicentric. Most of the tumours were classified as primary GBM (87.6%). During follow-up, 72 patients (26.4%) underwent recraniotomy for GBM recurrence and 3 patients (1.1%) developed spinal drop metastases. Overall median survival was 47 weeks (range, 5–305 weeks). The following parameters were significantly associated with prolonged survival: (1) age 61 years or younger, $p < 0.001$; (2) KPS score of 70 or more, $p < 0.001$; (3) RT with a total dose of at least 54 Gy, $p < 0.001$; (4) chemotherapy, $p < 0.001$; (5) total tumor resection, $p = 0.014$; (6) recraniotomy for GBM recurrence, $p = 0.012$. GBM remains an important cause of morbidity and mortality from intracranial tumours. The overall prognosis is dismal, although interdisciplinary therapy can significantly prolong survival and allow a small subgroup of patients to survive 3 years or more	Data for patients who received TMZ not reported separately
Tuettenberg J, Grobholz R, Korn T, Wenz F, Erber R, Vajkoczy P. Continuous low-dose chemotherapy plus inhibition of cyclooxygenase-2 as an antiangiogenic therapy of glioblastoma multiforme. *J Cancer Res Clin Oncol* 2005;**131**:31–40	(CS)	PURPOSE – GBM represents the prototype of an angiogenic tumour. Recently, the continuous low-dose scheduling of chemotherapeutic drugs in combination with an inhibition of cyclooxygenase-2 (COX-2) has been suggested as a novel anti-angiogenic approach. The aim of this study was to evaluate the safety and activity of continuous low-dose TMZ plus the COX-2 inhibitor rofecoxib in patients with newly diagnosed GBM. METHODS – *In vitro*, endothelial cells were characterised by a 10-fold higher sensitivity to TMZ than glioma cells. Consequently, a subgroup of patients with incompletely resected GBM ($n = 13$) was divided into three groups aiming at a dose escalation to 1/10 of the daily MTD for TMZ – (a) TMZ 10 mg/m^2 every third day and rofecoxib 25 mg/d; (b) TMZ 10 mg/m^2/d and rofecoxib 25 mg/d; (c) TMZ 5 mg/m^2 twice a day and rofecoxib 12.5 mg twice a day. COX-2, VEGF, VEGF Receptor-2 and CD34 were assessed immunohistochemically, in the clinical setting. RESULTS – The mean follow-up period was 15 months. We observed no severe toxicity attributable to the therapy. QoL was not impaired. For the whole study population, median time to progression and overall survival were 8 and 16 months, respectively. Immunohistochemistry suggested that tumours with higher vessel densities were characterized by a significantly better control than those with lower vessel densities. CONCLUSIONS – Continuous low-dose TMZ plus rofecoxib is feasible, safe and maintains good QoL. This study is indicative of an anti-angiogenic efficacy of continuous low-dose TMZ plus rofecoxib in GBMs, especially in those tumours that are characterized by a high angiogenic activity	TMZ not given as an adjunct to RT (only given as adjuvant treatment)

continued

Reference	(Type)	Abstract	Reason for exclusion
Wasserfallen JB, Ostermann S, Pica A, Mirimanoff RO, Leyvraz S, Villemure JG, *et al*. Can we afford to add chemotherapy to radiotherapy for glioblastoma multiforme? Cost-identification analysis of concomitant and adjuvant treatment with temozolomide until patient death. *Cancer* 2004;**101**:2098–105	(CS)	BACKGROUND – Adding TMZ to standard RT as a first-line therapy for glioma may increase costs to a disproportionate degree compared with the resulting survival benefits. METHODS – Forty-six consecutive patients (28 males and 18 females; median age, 52 years; age range, 24–70 years) received concomitant TMZ with RT for 6 weeks followed by adjuvant TMZ for 6 cycles, and they were followed until disease recurrence and then until death. The authors assessed the costs associated with the four phases of treatment from a hospital-centred perspective. RESULTS – Treatment was discontinued early in 3, 9, and 15 patients during concomitant TMZ, before adjuvant TMZ and during adjuvant TMZ, respectively. KPS index values varied between 85% (at the beginning of treatment) and 76% (at the end of treatment). The nature of care after disease recurrence was diverse. Overall survival ranged from 1.4 to 64.3 months (median, 15.8 months) and was better if surgical debulking could be carried out before treatment. Global costs amounted to Euros 39,092 ± 21,948 (concomitant TMZ, Euros 14,539 ± 4998; adjuvant TMZ, Euros 13,651 ± 4320; follow-up, Euros 6363 ± 6917; and recurrence, Euros 12,344 ± 18,327), with 53% of these costs being related to the acquisition of TMZ; this represented an eightfold increase in cost compared with RT alone. CONCLUSIONS – TMZ may be an effective but costly adjuvant outpatient therapy for patients with GBM. Definite cost-effectiveness/utility must be assessed in a randomized Phase 3 trial	Patients reported in detail elsewhere[183]

Carmustine Implants

Reference	(Type)	Abstract	Reason for exclusion
Giese A, Kucinski T, Knopp U, Goldbrunner R, Hamel W, Mehdorn HM, *et al.* Pattern of recurrence following local chemotherapy with biodegradable carmustine (BCNU) implants in patients with glioblastoma. *J Neurooncol* 2004;**66**:351–60	(RCT)	OBJECTIVE – Recently a randomized placebo-controlled Phase 3 trial of biodegradable polymers containing carmustine has demonstrated a significant survival benefit for patients treated with local chemotherapy. A local chemotherapy applied directly to the resection cavity may act directly on residual tumour cells in adjacent brain possibly leading to a local control of the tumor and increased survival. METHODS – We analysed the pattern of recurrence using serial MRI studies of 24 patients treated with Gliadel® Wafers or placebo wafers following resection of glioblastomas. RESULTS – Of 24 patients, 11 received carmustine wafers and 13 placebo. The age distribution and KPS of the two populations were not different. However, the median survival (14.7 versus 9.5 months; $p = 0.007$) and the time to neurological deterioration (12.9 ± 4.85 vs 9.4 ± 2.73 months; $p = 0.035$) was significantly longer in the treatment group versus the placebo-treated control. Preoperative and follow-up MRI studies were evaluated in a blinded fashion. Out of 24 patients who entered the analysis, 11 showed clearance of all contrast enhancement following resection of glioblastomas. Seventeen tumours progressed locally and 7 showed different patterns of distant failure. Within the carmustine-treated group 8 patients showed a local treatment failure with recurrent tumours immediately adjacent to the resection cavity or progression from a residual tumour. Three patients showed a multifocal distant and local pattern of failure after complete or subtotal removal. In no case did the local chemotherapy result in a distant recurrence only. However, the time to radiographic progression was 165.1 ± 80.75 days for the Gliadel® wafer group and 101.9 ± 43.06 days for the placebo group ($p = 0.023$). CONCLUSION – In this subgroup analysis of a Phase 3 trial population both the clinical progression and radiological progression were significantly delayed in patients treated with local chemotherapy, resulting in an increased survival time. Local chemotherapy with carmustine-containing wafer implants did not result in an altered pattern of recurrence and did not promote multifocal patterns of recurrence	Patients reported in detail elsewhere[151] (NB – extra data from this study were extracted alongside data from the main paper)
National Horizon Scanning Centre. Carmustine implants for glioma. New and Emerging Technology Briefing 2002	(SR)	–	Not a systematic review

continued

Reference	(Type)	Abstract	Reason for exclusion
Riva M, Brioschi A, Candelise L, Marchioni E. Loco-regional versus standard chemotherapy for high grade gliomas. *Cochrane Database of Systematic Reviews – Protocols* 2003;(3)	(SR)	This is the protocol for a review and there is no abstract. The objectives are as follows: to investigate if loco-regional chemotherapy using implants of biopolymers loaded with antineoplastic agents is more effective and less toxic than intravenous and/or oral administration of standard, nitrosurea-based, chemotherapy	Protocol only available; systematic review not yet published

CS, case study; CT, controlled trial; RCT, randomised controlled trial; SR, systematic review.

Appendix 7

Included systematic reviews: quality assessment using QUOROM framework

Brophy and Chen (2004). Use of carmustine implants (Gliadel® wafer) in patients with malignant glioma[149]

TITLE
Identify the report as a meta-analysis or systematic review of RCTs? No

ABSTRACT
Uses a structured format? No, there is only an unstructured summary

Background:	Technology is described
Objectives:	Clinical question not given
Search strategy:	None stated
Selection criteria:	None stated
Data collection and analysis:	None stated
Main results:	Characteristics of included trials not reported. Median increased survival time reported, no CIs
Reviewers' conclusions:	Related to finding for wafers in one Canadian hospital. Evidence 'less than ideal' and therefore treatment limited to recurrent patients, refractory to other chemo only

INTRODUCTION
The clinical problem and the biological rationale for the intervention is made explicit. The rationale for the review is given.

METHODS

Searching:	Details of databases and websites searched are listed. No restrictions of publication status, language or year of publication are given
Selection:	No inclusion criteria are given. However, the evidence base is known to be small and the paper includes the available RCTs. The review includes gliadel used on both recurrent and newly diagnosed gliomas
Validity assessment:	Quality assessed use in Jadad score (all rated as 'acceptable')
Data abstraction:	No details given – not known how many reviewers undertook this
Study characteristics:	Study design, patient characteristics, intervention details, outcome definitions, survival benefit and safety are assessed. Clinical heterogeneity was not assessed but no meta-analysis is attempted
Quantitative data synthesis:	None. Trial details are presented descriptively

RESULTS

Trial flow:	Not included
Study characteristics:	Patient and trial characteristics are given; gender, age, KPS and GBM, inclusion and exclusion criteria, intervention, dose, duration and follow-up period
Quantitative data synthesis:	Not applicable

DISCUSSION
The discussion summarises key findings; clinical inferences based on internal and external validity are not discussed, the results are interpreted based on the total evidence included in the review, potential biases (diverse initial pathology, lack of control of subsequent treatments) are discussed. Potential biases in the review process (e.g. publication bias) are not discussed. No future research agenda is suggested

Meldorf (2003). Long-term efficacy of the Gliadel® wafer in patients with high-grade malignant gliomas: a meta-analysis[150]

TITLE
Identify the report as a meta-analysis or systematic review of RCTs? Yes, as a meta-analysis.

ABSTRACT
Uses a structured format? No, there is only an unstructured summary

Background:	None
Objectives:	None stated
Search strategy:	None stated
Selection criteria:	None stated
Data collection and analysis:	None stated
Main results:	Characteristics of included trials not reported. Description of meta-analysis of survival time with point estimate and CIs
Reviewers' conclusions:	Reports the main results

INTRODUCTION
The clinical problem is not made explicit, nor is the rationale for the intervention. The rationale for the meta-analysis is given

METHODS

Searching:	No details of databases searched or handsearching listed. However, the evidence base is known to be small and both the available RCTs are included. No restrictions of publication status, language or year of publication are given
Selection:	No inclusion criteria are given
Validity assessment:	Methodological quality of the RCTs is not described at all so no details about adequate concealment prior to randomisation, power calculations for sample size, ITT analysis or attrition rates are given
Data abstraction:	Not relevant – the authors obtained patient-level data which they re-analysed
Study characteristics:	Study design, patient characteristics, intervention details, outcome definitions, etc., are not assessed. Clinical heterogeneity was not assessed but the trial designs are described as 'almost identical'
Quantitative data synthesis:	Survival data are assessed using the Kaplan–Meier technique and Cox proportional hazards model is used to estimate hazard ratios. Survival is defined as time from randomisation to death. Surviving patients are censored from analysis on the date of last contact. Log-rank test, stratified by trial to test for significant differences in survival

RESULTS

Trial flow:	Not included
Study characteristics:	Only basic patient characteristics of the combined data set, not each included trial, are given; gender, age, KPS and GBM
Quantitative data synthesis:	Agreement on selection and validity assessment is not reported. Results of meta-analysis presented as a survival curve. Cox proportional hazards for whole group and by KPS and age are tabulated. Analyses for tumour type and country of treatment where undertaken, but are not reported

DISCUSSION
The discussion summarises key findings; clinical inferences based on internal and external validity are not discussed, the results are interpreted based on the total evidence included in the review although it is not clear that the body of the review reports all findings of the analysis, potential biases (publication bias, use of heterogeneous data sets) are discussed and concluded to be unimportant in this case. No future research agenda is suggested

Appendix 8

Data extraction tables

Carmustine implants: systematic reviews

STUDY

Meldorf, 2003[150]

Study topic: Effectiveness of BCNU-W for high-grade malignant gliomas

Study aim: To assess and define better all of the randomised trial data concerning the effects of BCNU-W on survival in adults with primary malignant glioma

Search strategy: None stated. Only 2 trials available. Completeness ensured through "constant surveillance of literature/meetings" and contact with experts in the field

Search terms: None used

PATIENT CHARACTERISTICS (for combined trials)

***n* = 272**	**Placebo (*n* = 136)**	**Gliadel (*n* = 136)**
Age: mean ± SD (years):	53.6 ± 8.2	52.7 ± 9.2
Sex: % M	66.2	61.8
KPS: % ≤70	26.4	33.1
Pathology: % GBM	89.7	82.4

INCLUSION AND QUALITY CRITERIA

Inclusion criteria:
None explicitly stated. By implication of the study aim:

- Design – RCTs
- Population – adults with primary malignant glioma
- Setting – not stated
- Outcome measures – not stated, but survival analysed

Quality criteria:
None stated

Application of methods:
None stated

RESULTS – INCLUDED STUDIES

Quantity of included studies:
Two RCTs, 272 participants

Quality of included studies:
No details given. Both described as "double blind, placebo-controlled" trials. One included 240 patients and one 32

RESULTS – TREATMENT EFFECT

Survival	**Placebo (*n* = 136)**	**Gliadel (*n* = 136)**	***p***
Median: months (95% CI)	11.2 (9.9 to 12.4)	13.7 (12.3 to 15.1)	0.0021

Cox proportional hazards	**HR (95% CI)**	***p***
BCNU-W vs placebo	0.69 (0.53 to 0.90)	0.006
KPS ≤70 vs >70	1.43 (1.09 to 1.94)	0.0002
Age ≥60 vs <60	2.14 (1.39 to 3.29)	0.0005

METHODOLOGICAL COMMENTS

Search strategy?
None given – but limited research and contact with manufacturer and experts make it unlikely RCT data are missing

Participants?
Few details given

Inclusion exclusion criteria:
Not stated, but see above

Quality assessment of studies:
Not undertaken

Method of synthesis:
Survival analysis (Kaplan–Meier) of patient-level data

Generalisability:
Difficult to say as so few details about the participants are given

Appropriate outcome measures used?
Yes

Any differences between baseline characteristics of patients and controls?
Yes – more GBM patients in the placebo arm. Not stated if this is significant

Appropriate analysis?
Main analysis yes. But crucially, sub-analysis by tumour type is not reported. Stratification by country not justified

Funding:
Guilford Pharmaceuticals

STUDY
Brophy and Chen 2004[149]

Study topic: BCNU-W for the treatment of recurrent or newly diagnosed malignant gliomas

Study aim: To review the impact on survival and QoL of BCNU-W for newly diagnosed or recurrent malignant gliomas

Search strategy: Electronic databases searched, including Cochrane Library, EMBASE, MEDLINE, PubMED, DARE, DEC, Trip, Medscape

Search terms: Brain tumour, GBM, carmustine, cost-effectiveness, malignant glioma, gliadel wafer, BCNU, temozolomide, cost

RESULTS – INCLUDED STUDIES

Quantity of included studies
Three RCTs: two in newly diagnosed, 272 participants; one in recurrent, 222 patients

Quality of included studies
Jadad score "acceptable"

INCLUSION AND QUALITY CRITERIA

Inclusion criteria
Not stated – details below based on included studies:

- Design – RCTs included plus some AE details from case studies
- Population – those with malignant gliomas
- Setting – not stated
- Outcome measures – survival, safety, QoL

Quality criteria
Jadad

Application of methods
Not stated

RESULTS – TREATMENT EFFECT
Study 1 *n* = 240

Survival	Placebo	Gliadel	*p*
Median, months (95% CI)	11.2	13.7	Not stated
Unadjusted 1 year (%)	49.6	59.2	Not stated
GBM subgroup	11.4	11.4	Not stated

Kaplan–Meier estimates for GBM not significant (stratified log-rank, $p = 0.1$)
PFS same in both groups

Log-rank (stratified by country)	HR	(95% CI)	*p*
BCNU-W v. placebo	0.71	(0.52,0.96)	0.03
Adjusted for prognostic factors	0.72	(0.53,0.98)	0.03
Time-to-KPS decline	0.74	(0.55,1.0)	not stated

Study 2 *n* = 32

Survival	Placebo	Gliadel	*p*
Median – months	40	58	0.012
GBM subgroup	40	53	0.008

QoL – No significant differences in KPS and MMSE changes from baseline to final visit in between treatment group comparisons.

RESULTS – SAFETY

Study 1 – *n* = 240
Significantly higher incidence of:
CSF 5% vs 0.8% and
Inter-cranial hypertension 9.1% vs 1.7%

Study 2 – *n* = 32
Incidence of AEs 56% placebo vs 75% BCNU-W

METHODOLOGICAL COMMENTS

Search strategy?
Search terms limited, but see below

Participants?
No comment made on the grade III tumour patients

Inclusion exclusion criteria:
None stated – but all relevant RCTs included. Some safety data also given from case studies – not clear how these have been selected

Quality assessment of studies:
No details given – Jadad score "acceptable". FDA reports offer severe methodological criticism of the large RCT

Method of synthesis:
Descriptive

Appropriate outcome measures used?
Yes

Any differences between baseline characteristics of patients and controls?
Possibly – uncontrolled use of other treatments noted

Appropriate analysis?
Not applicable

Funding:
Internally funded for treatment decision making in one Canadian hospital

Carmustine implants: randomised controlled trials

STUDY

Westphal *et al.*, 2003[151]

Country: International (14 countries – AUS, A, B, CH, D, E, F, GB, GRC, ISR, I, NL, NZ, USA)
Setting: Multiple (38) centres
Recruitment dates: December 1997–July 1999
Study design: RCT

SUBJECTS

Total number: 240

Inclusion criteria:
- Age 18–65 years
- Radiological (MRI) determination of single, contrast-enhancing, unilateral, supratentorial cerebral tumour
- Intraoperative frozen section diagnosis of malignant glioma
- KPS ⩾60
- Surgery within 2 weeks of baseline MRI

Exclusion criteria:
- Prior cytoreductive therapy or radiotherapy to the brain
- Known hypersensitivity to nitrosoureas
- "Clinically significant laboratory abnormalities (in the judgement of the investigator)"

Subgroups? GBM only

INTERVENTION

Intervention:
BCNU-W

Intervention regimen:
Intraoperative (following tumour resection) placement of ⩽8 wafers containing 7.7 mg BCNU (3.85% by weight), i.e. a maximum dose of 61.6 mg

Comparator regimen:
Implantation of placebo wafers in identical manner

Concurrent treatment:
Surgery:
- Maximum tumour resection prior to wafer placement

Radiotherapy:
"Standard" RT starting 14 days after surgery:
- Fractionated focal irradiation, in 30–33 daily fractions, 5 days per week (Monday–Friday), total dose of 55–60 Gy
- No compulsory definition of target volume; recommended definition was radiographically apparent contrast-enhancing tumour volume plus 2–5-cm margin

Chemotherapy:
- In patients with AO only, additional conventional (systemic) chemotherapy was allowed

Notes:
- Treatment at investigator's discretion after diagnosis of tumour progression
- Histological diagnoses were verified at central review; disputed diagnoses of GBM resolved by a 3rd pathologist

PATIENT CHARACTERISTICS

	Placebo (*n* = 120)	BCNU-W (*n* = 120)
Age (years):		
Mean ± SEM	53.6 ± 0.8	52.6 ± 0.8
Range	30–67	21–72
Sex:		
M	84 (70%)	76 (63.3%)
F	36 (30%)	44 (36.7%)
KPS:		
60	16 (13.3%)	16 (13.3%)
70	17 (14.2%)	21 (17.5%)
80	24 (20.0%)	25 (20.8%)
85	0 (0.0%)	2 (1.7%)
90	40 (33.3%)	31 (25.8%)
95	1 (0.8%)	0 (0.0%)
100	22 (18.3%)	25 (20.8%)
Final histological diagnosis:		
GBM	106 (88.3%)	101 (84.2%)
AA	1 (0.8%)	1 (0.8%)
AO	4 (3.3%)	5 (4.2%)
AOA	3 (2.5%)	7 (5.8%)
Metastasis/brain metastasis	1 (0.8%)	2 (1.7%)
Other	5 (4.2%)	4 (3.3%)
Tumour volume (cm^3): mean ± SEM	50.8 ± 5.3	66.8 ± 5.9
Extent of surgery:		
Total resection[a]	49[a] (40.8%)[a]	56[a] (46.7%)[a]
Subtotal resection[a]	66[a] (55.0%)[a]	62[a] (51.7%)[a]
Lobectomy[a]	4[a] (3.3%)[a]	2[a] (1.7%)[a]
% resected – mean ± SEM	88.3 ± 1.6%	89.9 ± 1.3%

OUTCOME MEASURES

Primary outcome measure:
Survival (randomisation → death or last follow-up)

Secondary measures:
1. Time-to-progression measures:
   (a) Time-to-KPS decline:
      (i) decline = KPS <60 for 2 consecutive assessments during days 7–30 or for any 1 during months 1–12
   (b) Time-to-neurological progression:
      (i) neuroperformance scale of 11 indices assessed by clinicians on 6-point scale: 1 (normal) – 6 (not done)
      (ii) progression = decline in scale for 2 consecutive assessments during days 7–30 or for any 1 during months 1–12
   (c) Time-to-disease progression:
      (i) tumour growth ⩾25% and/or new lesions on MRI, or
      (ii) "a documented clinical/neurological decline"
2. QoL (EORTC QLQ-C30 + BCM-20 brain cancer module)
3. Safety

continued

Method of assessing outcomes:
Clinical and radiological evaluations at prespecified intervals:
1. frequency of clinical evaluations not reported
2. radiological evaluation (MRI) performed
   (a) at baseline and within 48 h of surgery
   (b) at 3 months postoperatively
   (c) "if there was clinical suspicion of tumor progression"

Length of follow-up:
At least 12 months after last enrolment (range: 12–30 months) **[Confidential information removed]**.

RESULTS

	Placebo	BCNU-W	Stratified by country		Unstratified	
			HR (95% CI)	*p*	HR (95%CI)	*p*
All patients	**(*n* = 120)**	**(*n* = 120)**				
Median survival: months	11.6	13.9	0.71	0.03	0.77[a]	
(95% CI)	(10.2 to 12.6)[a]	(12.1 to15.3)[a]	(0.52 to 0.96)		(0.57 to 1.03)[a]	0.08[a]
			Cox: 0.72 (0.53 to 0.98)	*0.03*		*0.08*[a]
Survival at 12 months: %	49.6%	59.2%		0.11[a]		
(95% CI)	(40.6 to 58.6%)[a]	(50.4 to 68%)[a]				
Updated[c] median survival:	11.6[a]	13.8[a]			0.73[a]	0.02[a]
months (95% CI)	(10.2 to 12.7)[a]	(12.1 to 15.1)[a]			(0.56 to 0.95)[a]	
		Cox:				*0.045*[a]
	[Confidential information removed]					
Censoring reoperated patients						
Median survival: months	11.4	14.8		0.01[a]		
(95% CI)	(9.9 to 12.7)[a]	(12.5 to 16.1)[a]				
Survival at 12 months: %	48.8%[a]	61%[a]		0.13[a]		
(95% CI)	(38.8 to 58.9%)[a]	(51.4 to 70.6%)[a]				
KPS decline:						
Median time-to-decline: months	10.4	11.9	0.74	0.05		0.11[a]
(95% CI)	(9.5 to 11.9)[a]	(10.4 to 13.7)[a]	(0.55 to 1.00)			
Decline-free at 12 months: %	39.3%	47.5%				
(95% CI)	(30.3 to 48.3%)[a]	(38.4 to 56.5%)[a]				
Disease progression:						
Median PFS: months (95% CI)	5.9	5.9		0.90		
	(4.7 to 7.4)[a]	(4.4 to 8.3)[a]				
Neuroperformance:						
Median time without deterioration: weeks:						
Vital signs	49.1	54.9			0.010	0.59[a]
Level of consciousness	45.4	52.1			0.016	0.60[a]
Personality	40.0	51.7			0.008	0.73[a]
Speech	36.7	49.6			0.003	0.01[a]
Visual status	42.4	44.0			0.087	0.32[a]
Fundus	46.3	55.1			0.007	0.89[a]
Cranial nerves, II, IV, VI	49.1	54.9			0.016	0.84[a]
Cranial nerves, other	46.3	54.3			0.003	0.94[a]
Motor status	31.4	45.4			0.013	0.21[a]
Sensory status	44.1	51.6			0.024	0.75[a]
Cerebellar status	46.7	54.1			0.011	0.34[a]

continued

	Placebo	BCNU-W	Stratified by country		Unstratified	
			HR (95% CI)	*p*	HR (95%CI)	*p*
GBM only	**(*n* = 106)**	**(*n* = 101)**				
Median survival: months (95% CI)	11.4 (10.2 to 12.6)[a]	13.5 (11.4 to 14.8)[a]	0.76 (0.55 to 1.05)	0.10	0.82[a] (0.60 to 1.11)[a]	0.2[a]
			Cox: 0.69 (0.49 to 0.97)	*0.04*		*0.2*[a]
Survival at 12 months: % (95% CI)	48.6%[a] (39 to 58.1%)[a]	57.4%[a] (47.8 to 67.1%)[a]		0.21[a]		
Updated[c] median survival: months (95% CI)	11.4[a] (10.2 to 12.6)[a]	13.1[a] (11.4 to 14.7)[a]			0.78[a] (0.59 to 1.03)[a]	0.08[a]
Median PFS: months (95% CI)	5.7[a] (3.6 to 6.6)[a]	5.8[a] (3.9 to 8.3)[a]		0.62[a]		
Non-GBM only	**(*n* = 19)**	**(*n* = 14)**				
Median survival: months (95% CI)	12.9[a]	23.8[a]	0.45[a] (0.13 to 1.52)[a]	0.20[a]		

Safety	***Long-term survivors (16 August 2002)***[b]					
	Placebo (*n* = 120)	**BCNU-W (*n* = 120)**	***p***		**Placebo (*n* = 2)**[b]	**BCNU-W (*n* = 9)**[b]	**All (*n* = 11)**[b]
***Deaths within 30 days of randomisation*: *n* (%):**	2 (1.7%)	5 (4.2%)		Median: months (range)	37[b] (36–38)[b]	40.3[b] (36.3–48.5)[b]	40.3[b] (36–48.5)[b]
Cerebral haematoma ± oedema	0	3 (2.5%)		***Diagnoses***			
Pulmonary embolism	0	1 (0.8%)		Grade III	2[b] (100.0%)[b]	7[b] (77.8%)[b]	9[b] (81.8%)[b]
Acute abdominal or coronary event	0	1 (0.8%)		AA	0[b]	1[b] (11.1%)[b]	1[b] (9.1%)[b]
Sepsis	1 (0.8%)	0		AO	1[b] (50.0%)[b]	4[b] (44.4%)[b]	5[b] (45.5%)[b]
Malignant disease	1 (0.8%)	0		AOA	1[b] (50.0%)[b]	2[b] (22.2%)[b]	3[b] (27.3%)[b]
***Local complications*: *n* (%):**				Grade IV (GBM)	0[b]	2[b] (22.2%)[b]	2[b] (18.2%)[b]
Cerebral oedema (new or worse)	23 (19.2%)	27 (22.5%)					
Intracranial hypertension	2 (1.7%)	11 (9.2%)	0.019				
Brain abscess	8 (6.7%)	8 (6.7%)					
Cerebral haemorrhage	5 (4.2%)	8 (6.7%)					
CSF leak	1 (0.8%)	6 (5.0%)					
Brain cyst	3 (2.5%)	2 (1.7%)					

1. Insufficient QoL data were collected to permit analysis (no significant differences between arms in data available to FDA[a])
2. The adverse event profile was "similar" for both groups:
   (a) Of 16 nervous system adverse events analysed, only intracranial hypertension was significantly more common in either arm
   (b) Convulsions, CNS infections and healing abnormalities were "not more common" in the BCNU-W group
3. 29% of the BCNU-W group and 25% of the placebo group underwent reoperation for tumour progression
4. The "frequency and type of postoperative radiotherapy and posttumor recurrence chemotherapy" was "comparable" between arms

continued

METHODOLOGICAL COMMENTS

Prospective?
Yes

Selection/randomisation:
Intraoperative randomisation (following confirmation of diagnosis) by selection of blinded boxes of wafers provided to each centre in blocks of 4 (2 BCNU-W, 2 placebo)

Groups similar at baseline?
Mean tumour size was larger in the BCNU-W group.

Eligibility criteria stated?
Yes

Blinding:
Double-blind (radiographic assessors in subsequent subgroup analysis also blinded[130])

Outcome measures:
Predominantly objective. Definition of disease progression includes "a documented clinical/neurological decline".

ITT?
Yes. Withdrawn patients were censored alive at time of last contact.

Protocol violations specified:
Yes. 1 patient in the BCNU-W group with anaplastic oligoastrocytoma received systemic chemotherapy.

Follow-up/attrition:
All patients accounted for? Yes.
Withdrawal specified? Yes (3)
Withdrawal reasons given? Yes (2 lost to follow-up and 1 withdrew consent).

Data analysis:
Statistical tests used:

- Kaplan–Meier estimates of survival function
- Log-rank test (stratified by country) for significance of unadjusted differences between groups
- Cox proportional-hazards model (stratified by country) for adjusting hazard ratio to account for possible confounding factors [baseline KPS ($\leqslant$70 vs >70), age ($\geqslant$60 vs <60), final histological diagnosis (GBM vs non-GBM), sex, number of wafers implanted]

Power calculation at design?
Yes – 90% power at a significance level of 0.05 to detect an 18% difference in 12-month survival between the treatment groups (based on survival rates of 68% in BCNU-W group and 50% in placebo group, and assuming 18 months of accrual, 12 months of follow-up and a 15% patient-loss rate)

Generalisability:
FDA committee members were uneasy about the generalisability of results, especially as trial eligibility criteria excluded those over 65 (a substantial proportion of the general population with high-grade gliomas) and those with bilateral and/or multifocal tumours (FDA proceedings 324–25)

Conflict of interest:
Study sponsored and funded by Guilford Pharmaceuticals

[a] Data do not appear in the published findings of the trial and have been extracted from additional findings and analysis contained in material presented to the FDA's Oncologic Drugs Advisory Committee.[155]
[b] Data do not appear in the published findings of the trial and have been extracted from p. 4 of http://virtualtrials.com/Gliadel/gliadelstudies.pdf.
[c] 'Updated' survival data as at 16 August 2002 (from FDA material).
[d] **[Confidential information removed]**.[167]

STUDY

Valtonen *et al.*, 1997[152]

Country: Finland and Norway
Setting: Four university hospital neurosurgical units
Recruitment dates: 23 March 1992–19 March 1993
Study design: RCT

SUBJECTS

Total number: 32

Inclusion criteria:
- Age 18–65 years
- Radiological (CT or MRI) determination of unilateral, unifocal brain tumour of at least 1 cm in diameter
- Histopathological (frozen section) diagnosis of grade III or IV glioma at time of surgery
- KPS $\geqslant$60

Exclusion criteria:
- Significant renal, hepatic or haematological dysfunction
- Other concomitant life-threatening disease
- Pregnancy
- Hypersensitivity to radiographic contrast media

Subgroups?
GBM only

INTERVENTION

Intervention:
BCNU-W

Intervention regimen:
- Intraoperative placement of $\leqslant$8 wafers ("as many ... as the space allowed") containing 7.7 mg BCNU (3.85% BCNU by weight), i.e. a maximum dose of 61.6 mg
- "Materials such as absorbable gelatin sponge" were "occasionally" used to keep the polymers in place
- Decompression cavity filled with irrigation fluid

Comparator regimen:
Implantation of placebo wafers in identical manner

Concurrent treatment:
Surgery:
- Maximum tumour resection prior to wafer placement
- All patients received perioperative corticosteroids to reduce brain swelling

Radiotherapy:
- "Standard" radiotherapy (regimen not detailed)
- Median cumulative dose (BCNU-W group) 54.92 Gy
- Median cumulative dose (placebo group) 54.03 Gy

Chemotherapy:
No conventional (i.v.) chemotherapy was given

Notes:
"Subsequent operations were allowed if considered necessary"

PATIENT CHARACTERISTICS

	Placebo (n = 16)	Gliadel (n = 16)
Age: median (range) (years):	53 (36–65)	55.5 (36–67)
Sex:		
M	6 (38%)	8 (50%)
F	10 (63%)	8 (50%)
KPS: median (range):	90 (40–100)	75 (60–100)
Diagnosis:		
GBM	16 (100%)	11 (69%)
AA		2 (13%)
AO		2 (13%)
Malignant ependymoma		1 (6%)
Extent of surgery:		
Lobectomy	0[a]	1[a] (6%)[a]
Subtotal resection	15[a] (94%)[a]	14[a] (88%)[a]
Total resection	1[a] (6%)[a]	1[a] (6%)[a]
Median tumour size: mg (range):	20 (6.25–28)	20 (12–38.5)

OUTCOME MEASURES

Primary outcome measure:
Survival

Secondary measures:
2-year survival
Time-to-treatment failure (= PFS)[a]

Method of assessing outcomes:
3-monthly assessment, including
- KPS determination
- Neurological examination
- MMSE
- Radiographic tumour imaging
- Laboratory examinations

Length of follow-up:
2 years

RESULTS

1. In Cox model for whole population, significant covariates of outcome other than treatment allocation were:
   (a) KPS: HR 0.96 (95% CI 0.93 to 0.99); p = 0.01
   (b) Age: HR 1.09 (95% CI 1.02 to 1.15); p = 0.007
   (c) Tumour type: HR 5.62 (95% CI 0.69 to 46.05); p = 0.108
   (d) MMSE (p = 0.016); no further details stated
2. In Cox model for GBM-only subgroup, significant covariates of outcome other than treatment allocation were:
   (a) KPS: HR 0.96 (95% CI 0.93 to 0.99); p = 0.019
   (b) Age: HR 1.08 (95% CI 1.01 to 1.14); p = 0.018
3. There were no perioperative deaths

continued

4. One patient in the BCNU-W group underwent subsequent surgery
5. The 10 "serious" AEs in the BCNU-W group occurred in 5 patients, and included:
   (a) Pneumonia with an increase in aphasia, visual disturbances and hemiparesis
   (b) Septic inflammation with meningismus
   (c) Cerebrospinal fluid leukocytosis with hydrocephalus
   (d) Deep venous thrombosis with pulmonary embolism
   (e) Wound infection
6. The 5 "serious" AEs in the placebo group occurred in 4 patients, and included:
   (a) Pulmonary embolism
   (b) Meningitis
   (c) Wound infection
   (d) Deep venous thrombosis with pulmonary embolism

Adverse events	**Placebo (*n* = 16)**	**Gliadel (*n* = 16)**
Patients suffering any AE	9 (56%)	12 (75%)
Patients suffering "serious" AEs	4 (25%)	5 (31%)
Treatment-emergent adverse events		
Hemiparesis	4 (25%)	6 (38%)
Convulsions	3 (19%)	3 (19%)
Aphasia		2 (13%)
Visual field defect		2 (13%)

Survival	**Placebo**	**Gliadel**	***p* (log-rank)**	**Cox model**	
				HR (95% CI)	***p***
All patients	**(*n* = 16)**	**(*n* = 16)**			
Median survival: weeks (95% CI)	39.9 (37.6 to 45)	58.1 (42 to ?)	0.012	0.27 (0.11 to 0.68)	0.006
1-year survival: *n* (%)[a]	3[a] (18.8%)[a]	10[a] (62.5%)[a]	0.0087[a]	0.154[a] (0.05 to 0.47)[a]	0.001[a]
2-year survival: *n* (%)	1 (6.3%)	5 (31.3%)	0.012[a]	0.177[a] (0.07 to 0.47)[a]	0.0005[a]
PFS: months (95% CI)[a]	6.7[a] (3.0 to 9.9)[a]	7.8[a] (3.2 to 9.7)[a]	0.467[a]		
GBM only	**(*n* = 16)**	**(*n* = 11)**			
Median survival: weeks (95% CI)	39.9 (37.6 to 45)	53.3 (45 to 77.7)	0.008	0.27 (0.10 to 0.71)	0.008
1-year survival: *n* (%)[a]	3[a] (18.8%)[a]	6[a] (54.5%)[a]	0.059[a]	0.196[a] (0.06,0.64)[a]	0.0072[a]
2-year survival: *n* (%)[a]	1[a] (6.3%)[a]	2[a] (18.2%)[a]	0.126[a]	0.213[a] (0.08 to 0.60)[a]	0.0035[a]

METHODOLOGICAL COMMENTS

Prospective?
Yes

Selection/randomisation:
Randomisation in blocks of 4 (2 active and 2 placebo, in random order)

Groups similar at baseline?
All patients in placebo group had grade IV gliomas, whereas 5/16 of the BCNU-W group had grade III tumours (subgroup analysis on grade IV patients only eliminates this bias). Slight differences in KPS in favour of placebo group

Eligibility criteria stated?
Yes

Blinding:
Double-blind for 2 years after the last patient was entered

Outcome measures:
Objective

ITT?
Yes

Follow-up/attrition:
No withdrawals specified

Protocol violations:
None reported

Data analysis:
Statistical tests used:
- Kaplan–Meier estimates of survival function
- Log-rank test for significance of unadjusted association between treatment and survival

continued

- Cox proportional-hazards model for adjusting hazard ratio to account for possible confounding factors (age, sex, KPS, tumour size, tumour type, cumulative dose of RT received)

Power calculation at design?
Not stated (100 patients were to be enrolled, but study prematurely terminated)

Generalisability:
Subjects are young relative to population at large. This study provides no evidence as to relative efficacy of treatment in grade III tumours

Conflict of interest:
Wafers supplied by Nova. Study supported by Orion Pharma (Scandinavian distributors of BCNU-W)

GENERAL COMMENTS
- The study was prematurely terminated as "the manufacturer of the drug was not able to deliver more of the product. There were no scientific reasons for the premature termination"
- The "high number of infectious complications" across both arms may be explained by inadvertent failure to ensure sterility of wafer packages in one participating centre

[a] Data do not appear in the published findings of the trial and have been extracted from additional findings and analysis contained in material presented to the FDA's Oncologic Drugs Advisory Committee.[155]

Carmustine implants: case series

STUDY

Kleinberg *et al.*, 2004[154]
Country: USA
Setting: University Hospital Oncology Centre
Recruitment dates: March 1990–August 1999
Study design: Retrospective case series

SUBJECTS

Total number: 46

Inclusion criteria:
- Surgically resectable, unilateral, contrast-enhancing tumour, thought likely to be a primary malignant glioma
- Histopathological (intraoperative frozen section) confirmation of malignant glioma

Exclusion criteria:
- Evidence of systemic disease

Subgroups?
GBM only

PATIENT CHARACTERISTICS

***N*:**	**45**
Age: median (range) (years):	57 (34–77)
Preoperative KPS:	
<70	9
⩾70	36
Diagnosis:	
GBM	39
AA	4
AO	1
Malignant xanthroastrocytoma	1

INTERVENTION
Intervention:
BCNU-W

Intervention regimen:
Intraoperative placement of ⩽8 wafers ("as needed to cover the surface of the resection cavity") containing 7.7 mg BCNU (3.85% BCNU by weight), i.e. a maximum dose of 61.6 mg

Concurrent treatment:
Radiotherapy:
Details available for 40 patients. Regimen not uniform:
- 6 patients received 51 Gy in 17 fractions
- 1 patient received 66.6 Gy in 37 fractions
- 1 patient received 55.8 Gy in 31 fractions
- 33 patients received 59.5–60 Gy at 1.8–2 Gy per day

Chemotherapy:
No details specified

OUTCOME MEASURES
Primary outcome measure:
1. Surgical outcome:
   (a) perioperative death
   (b) infection
   (c) length of hospital stay
   (d) readmission within 30 days
   (e) reoperation within 30 days

Secondary measures:
1. Survival (from date of histological diagnosis)
2. Toxicity
3. Corticosteroid (dexamethasone) dosing
4. Histopathological findings at reoperation

continued

Method of assessing outcomes:
1. Retrospective review of patient records and histological sections
   (a) toxicity = recorded evidence of new or worsening neurological symptoms ⩽30 days after treatment requiring "at least an alteration in medication"

Length of follow-up:
Median follow-up 16.8 months

RESULTS

Surgical phase (*N* = 45):

Perioperative death: *n* (%)	0
Infection: *n* (%)	1 (2.2%)
Readmission within 30 days: *n* (%)	2 (4.4%)
Reoperation within 30 days: *n* (%)	1 (2.2%)
Length of hospital stay: mean (range) (days)	5.61 (4–21)
Length of hospital stay (1996–): mean (range) (days)	4.63 (4–14)

Radiotherapy phase (*N* = 28):

Readmission during/within 30 days of RT	4 (14.3%)
Mortality during/within 30 days of RT	1 (3.6%)
Increased neurological symptoms during RT	5 (17.9%)
Neurological symptoms during D taper	8 (28.6%)
Dexamethasone therapy:	(0.0%)
On D at start of RT	23 (82.1%)
Began D during RT	2 (7.1%)
D dose increased during RT	8 (28.6%)
Survivors still on D 30 days after RT	16/27 (59.3%)

Reoperation phase

First reoperation (*N* = 15):	
Median time after first operation: months (?range)	7.4 (2.8–79.5)
Histopathology at first reoperation:	
Necrosed/quiescent tumour	5 (33.3%)
Median survival from diagnosis: months (?range)	15.6 (7.0–20.8)
Active tumour	10 (66.7%)
Median survival from diagnosis: months (?range)	12.1 (8.7–17.4)
Second reoperation (*N* = 4):	
Median time after first reoperation: months (?range)	6.0 (2.9–9.0)
Histopathology at second reoperation:	
Necrosed/quiescent tumour	3 (75.0%)
Active tumour	1 (25.0%)

Median overall survival

GBM: months (95% CI)	12.8 (9.6 to 15.9)
GBM age <55: months (95% CI)	15.9 (13.5 to ?)
GBM age ⩾55: months (95% CI)	9.6 (7.7 to 14.4)
AA (*n* = 4): months	33.4
AO (*n* = 1): months	26.5+
Malignant xanthroastrocytoma (*n* = 1): months	32.4+

[a] No difference in survival relative to baseline KPS (<70 vs ⩾70)

METHODOLOGICAL COMMENTS

Prospective?
No

Selection/randomisation:
Retrospective review of all BCNU-W implantations followed by RT at unit

Consecutive patients?
No. First 10 patients treated in 1990–91 (as part of Phase 1 trial[129]); subsequent 36 treated 1996–. Within these periods, unclear whether consecutive eligible patients received BCNU-W; however, all consecutive BCNU-W patients are analysed

Eligibility criteria stated?
Yes

Outcome measures:
Predominantly objective end-points chosen; however, data extracted from historical patient notes (presumably varying quality)

Follow-up/attrition:
1 patient lost to follow-up excluded from analyses

Data analysis:
Statistical tests used:
• Kaplan–Meier median estimates of survival

Generalisability:
Patients 11–46 in this study received BCNU-W in general clinical practice (i.e. not as part of a prospective trial)

Conflict of interest:
1 author (Dr Brem) is consultant to Guilford Pharmaceuticals. The University and Dr Brem own Guilford stock.

GENERAL COMMENTS
10 patients are common to this review and the Phase 1 trial[129]

STUDY

Brem *et al.*, 1995[129]
Country: USA
Setting: Multiple (3) centres
Recruitment dates: 5 July 1990–14 August 1991
Study design: Prospective Phase I case series

SUBJECTS

Total number: 22

Inclusion criteria:
- Age ⩾18 years
- RT (CT or MRI) determination of single, unilateral, supratentorial cerebral tumour of at least 1 cm^3
- Histopathological (intraoperative frozen section or squash preparation) diagnosis of malignant glioma
- KPS ⩾60
- Ability to give informed consent

Exclusion criteria:
- Significant renal, hepatic or haematological dysfunction
- Other concomitant life-threatening disease "such that the patient could not be reasonably expected to live 6 months after surgery"
- Pregnancy
- Hypersensitivity to radiographic contrast media

Subgroups?
None

INTERVENTION

Intervention:
BCNU-W (Gliadel)

Intervention regimen:
- Intraoperative placement of 7 or 8 wafers containing 7.7 mg BCNU (3.85% BCNU by weight), i.e. a maximum dose of 61.6 mg
- "Material such as absorbable gelatin sponge … or oxidized regenerated cellulose" were "occasionally" used to keep the polymers in place

Concurrent treatment:
Surgery:
- Maximum tumour resection prior to wafer placement
- Haemostatic agents were applied to the brain surface "where necessary"

Radiotherapy:
All patients underwent "standard" external beam RT (protocol "determined by the treating radiation oncologist at each center on a patient by patient basis")

Chemotherapy:
No patient received additional chemotherapy "in the first 6 months"

Notes:
Patients underwent reoperation "for standard clinical indications such as worsening neurological deficit or increasing steroid requirement in combination with radiographic evidence of tumor recurrence or increasing mass effect"

PATIENT CHARACTERISTICS

***N*:**	**22**
Age: mean (range) (years):	60 (45–86)
Sex:	
M	15
F	7
Handedness:	
R	21
L	1
Diagnosis:	
GBM	21
AA	1
Baseline KPS: mean (range):	84.3 (40–100)[a]
Baseline MMSE: mean (score/30):	26.3
Extent of surgery:	
Lobectomy	5
Subtotal resection	14
Total resection	3
Estimated % resection: average:	95%

OUTCOME MEASURES

Primary outcome measures:
1. Complications:
   (a) neurological
   (b) system
   (c) infections
2. Functional status:
   (a) KPS
   (b) MMSE
   (c) neurological evaluation

Secondary measures:
1. Survival

Method of assessing outcomes:
1. Follow-up evaluations ⩽72 hours after surgery and "on approximately postoperative days 21, 60, 120, 180 and 210", including:
   (a) neurological assessment
   (b) KPS
   (c) MMSE
   (d) CT/MRI
2. Complications graded (severe, moderate or mild) by clinician

Length of follow-up:
Final evaluation "an average of 210 days after entry in the study"

RESULTS

Severe postoperative complications
10 patients suffered 15 AEs graded as severe by their neurosurgeon, categorised as follows [*n*(%)]:

Neurological – seizures [3(14%)]; Decline in neurological examination [3(14%)] – 1 postoperative stupor; 1 confusion; 1 decline with increased MR enhancement); intracranial hypertension [1(5%)]; clinically significant necrosis [1(5%)]

continued

Other – gastrointestinal bleeding [1(5%)]; vomiting [1(5%)]; dehydration [1(5%)]; pneumonia [1(5%)]; deep vein thrombosis [1(5%)]; phenytoin allergy [1(5%)]; intraabdominal lymphoma [1(5%)]

Moderate or mild postoperative complications [n(%)]:
Neurological – seizures [9(41%)]; headache [3(14%)]; clinically significant necrosis [2(9%)]; confusion [1(5%)]; weakness [1(5%)]; intracranial hypertension [1(5%)]; depression [1(5%)]; ataxia [1(5%)]; hallucinations [1(5%)]

Infectious – pneumonia [3(14%)]; urinary tract infections [3(14%)]; bronchitis [1(5%)]; costochondritis [1(5%)]

Other – postsurgical subgaleal fluid collection [1(5%)]; nausea [1(5%)]; deep vein thrombosis [1(5%)]; hypertension [1(5%)]; phenytoin toxicity [2(9%)]; carbamazepine allergy [1(5%)]; back pain [1(5%)]; hip pain [1(5%)]; rash [1(5%)]

- In total, 12/22 (55%) patients had seizures of one degree or another (average time from surgery to first seizure: 2.7 months)
- No wound infections were recorded in any patient

Perioperative period:

Perioperative death: *n* (%)	0
Reoperation within 30 days: *n* (%)	1 (5%)
Seizures within 30 days: *n* (%)	2 (9%)
Length of hospital stay: median	8

Radiotherapy:

Median cumulative dose: Gy (interquartile range)	55.8 (51.0–61.2)

Reoperation:

Patients undergoing reoperation	9 (1 twice)
Mean time after first operation: weeks	34
Histopathology at reoperation:	
Necrosed/quiescent tumour	2 (22%)
Active tumour	7 (78%)

Survival

Median survival: weeks (95% CI)	42 (31.9 to 54.0)[a]
6-month survival: *n* (%)	18 (82%)
12-month survival: *n* (%)	8 (36%)
18-month survival: *n* (%)	4 (18%)

Mean KPS

Initial evaluation	82
Surgery night	67
Discharge	78
Start of RT	80
Final evaluation (average 210 days after entry)	58

Average dexamethasone dose:

Postoperative day 1: mg/day (range)	45 (16–120)
Postoperative day 7: mg/day (range)	25 (1.5–120)
Postoperative day 21: mg/day (range)	15 (1–96)
Postoperative day 60: mg/day (range)	7 (0.5–32)

MMSE
Serial assessments "showed no significant differences in cognitive function"

METHODOLOGICAL COMMENTS

Prospective?
Yes

Consecutive patients enrolled?
Unclear

Selection/randomisation:
Details recorded for all eligible patients

Eligibility criteria stated?
Yes

Outcome measures:
Some primary outcomes dependent on subjective judgement, particularly with respect to "severe" vs "mild or moderate" postoperative events

Protocol violations specified:
1 patient mistakenly enrolled despite KPS of 40

Follow-up/attrition:
All patients accounted for (no withdrawals). Survivors censored alive at last follow-up.

Data analysis:
Statistical tests used:
- Kaplan–Meier median estimates of survival

Generalisability:
Age profile of cohort is more representative of affected population than other trials.

Conflict of interest:
Study supported by Guilford Pharmaceuticals

GENERAL COMMENTS
- The one AA patient is the only long-term survivor (alive at 169 weeks)
- 10 patients are common to this review and a subsequent retrospective analysis of patients treated at Johns Hopkins University[154]
- Median survival varied by centre (182 vs 292 vs 373 days)

[a] Data do not appear in the published findings of the trial and have been extracted from additional findings and analysis contained in material presented to the FDA's Oncologic Drugs Advisory Committee.[155]

Temozolomide: randomised controlled trials

STUDY

Athanassiou *et al.*, 2005[182]

Country:	Greece
Setting:	"Multicenter"; unclear how many centres participated (listed authors are from 5 different oncology departments)
Recruitment dates:	January 2000–December 2002
Study design:	RCT

SUBJECTS

Total number: 130

Inclusion criteria included:
- Age ⩾18 years
- Histologically confirmed GBM (WHO classification)
- KPS ⩾60 years
- Adequate haematological, renal and hepatic function

Exclusion criteria:
- "Poor medical condition because of non-malignant systemic disease or acute infection"
- Any medical condition that could interfere with oral administration of TMZ

Subgroups?
KPS ⩽80

INTERVENTION

Intervention:
TMZ + RT

Intervention regimen:
1. During RT (6 weeks):
   (a) TMZ 75 mg/m^2/day for 7 days/week
2. 4-week break
3. Adjuvant treatment:
   (a) 150 mg/m^2/day on days 1–5 and 15–19 of 28-day cycles
   (b) 28-day cycle repeated 6 times
   (c) Antiemetic (unspecified) "routinely used"

Comparator regimen:
RT alone

Concurrent treatment:
Radiotherapy:
1. Fractionated focal irradiation at 2 Gy per fraction
2. Delivered once daily, 5 days per week for 6 weeks
3. Total dose = 60 Gy
4. Target volumes calculated on basis of preoperative CT/MRI:
   (a) For first 46 Gy – tumour + oedema + 2-cm margin (2.5-cm margin if no oedema)
   (b) For subsequent 14 Gy – tumour + 2.5cm margin

Notes:
Anticonvulsants and corticosteroids were given "as needed"

OUTCOME MEASURES

Primary outcome measure:
- PFS
- Survival

Secondary measures:
- Treatment-related toxicity

Method of assessing outcomes:
1. During RT:
   (a) weekly CBC counts
   (b) monthly blood chemistry
2. Subsequently:
   (a) follow-up appointments [every 2 months during year 1 and every 3 months during year 2; every adjuvant TMZ cycle (TMZ group only)], comprising:
      (i) neurological examination
      (ii) serum chemistry evaluation
      (iii) anticonvulsant level evaluation
      (iv) toxicity evaluations
   (b) CT/MRI before first adjuvant treatment cycle, every 2 months during year 1 and every 3 months during year 2
3. Progression was defined as
   (a) ⩾25% tumour growth or any new tumour on MRI/CT;
   (b) neurological progression (not defined); and/or
   (c) clinical progression (not defined)
4. AEs graded according to Common Toxicity Criteria (v 2.0)

Length of follow-up:
Median 11.2 months (range: 3.4–27 months)

PATIENT CHARACTERISTICS

	RT-only (*N* = 53)	**RT + TMZ (*N* = 57)**
Age: *n* (%) (years):		
⩽50	11 (20.8%)	9 (15.8%)
>50	42 (79.2%)	48 (84.2%)
Sex: *n* (%):		
M	34 (64.2%)	36 (63.2%)
F	19 (35.8%)	21 (36.8%)
KPS: *n* (%):		
⩽80	36 (67.9%)	30 (52.6%)
>80	17 (32.1%)	27 (47.4%)
Previous surgery: *n* (%):		
Biopsy	22 (41.5%)	24 (42.1%)
Partial resection	23 (43.4%)	23 (40.4%)
Complete resection	8 (15.1%)	10 (17.5%)
Mean days from diagnosis to treatment (95% CI):	35.6 (28.7 to 42.5)	34.4 (28.1 to 40.7)

[ambiguities in published table clarified by lead author in correspondence with PenTAG]

continued

RESULTS

Outcomes

	RT-only (*N* = 53)	RT + TMZ (*N* = 57)	*p*	Cox	
				HR	*p*
Survival					
Median: months (95% CI):	7.7 (5.3 to 9.2)	13.4 (9.5 to 17.1)	<0.0001	0.66	0.0003
Survival: % (95% CI):					
At 6 months	58.3 (46.4 to 73.3)	80.2 (70.4 to 91.4)			
At 12 months	15.7 (8.2 to 30.1)	56.3 (44.1 to 71.6)			
At 18 months	5.4 (1.5 to 19.6)	24.9 (14.7 to 42.1)			
PFS					
Median: months (95% CI):	5.2 (3.9 to 7.4)	10.8 (8.1 to 14.7)	<0.0001	0.68	0.0008
PFS: % (95% CI):					
At 6 months	44.9 (33.3 to 60.7)	67.1 (54.5 to 79.6)			
At 12 months	7.7 (2.8 to 21)	36.6 (25.2 to 52.7)			
At 18 months	0	10.1 (3.7 to 27.7)			
Subgroup – KPS ⩽60:					
Survival					0.065
PFS					0.26

Cox proportional hazards regression (factors other than treatment allocation)

	Survival		PFS	
Variable	**HR**	***p***	**HR**	***p***
Age: >50 vs ⩽50	1.86	0.0580	1.75	0.0670
KPS: >80 vs ⩽80	0.47	0.0420	0.60	0.0370
Extent of surgery: partial vs complete resection	1.24	0.2100	1.21	0.2200
Extent of surgery: biopsy vs complete resection	1.01	0.8800	0.96	0.5600

Adverse events
(RT + TMZ group: no AEs reported in RT-only group; percentages recalculated by PenTAG)

	n (%)
RT + concomitant TMZ phase	
Per patient (*N* = 57)	
Grade 3–4 leukopenia	2 (3.5%)
Grade 3–4 thrombocytopenia	3 (5.3%)
Fatal sepsis	1 (1.8%)
Adjuvant TMZ phase	
Per cycle (*N* = 240)	
Grade 3–4 leukopenia	5 (2.1%)
Grade 3–4 thrombocytopenia	12 (5.0%)
During the entire study period	
Per patient (*N* = 57)	
Rash	3 (5.3%)
Constipation	2 (3.5%)
Arthralgia	1 (1.8%)

- 46 (80%) of the RT + TMZ group completed ⩾1 cycle of adjuvant TMZ
- 35 (61.4%) of the RT + TMZ group completed all 6 cycles of adjuvant TMZ
- 9 (15.8%) of the RT + TMZ group had TMZ therapy reduced or interrupted because of myelotoxicity
- Late neurological AEs were not assessed "because of the short duration of follow-up"
- 10 (18.9%) of the RT-only group received TMZ as salvage therapy at disease progression
- None of the RT + TMZ group received chemotherapy at disease progression

METHODOLOGICAL COMMENTS

Prospective?
Yes

Selection/randomisation:
Randomisation methods not detailed

Groups similar at baseline?
Yes

Eligibility criteria stated?
Yes (although exclusion criteria are not necessarily completely reported)

Blinding:
None detailed

continued

Outcome measures:
Predominantly objective; however, definition of disease progression appears to be substantially dependent on assessment of treating clinician

ITT:
No. 20 patients were excluded as ineligible – 5 were randomised but not treated, 6 had ineligible histology (AA) and 9 were treated with hyperfractionated RT.

Follow-up/attrition:
All patients accounted for? Yes
Withdrawal specified? Yes (see table)
Withdrawal reasons given? Not in full (reasons for withdrawals from adjuvant TMZ phase not specified)

Reason for withdrawal	RT-only (*N* = 53)	RT + TMZ (*N* = 57)
Disease progression	2 (3.8%)	4 (7.0%)
Toxic effects		1 (1.8%)
Fatal sepsis		1 (1.8%)
Other/unspecified		16 (28.1%)
Total	**2 (3.8%)**	**22 (38.6%)**

Data analysis:
Statistical tests used:
- Kaplan–Meier method for survival and PFS
- 2-sided log-rank test for significance of difference in survival
- Multivariate Cox proportional-hazards model adjusting for possible confounding factors
- χ^2 test for difference between categorical variables at baseline
- *t*-test for difference between continuous variables at baseline

Power calculation at design?
None detailed

Generalisability:
Control arm survival and PFS were "relatively low compared with other series"; however, "considering age, KPS, and type of surgery, the majority of our patients had unfavorable baseline characteristics" when compared with Stupp *et al.*, 2005[181] and Stupp *et al.*, 2002.[183] Arguably, then, this cohort is more representative of the population at large

Conflict of interest:
None declared

STUDY

Stupp *et al.*, 2005[181]

Country: International (15 countries – AUS, A, B, CAN, CH, D, E, F, GB, ISR, I, NL, PL, SVN, S)
Setting: Multiple (85) centres
Recruitment dates: August 2000–March 2002
Study design: RCT

SUBJECTS

Total number: 573

Inclusion criteria:
- Age 18–70 years
- Grade IV glioblastomas
- Newly diagnosed
- WHO PS ⩽2
- Adequate haematological, renal and hepatic function

Exclusion criteria:
- Unstable or increasing dose of corticosteroids <14 days before randomisation

Subgroups?
- Supplementary appendix provides survival data by age, gender, extent of surgery, PS and baseline steroid status
- Analysis of sample of participants according to genetic classification (MGMT silencing status) in separate publication[56]

INTERVENTION

Intervention:
TMZ + RT

Intervention regimen:
1. During RT (⩽49 days):
   (a) TMZ 75 mg/m^2/day for 7 days/week
   (b) Prophylaxis against pneumonia (inhaled pentamidine or oral trimethoprim–sulfamethoxazole)
   (c) Optional antiemetic (metoclopramide or 5-hydroxytryptamine3 antagonist)
2. 4-week break
3. Adjuvant treatment:
   (a) 150 mg/m^2/day for 5 days; 23-day break
   (b) 28-day cycle repeated until disease progression or 6 cycles completed
   (c) Dose escalated to 200 mg/m^2/day at cycle 2 if tolerated
   (d) Required antiemetic (metoclopramide or 5-hydroxytryptamine3 antagonist)

Comparator regimen:
RT alone

Concurrent treatment:
Radiotherapy:
- Fractionated focal (2–3-cm margin) irradiation at 2 Gy per fraction
- Delivered once-daily, 5 days per week for 6 weeks
- Total dose = 60 Gy

continued

Chemotherapy:
During the trial period, no patients received chemotherapy other than oral TMZ as described. Following disease progression, TMZ was administered as 'salvage' chemotherapy in 60% of the RT only group and 25% of the RT + TMZ group.

Notes:
- Treatment commenced within 6 weeks of histological diagnosis
- Treatment at investigator's discretion after disease progression or 2 years' follow-up

PATIENT CHARACTERISTICS

	RT-only (*N* = 286)	RT + TMZ (*N* = 287)
Age (years):		
Median (range)	57 (23–71)	56 (19–70)
⩾50	205 (72%)	197 (69%)
Sex:		
M	175 (61%)	185 (64%)
F	111 (39%)	102 (36%)
PS (WHO):		
0	110 (38%)	113 (39%)
1	141 (49%)	136 (47%)
2	35 (12%)	38 (13%)
Previous surgery:		
Biopsy	45 (16%)	48 (17%)
Partial resection	113 (40%)	113 (39%)
Complete resection	128 (45%)	126 (44%)
Corticosteroid therapy at time of randomisation:		
Yes	215 (75%)	193 (67%)
No	70 (24%)	94 (33%)
Data missing	1 (<1%)	0
Diagnosis on central histopathological review:	(246 reviewed)	(239 reviewed)
GBM	229 (93%)	221 (92%)
AA/AOA	9 (4%)	7 (3%)
Inconclusive	3 (1%)	3 (1%)
Other	5 (2%)	8 (3%)
MGMT promoter status:[b]	(100 reviewed)	(106 reviewed)
Methylated	46 (46%)	46 (43%)
Unmethylated	54 (54%)	60 (57%)

OUTCOME MEASURES

Primary outcome measure:
Survival

Secondary measures:
1. PFS
   (a) "progression" is defined (per WHO criteria) as
      (i) increase in tumour size by 25%, and/or
      (ii) appearance of new lesions, and/or
      (iii) increased need for corticosteroids
2. Safety
3. QoL

Method of assessing outcomes:
1. During RT:
   (a) weekly clinical review
2. Commencing 21–28 days after RT:
   (a) 3-monthly comprehensive evaluation to establish:
      (i) progression (radiological assessment of tumour and review of need for corticosteroids)
      (ii) QoL (questionnaire and MMSE)
   (b) monthly clinical review (TMZ group only)

Length of follow-up:
- Median follow-up 28 months (cut-off at 10 May 2004)

RESULTS
1. Unadjusted HR for death (RT + TMZ vs RT- only) = 0.63 (95% CI 0.52 to 0.75; $p < 0.001$ by log-rank)
2. Unadjusted HR for death or disease progression (RT + TMZ vs RT- only) = 0.54 (95% CI 0.45 to 0.64; $p < 0.001$ by log-rank)
3. Adjusted HR for death (Cox proportional-hazards model) = 0.62 (95% CI 0.51 to 0.75)
4. Interruptions in therapy due to AEs occurred in 8 (3%) of the RT-only group and 12 (4%) of the RT + TMZ group
5. Maximum adjuvant TMZ (6 complete cycles) was received by 105 patients (47% of those who started adjuvant TMZ therapy; 37% of the whole RT + TMZ group)
6. Post-recurrence:
   (a) reoperation: 23% (RT + TMZ); 23% (RT)
   (b) chemotherapy: 58% (RT + TMZ); 72% (RT)
      (i) chemotherapy = TMZ: 25% (RT + TMZ); 60% (RT)
7. QoL measures were not reported
8. In subanalysis according to genetic status:[b]
   (a) in the methylated MGMT promoter group, unadjusted HR for death (RT + TMZ vs RT-only) was 0.51 (95%CI 0.31 to 0.84)
   (b) in the unmethylated group, unadjusted HR for death (RT + TMZ vs RT-only) was 0.69 (95% CI 0.47 to 1.02)

Grade 3/4 haematological toxicities: n (%)

	RT only (*N* = 286)	RT + TMZ (*N* = 287)
RT ± TMZ phase		
Leukopenia	0	7 (2.4%)
Neutropenia	0	12 (4.2%)
Thrombocytopenia	0	9 (3.1%)
Anaemia	0	1 (0.3%)
Any	0	19 (6.6%)
Adjuvant TMZ phase		
Leukopenia	0	11 (3.8%)
Neutropenia	0	9 (3.1%)
Thrombocytopenia	0	24 (8.4%)
Anaemia	0	2 (0.7%)
Any	0	32 (11.1%)
Entire study period		
Leukopenia	0	20 (7.0%)
Neutropenia	0	21 (7.3%)
Thrombocytopenia	0	33 (11.5%)
Anaemia	0	4 (1.4%)
Any	0	46 (16.0%)

continued

Survival

	RT-only (*N* = 286)	RT + TMZ (*N* = 287)	*p*
Median survival: months (95% CI)	12.1 (11.2 to 13.0)	14.6 (13.2 to 16.8)	0.001
Periodic survival rate: % (95% CI):			
6 months	84.2 (80.0 to 88.5)	86.3 (82.3 to 90.3)	
12 months	50.6 (44.7 to 56.4)	61.1 (55.4 to 66.7)	
18 months	20.9 (16.2 to 26.6)	39.4 (33.8 to 45.1)	
24 months	10.4 (6.8 to 14.1)	26.5 (21.2 to 31.7)	
Subgroups (*N*) – median survival: months[a]			
Age:			
<50 (172)	13.2	17.4	<0.001
⩾50 (401)	11.9	13.6	<0.001
Gender:			
Male (360)	11.4	14.1	<0.001
Female (213)	12.8	16.3	<0.001
Prior surgery:			
Resection (480)	12.9	15.8	<0.001
Biopsy only (93)	7.9	9.4	(NS)
WHO PS:			
0 (223)	13.3	17.4	<0.001
1 (277)	11.9	14.0	<0.001
2 (73)	10.5	9.9	(NS)
Baseline steroids:			
Yes (408)	11.0	13.5	<0.001
No (164)	16.2	19.7	0.005
PFS:			
Median PFS: months (95% CI)	5.0 (4.2 to 5.5)	6.9 (5.8 to 8.2)	<0.001
PFS: % (95% CI):			
At 6 months	36.4 (30.8 to 41.9)	53.9 (48.1 to 59.6)	
At 12 months	9.1 (5.8 to 12.4)	26.9 (21.8 to 32.1)	
At 18 months	3.9 (1.6 to 6.1)	18.4 (13.9 to 22.9)	
At 24 months	1.5 (0.1 to 3.0)	10.7 (7.0 to 14.3)	
Subanalysis according to MGMT promoter status:[b]			
Methylated:	**(*n* = 46)**	**(*n* = 46)**	
median survival: months (95% CI)	15.3 (13.0 to 20.9)	21.7 (17.4 to 30.4)	<0.007
median PFS: months (95% CI)	5.9 (5.3 to 7.7)	10.3 (6.5 to 14.0)	0.001
Unmethylated:	**(*n* = 54)**	**(*n* = 60)**	
median survival: months (95% CI)	11.8 (9.7 to 14.1)	12.7 (11.6 to 14.4)	0.06
median PFS: months (95% CI)	4.4 (3.1 to 6.0)	5.3 (5.0 to 7.6)	0.02

Non-haematological toxicities: n (%)[a]

	RT-only (*N* = 286)		RT + TMZ (*N* = 287)	
	Grade 2	**Grade 3/4**	**Grade 2**	**Grade 3/4**
RT ± TMZ phase				
Fatigue	61 (21.3%)	14 (4.9%)	74 (25.8%)	19 (6.6%)
Other constitutional	14 (4.9%)	2 (0.7%)	20 (7.0%)	5 (1.7%)
Rash/dermatological	15 (5.2%)	2 (0.7%)	26 (9.1%)	4 (1.4%)
Infection	4 (1.4%)	6 (2.1%)	3 (1.0%)	9 (3.1%)
Vision	35 (12.2%)	4 (1.4%)	39 (13.6%)	3 (1.0%)
Nausea/vomiting	9 (3.1%)	2 (0.7%)	38 (13.2%)	2 (0.7%)
Adjuvant TMZ phase				
Fatigue	–	–	73 (25.4%)	18 (6.3%)
Other constitutional	–	–	12 (4.2%)	6 (2.1%)
Rash/dermatological	–	–	13 (4.5%)	5 (1.7%)
Infection	–	–	6 (2.1%)	12 (4.2%)
Vision	–	–	28 (9.8%)	2 (0.7%)
Nausea/vomiting	–	–	52 (18.1%)	4 (1.4%)

continued

	RT-only (*N* = 286)		RT + TMZ (*N* = 287)	
	Grade 2	**Grade 3/4**	**Grade 2**	**Grade 3/4**
Entire study period				
Fatigue	65 (22.7%)	20 (7.0%)	108 (37.6%)	38 (13.2%)
Other constitutional	18 (6.3%)	2 (0.7%)	27 (9.4%)	12 (4.2%)
Rash/dermatological	17 (5.9%)	3 (1.0%)	35 (12.2%)	9 (3.1%)
Infection	5 (1.7%)	8 (2.8%)	7 (2.4%)	20 (7.0%)
Vision	44 (15.4%)	6 (2.1%)	59 (20.6%)	5 (1.7%)
Nausea/vomiting	9 (3.1%)	3 (1.0%)	79 (27.5%)	6 (2.1%)

Other adverse events: n (%)

	RT-only (*N* = 286)	**RT + TMZ (*N* = 287)**
RT ± TMZ phase		
Thromboembolic events	16 (6%)	12 (4%)
Fatal brain haemorrhage	0 (0%)	2 (1%)
Pneumonia	5 (2%)	3 (1%)
Opportunistic infections	1 (<1%)	1 (<1%)

METHODOLOGICAL COMMENTS

Prospective?
Yes

Selection/randomisation:
Central randomisation (methods not detailed)
Stratification according to PS, type of surgery and treatment centre

Groups similar at baseline?
Yes ("slightly more" patients in the RT only group than in the RT + TMZ group were receiving corticosteroids at the time of randomisation: 75% vs 67%)

Eligibility criteria stated?
Yes

Blinding:
None stated

Outcome measures:
Objective

ITT:
Yes

Follow-up/attrition:
All patients accounted for? No: in the RT + TMZ group, specified withdrawals pre adjuvant TMZ total 60 and specified number starting adjuvant TMZ is 223 (totalling 4 less than entire group of 287)
Withdrawal specified? Yes (see table)
Withdrawal reasons given? Yes (see table)

Reason for withdrawal	**RT-only (*N* = 286)**	**RT + TMZ (*N* = 287)**
Disease progression	17 (6%)	108 (38%)
Toxic effects	0	31 (11%)
Decision by patient	0	8 (3%)
Other/unspecified	9 (3%)	31 (11%)
Total	**26 (9%)**	**178 (62%)**

Protocol violations:
1 patient assigned to RT-only received RT + TMZ

Data analysis:
Statistical tests used:
- Kaplan–Meier method for overall survival and PFS
- 2-sided log-rank test for significance of unadjusted HR
- Cox proportional-hazards model for adjusting HR to account for possible confounding factors (extent of prior surgery, PS, centre, age, corticosteroid use at randomisation, sex, MMSE, tumour location)

continued

Power calculation at design?
Yes (80% power at a significance level of 0.05 to detect a 33% increase in median survival, assuming that 382 deaths occurred)

Generalisability:
Although the protocol of this study specified GBM only, 7–8% of patients were found, on central review, to have grade III tumours. Failure to report confirmed GBM separately complicates application of this data to grade III or IV patients

Conflict of interest:
Trial and lead authors substantially funded by Schering-Plough

[a] Data extracted from supplementary appendix published on NEJM website.
[b] Data extracted from separate article by Hegi *et al.*, (2005).[56]

Temozolomide: case series

STUDY

Stupp *et al.*, 2002[183]
Country: Switzerland
Setting: 2 university hospitals
Recruitment dates: Not stated
Study design: CS (Phase 2 pilot study)

SUBJECTS

Total number: 64

Inclusion criteria:
- Age ⩾18 years
- Newly diagnosed, histologically proven GBM (per WHO)
- Eastern Cooperative Oncology Group PS ⩽2
- Adequate haematological, renal and hepatic function
- ⩽28 days since surgery (diagnostic biopsy or resection)

Exclusion criteria included:
- Other severe underlying disease
- Any medical condition that could interfere with the oral administration of TMZ
- Any previous or concurrent malignancies at other sites (except surgically cured carcinoma in situ of the cervix and non-melanoma skin cancer)

Subgroups?
Eligible patients with confirmed GBM

INTERVENTION

Intervention:
TMZ

Intervention regimen:
1. During RT (6–7 weeks):
   (a) TMZ:
      (i) 75 mg/m^2/day
      (ii) given to patients in a fasting state, 1 h before RT
      (iii) patients 1–16 took TMZ on RT days only
      (iv) patients 17– also had TMZ (in a.m.) on non-RT days
   (b) Patients 16– received prophylaxis against pneumonia (inhaled pentamidine)
   (c) Prophylactic antiemetics used "only as required"
2. 4-week break
3. Adjuvant TMZ:
   (a) 200 mg/m^2/day for 5 days; 23-day break
   (b) 28-day cycle repeated until disease progression or 6 cycles completed
   (c) Prophylactic antiemetics (5-hydroxytryptamine3 antagonists) routinely prescribed once a day before adjuvant TMZ

Concurrent treatment:
Radiotherapy:
- Fractionated focal (2–3-cm margin) at 2 Gy per fraction
- Delivered once-daily, 5 days per week for 6 weeks
- Total dose = 60 Gy

Chemotherapy:
During the trial period, no patients received chemotherapy other than oral TMZ as described

Notes:
Anticonvulsants and corticosteroids were administered "as needed"

PATIENT CHARACTERISTICS

N:	64
Age: median (range) (years):	52 (24–70)
Sex:	
M	39 (61%)
F	25 (39%)
PS (ECOG):	
0 or 1	55 (86%)
2	9 (14%)
PS (KPS):	
⩾90%	41 (64%)
⩽80%	23 (36%)
Previous surgery:	
Biopsy	15 (23%)
Partial resection	22 (34%)
Complete resection	27 (42%)
Median time from diagnosis to treatment: days (range):	25 (14–45)

continued

OUTCOME MEASURES

Primary outcome measure:
Safety

Secondary measures:
Survival

Method of assessing outcomes:
1. Haematology:
   (a) Complete blood counts
      (i) weekly during RT
      (ii) before and at day 21 of each cycle of adjuvant TMZ
   (b) Blood chemistry analysis
      (i) monthly during RT
      (ii) before each cycle of adjuvant TMZ
2. physical examination
   (a) "at least" 1 per month during adjuvant TMZ
3. MRI
   (a) before first cycle of adjuvant TMZ
   (b) subsequently, every 2 months during first year
   (c) every 2–3 months during the second year after study entry
4. Adverse events graded according to Common Toxicity Criteria (version 2.0)

Length of follow-up:
- Median follow-up 23 months (⩾10-month follow-up of survivors)

RESULTS
1. RT + TMZ:
   (a) Of 3 infections requiring hospitalisation:
      (i) 2 were for pneumonia (prophylaxis introduced to regimen for subsequent patients)
      (ii) 1 required surgical revision of scar infection and osteomyelitis 3 weeks after RT
2. Adjuvant TMZ:
   (a) Median number of cycles per patient: 5.5
   (b) Early discontinuation due to disease progression: 24 (39%)
3. 24 patients (39%) received all concomitant and adjuvant TMZ as planned in protocol
4. Median survival in eligible patients with confirmed GBM (n = 58) was 16 months

Incidence of haematological toxicity/infection

	Grade 3	Grade 4	All grades
RT + TMZ phase (*N* = 62):			
Haematological toxicity:			
Lymphocytopenia	14 (23%)	35 (56%)	49 (79%)
Neutropenia	2 (3%)	2 (3%)	4 (6%)
Thrombocytopenia	3 (5%)	1 (2%)	4 (6%)
Anaemia	2 (3%)	0	2 (3%)
Infection	1 (2%)	2 (3%)	3 (5%)
Adjuvant TMZ phase:			
Per patient (*N* = 49)			
Haematological toxicity:			
Lymphocytopenia	14 (29%)	20 (41%)	34 (69%)
Neutropenia	1 (2%)	2 (4%)	3 (6%)
Thrombocytopenia	5 (10%)	2 (4%)	7 (14%)
Anaemia	1 (2%)	0	1 (2%)
Infection	0	0	0
Per cycle (*N* = 216)			
Haematological toxicity:			
Lymphocytopenia	78 (36%)	60 (28%)	138 (64%)
Neutropenia	3 (1%)	2 (1%)	5 (2%)
Thrombocytopenia	12 (6%)	2 (1%)	14 (6%)
Anaemia	1 (0%)	0	1 (0%)
Infection	0	0	0

continued

Survival

	n	Median survival: months (95% CI)	12-month survival: months (95% CI)	18-month survival: months (95% CI)	24-month survival: months (95% CI)
All	64	16.0 (10.9 to 21.2)	58 (46 to 70)	36 (24 to 50)	31 (19 to 44)
Age (years)					
<50	22	18.8	73	56	50
≥50	42	11.1	50	25	20
Resection					
Complete	27	18.8	73	52	47
Partial	22	16.0	61	35	35
Biopsy	15	5.3	18	9	0
RPA class[a]					
III	18	>24			51 (26 to 76)
IV	28	13.8 (9.9 to 17.7)			32 (12 to 51)
V	14	9.2 (6.2 to 12.3)			0

Incidence of non-haematological toxicity

	Grade 2	Grade 3	All grades
RT + TMZ phase (*N* = 62):			
Nausea	5 (8%)	2 (3%)	7 (11%)
Rash	0	1 (2%)	1 (2%)
Fatigue	6 (10%)	2 (3%)	8 (13%)
Adjuvant TMZ phase (*N* = 49):			
Nausea	5 (10%)	3 (6%)	8 (16%)
Rash	0	0	0
Fatigue	7 (14%)	1 (2%)	8 (16%)

METHODOLOGICAL COMMENTS

Prospective?
Yes

Selection/randomisation:
Not detailed; unclear whether consecutive patients enrolled

Eligibility criteria stated?
Yes (although exclusion criteria are not necessarily completely reported)

Outcome measures:
Objective

ITT:
Yes (for survival analysis; safety results reported as proportions of treated patients)

Follow-up/attrition:
Not possible to account for all patients in data given: total cohort – specified withdrawals > adjuvant TMZ group
Withdrawals:
1. 2 patients withdrew before commencing TMZ (1 patient refused TMZ; 1 was ineligible because of chronic hepatitis)
2. During RT + TMZ
   (a) 3 patients were found to have ineligible histology (1 AA; 2 AOA)
   (b) 4 patients withdrew from TMZ owing to toxic effects
   (c) 4 patients withdrew because of progression (3 disease; 1 infection)
3. During adjuvant TMZ
   (a) 24 patients withdrew because of disease progression
   (b) 1 patient died of "chemotherapy overdose" (thrombocytopenia, neutropenia, septicaemia) after mistakenly receiving adjuvant TMZ for 30 consecutive days

continued

Data analysis:
Statistical tests used:
- Kaplan–Meier method for overall survival and PFS

Generalisability:
Age range appears low for patient group (oldest patient 70)

Conflict of interest:
Trial supported by Schering-Plough

[a] RPA class = Recursive Partitioning Analysis prognostic class derived from Radiation Therapy Oncology Group (RTOG) trial data, as reported by Curran and colleagues.[225] All patients in Class III are <50 years old; all patients in class V are ⩾50 years old.

STUDY

Lanzetta *et al.*, 2003[184]

Country:	Italy
Setting:	National neurotraumatology institute/university neurosurgical department
Recruitment dates:	October 1999–March 2001
Study design:	Prospective case series

SUBJECTS

Total number: 24

Inclusion criteria:
- Histopathological diagnosis of GBM
- Age ⩾18 years
- PS (ECOG) <2
- Life expectancy ⩾12 weeks at study entry
- Previous surgery (debulking or biopsy)

Exclusion criteria included:
- Significant renal, hepatic or haematological dysfunction
- Previous chemotherapy
- Any medical condition interfering with oral administration of TMZ
- Any previous or concurrent malignancies at other sites (except basal cell carcinomas and carcinoma *in situ* of the cervix)
- Any other severe underlying disease
- Pregnancy

Subgroups?
None specified

INTERVENTION

Intervention:
TMZ

Intervention regimen:
1. During RT:
   (a) TMZ at 75 mg/m^2/day, 7 days/week for 6 weeks
2. 4-week break
3. Adjuvant TMZ:
   (a) 200 mg/m^2/day for 5 days
   (b) Cycle (length unspecified) repeated 6 times

Concurrent treatment:
Radiotherapy:
- 2 Gy per fraction
- Delivered once daily, 5 days/week for 6 weeks
- Total dose = 60 Gy

Other:
- Antiemetics, corticosteroids and anticonvulsants "administered in case of need"

OUTCOME MEASURES

Primary outcome measure:
Safety

Secondary measures:
- Survival (study entry → death or last follow-up)
- Tumour response
- PFS
- QoL

Method of assessing outcomes:
1. Haematology:
   (a) during RT
      (i) weekly complete blood counts
      (ii) monthly blood chemistry analysis
   (b) during adjuvant TMZ
      (i) complete blood counts and blood chemistry analysis before and at day 21 of each cycle
2. Neurological evaluation and physical examination:
   (a) "at least" 1 per month during adjuvant TMZ
   (b) relative changes graded on 5-point scale: +2 (definitely better) to –2 (definitely worse)
3. MRI:
   (a) before first cycle of adjuvant TMZ
   (b) subsequently, every 3 months during first year
4. Complete response (CR) of tumour =
   (a) evidence of disappearance of enhancing tumour on consecutive MRIs ⩾1 month apart
   (b) no corticosteroid use "except for physiological doses"
   (c) stable or improved neurological condition
5. Partial response (PR) of tumour =
   (a) evidence of ⩾50% reduction of enhancing tumour on consecutive MRIs ⩾1 month apart
   (b) corticosteroid use stable or reduced
   (c) stable or improved neurological condition

continued

6. Disease progression =
   (a) increase in tumour size by 25%, and/or
   (b) appearance of new lesions, and/or
   (c) neurological deterioration + steroids stable or increased
7. QoL questionnaire (EORTC QLQ-C30):
   (a) on day 1 of treatment
   (b) after every clinical examination throughout the study
8. AEs graded according to NCIC-CTC scale

Length of follow-up:
Median follow-up 18 months (range: 9–28.5 months; cut-off January 2003)

PATIENT CHARACTERISTICS

N:	21
Age: median (range) (years):	44 (25–75)
Sex:	
M	13 (63%)
F	8 (37%)
PS (ECOG):	
0 or 1	17 (85%)
2	4 (15%)
PS (KPS):	
⩾90%	14 (67%)
⩽80%	7 (33%)
Previous surgery:	
Partial resection	17 (85%)
Biopsy	4 (15%)
Median time from diagnosis to treatment: days (range):	25 (14–45)

RESULTS

1. Non-haematological toxicity incompletely reported:
   (a) nausea:
      (i) 7 patients required antiemesis during RT + TMZ
      (ii) 6 patients required antiemesis during adjuvant TMZ
   (b) fatigue:
      (i) "Mild-to-moderate fatigue was reported in 3 patients both in the concomitant phase and in adjuvant TMZ phase"
2. Recursive partitioning analysis suggested age, PS and extent of prior surgery have an impact on survival rates.
3. QoL measures were not reported.

Incidence of haematological toxicity/infection

	Grade 3	Grade 4	Grade 3 or 4
RT + TMZ phase			
Per patient (*N* = 21):			
Haematological toxicity:			
lymphocytopenia	6 (29%)[a]	9 (43%)[a]	15 (71%)[a]
neutropenia	1 (5%)[a]	1 (5%)[a]	2 (10%)[a]
thrombocytopenia	2 (10%)[a]	1 (5%)[a]	3 (14%)[a]
anaemia	1 (5%)[a]	0	1 (5%)[a]
Infection	0	0	0
Adjuvant TMZ phase			
Per cycle (*N* = 85):			
Haematological toxicity:			
lymphocytopenia	28 (33%)[a]	11 (13%)[a]	39 (46%)[a]
neutropenia	3 (4%)[a]	2 (2%)[a]	5 (6%)[a]
thrombocytopenia	6 (7%)[a]	2 (2%)[a]	8 (9%)[a]
anaemia	1 (1%)[a]	0	1 (1%)[a]
Infection	0	0	0

[a] Percentages recalculated by PenTAG

Survival

Median survival: months (range)	15.7 (10.25–30.5)
12-month survival	"58%"
18-month survival	"36%"
Complete response:	
n (%)	2 (10%)
median duration: months (range)	26.7 (26.35–27)
Partial response:	
n (%)	4 (19%)
median duration: months (range)	19.1 (15.5–26)
Median PFS: months (range)	17 (11.5–27)

METHODOLOGICAL COMMENTS

Prospective?
Yes

Consecutive patients?
Not clear

Selection/randomisation:
Not detailed

Eligibility criteria stated?
Yes (although exclusion criteria are not necessarily completely reported)

Outcome measures:
Definition of tumour response and disease progression substantially dependent on subjective neurological assessment of treating clinician

ITT:
No (3 ineligible patients discounted from analysis)

Protocol violations specified:
In 6 patients, RT took place over a longer period than the planned 6 weeks

continued

Follow-up/attrition:
All patients accounted for? Yes
Withdrawal specified? Yes
Withdrawal reasons given? Yes:
- 2 patients withdrew before adjuvant TMZ phase following disease progression
- 7 patients withdrew during adjuvant TMZ phase following disease progression

Data analysis:
Statistical tests used:
- Recursive partitioning analysis to analyse prognostic factors affecting survival rates

Power calculation at design?
No

Generalisability:
Median age is low for patient group

Conflict of interest:
None specified

Appendix 9

NCI toxicity grades for reported adverse effects

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Haematological				
Anaemia – haemoglobin	<LLN – 100 g/L	80 – <100 g/l	65–80 g/l	<65 g/l
Leukopenia – total WBC	<LLN – 3.0 × 10^{9s}/l	⩾2.0 – <3.0 × 10^9/l	⩾1.0 – <2.0 × 10^9/l	<1.0 × 10^9/l
Lymphocytopenia – lymphocytes	<LLN – 1.0 × 10^9/l	⩾0.5 – <1.0 × 10^9/l	<0.5 × 10^9/l	–
Neutropenia – neutrophils	⩾1.5 – <2.0 × 10^9/l	⩾1.0 – <1.5 × 10^9/l	⩾0.5 – <1.0 × 10^9/l	<0.5 × 10^9/l
Thrombocytopenia – platelets	<LLN – <75.0 × 10^9/l	⩾50.0 – < 75.0 × 10^9/l	⩾10.0 – < 50.0 × 10^9/l	<10.0 × 10^9/l
Constitutional				
Fatigue	Increased fatigue over baseline, but not altering normal activities	Moderate (e.g. decrease in performance status by 1 ECOG level or 20% Karnofsky or Lansky) or causing difficulty performing some activities	Severe (e.g. decrease in performance status by ⩾2 ECOG levels or 40% Karnofsky or Lansky) or loss of ability to perform some activities	Bedridden or disabling
Other	Mild	Moderate	Severe	Life-threatening or disabling
Dermatological				
Rash/desquamation	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface area or localised desquamation or other lesions covering <50% of body surface area	Symptomatic generalised erythroderma or macular, papular or vesicular eruption or desquamation covering ⩾50% of body surface area	Generalised exfoliative dermatitis or ulcerative dermatitis
Gastrointestinal				
Nausea	Able to eat	Oral intake significantly decreased	No significant intake, requiring i.v. fluids	–
Vomiting	1 episode in 24 h over pretreatment	2–5 episodes in 24 h over pretreatment	⩾6 episodes in 24 h over pretreatment; or need for i.v. fluids	Requiring parenteral nutrition; or physiological consequences requiring intensive care; haemodynamic collapse
Infection				
Infection	Mild, no active treatment	Moderate, localised infection, requiring local or oral treatment	Severe, systemic infection, requiring. i.v. antibiotic or antifungal treatment or hospitalisation	Life-threatening sepsis (e.g. septic shock)

continued

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Ocular/visual				
Vision	Mild/asymptomatic	Symptomatic and interfering with function, but not interfering with activities of daily living	Symptomatic and interfering with activities of daily living	Unilateral or bilateral loss of vision (blindness)

LLN, lower limit of normality.

Appendix 10

Critical appraisal of BCNU-W industry economic submission

Critical appraisals are set out in *Tables 65* and *66*.

TABLE 65 *Appraisal of BCNU-W economic submission according to NICE criteria*

Aspect of method	NICE methodological requirement	Compliance of submission?
The need for a reference case	Submissions to NICE should include an analysis of results generated using these reference case methods Inclusion of additional analyses if these are justified and clearly distinguished from the reference case Failure to meet the reference case requirements should be clearly specified and justified, and the implications quantified (as far as possible)	Yes
Defining the decision problem	Estimating the clinical and cost-effectiveness should begin with a clear statement of the decision problem, in terms of: • technologies being compared • the relevant patient group(s) This statement should be consistent with the Institute's scope for the appraisal	Yes. Section 3 of the industry submission aims to assess the cost-effectiveness of: "surgery plus carmustine implants followed by radiotherapy and other usual care, vs. surgery plus placebo implants followed by radiotherapy and other usual care" In newly diagnosed high-grade glioma patients (Although not explicitly stated in the Introduction, the methods are clearer that this is being assessed in adults only)
Perspective	For outcomes, "include all direct health effects whether for patients or, where relevant, other individuals (principally carers)" For costs, an NHS and PSS perspective should be adopted	Direct health effects are included (QALYs) An NHS perspective on costs is implicitly adopted
Type of economic evaluation	Cost-effectiveness analysis = the appropriate form of evaluation Health effects should be expressed in QALYs	Yes. QALYs are the primary outcome in the decision model
Time horizon	Horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies compared	Yes. Time horizon for the model is until the death of all patients

continued

TABLE 65 *Appraisal of BCNU-W economic submission according to NICE criteria (cont'd)*

Aspect of method	NICE methodological requirement	Compliance of submission?
Synthesis of evidence on outcomes	The analysis of clinical effectiveness should consider the: • range of typical patients • normal clinical circumstances • clinically relevant outcomes • comparison with relevant comparators The analysis should include measures of both relative and absolute effectiveness, appropriate measures of uncertainty, and data from all relevant studies Any systematic review of outcomes should therefore: • describe the process of identifying relevant studies • describe study selection and data extraction methods • describe any critical appraisal tools used • identify probable treatment effect modifiers Meta-analysis (statistically pooled estimates of outcomes) is appropriate where there is sufficient relevant and valid data that use measures of outcome that are comparable	Clinical effectiveness estimates for the cost-effectiveness study are derived from a single Phase 3 trial (t-301: Westphal *et al.*, 2003[151]), so no evidence synthesis was conducted. (Evidence from another Phase 3 trial of carmustine implants was not included in the economic evaluation, presumably because of the small sample size, $n = 32$) Both relative and absolute measures of effectiveness were reported
Valuing health effects	Health effects should be valued as QALYs: as quantified using "a standardised and validated (non-disease-specific) instrument" for measuring health-related QoL In turn, "the value of changes in patients' health-related QoL (i.e. utilities) should be based on public preferences elicited using a choice-based method" Evidence should be presented with any data taken from the literature identified systematically	Health effects were modelled as QALYs The QALY values pre- and post-progression are based on very simple assumptions and loosely based on available estimates in the literature. They are not based on public preferences about the specific conditions elicited using a choice-based method (nevertheless, these reflect the methods used in the previous HTA appraisal of temozolomide for recurrent high-grade gliomas)
Evidence on costs	Costs should relate to resources that are under the control of the NHS and PSS, and where differential effects on costs between the technologies being compared are possible These resources should be valued using the prices relevant to the NHS and PSS. (Where the actual price paid differs from the public list price, the public list price should be used; sensitivity analysis should assess the implications of variations from this price) The Institute should be made aware of any situations where taking a broader perspective – that is, documenting differential impact on non-NHS or non-PSS costs – is justified	The only cost included in the base-case analysis is that of the implants themselves. Per bed-day costs per inpatient stay are also used in the sensitivity analysis They assume that all unused whole wafers from an 8-wafer pack would be frozen and used in other patients, but do not cost the time or other resources involved in doing this, or assess the likelihood of this in routine practice This is justified on the basis of evidence from the T-301 trial, in which side-effects (or other associated differences with implications for resource use) were equal in both arms. The cost implications of the statistically significantly higher chance of CSF and cerebral hypertension (as reported in the trial) is also explored in sensitivity analysis

continued

TABLE 65 *Appraisal of BCNU-W economic submission according to NICE criteria (cont'd)*

Aspect of method	NICE methodological requirement	Compliance of submission?
Discounting	For the reference case, an annual discount rate should be used of 1.5% for costs and 6% for effects (10th wave advice) When results are potentially sensitive to the discount rate used, sensitivity analysis should vary the rate between 0 and 6%	No discounting of costs or QALYs is conducted (NB discounting costs would make no difference to incremental costs)
Modelling methods	The models should "follow accepted guidelines", including full documentation and justification of structural assumptions and data inputs Also, probabilistic sensitivity analysis should be conducted on models to reflect the combined implications of uncertainty in parameters	The simple model adequately follows most elements of accepted guidelines (see following table) Probabilistic sensitivity analysis was carried out
Presentation: data values used and their sources	All data used to estimate clinical and cost-effectiveness should be presented in tabular form and include details of data sources For continuous variables, mean values should be presented and used For all variables, measures of precision should be detailed For probabilistic sensitivity analyses, the distributions used to characterise the uncertainty in input parameters should be defined and justified	All presented, in tabular form where appropriate All data sources stated (except cost of implants, but this cost is the same as the BNF published cost) Precision of assumed QALY value for living without symptoms not stated (because, not based on an empirical study)
Presentation: expected CE results	The expected value of each component of cost and expected total costs should be presented Expected QALYs for each option compared in the analysis should be presented ICERS should be calculated and presented as appropriate (i.e. using standard decision rules)	Yes (expected costs) Yes (expected QALYs) Yes (ICERs)
Presentation: parameter uncertainty in the CEA	Probabilistic sensitivity analysis should be carried out Confidence ellipses and scatter plots on the CE plane, and CEACs are the most appropriate ways of presenting this decision uncertainty	Yes (in addition to one-way sensitivity analysis of two key variables) Yes (CEAC only)
Presentation: other forms of uncertainty	For example, uncertainty about: the choice of studies included in any meta-analysis; the structural assumptions in the model Each alternative analysis should present separate probabilistic results	No alternative analyses presented
Presentation: analyses of patient subgroups	Where appropriate,[a] there should be separate estimates of clinical and cost-effectiveness for each relevant[a] patient subgroup For example, a 'per-protocol' (trial) subgroup analysis may be valid in addition to the ITT analysis of clinical effectiveness	No subgroup analyses presented

continued

TABLE 65 *Appraisal of BCNU-W economic submission according to NICE criteria (cont'd)*

Aspect of method	NICE methodological requirement	Compliance of submission?
Reflecting equity considerations in CEA	In the reference case, an additional QALY should receive the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs given equal weight

[a] Where capacity to benefit from treatment and/or costs is likely to differ (based on clear clinical justification, or biological plausibility).

TABLE 66 *Appraisal of Gliadel® economic submission according to criteria of Sculpher* et al.[211]

Judgement criterion	Assessment
1. Model structure	
Is there a clear statement of the decision problem, the context and the perspective?	Yes
Is a theory of the underlying disease detailed?	Yes – in fairly basic terms
Are the underlying assumptions involved in the model clearly specified? Are they justified? Are the implications of relaxing these assumptions described?	Specified – Yes Justified – mostly, and on the basis of little available relevant evidence [e.g. QALY values for living without symptoms post-surgery, or declining QoL once tumour progresses (e.g. assumed linear decline to zero in the absence of other reliable evidence)]
2. Disease states	
Is the chosen model type appropriate for the time dimension of the disease process?	Yes – although a Markov model would have allowed more detailed costing of resource consequences post-surgery
Is a justification of the choice of states within the model provided? If so, does this accord with the theory of disease process?	Not applicable – simple classification of post-surgery survival into pre- and post-progression phases
Is any empirical evidence provided on the suitability of the states (e.g. sensitivity to change in the underlying disease)?	Not applicable
Have any important disease states been omitted from the model?	Arguably the phase of receiving radiotherapy, and/or any concomitant and adjuvant chemotherapy, should be represented as separate disease/health states (as both health-related QoL and resource consumption will be different from pre-progression patients not receiving treatment)
3. Options	
Is there a clear statement of the options being evaluated?	Yes
Do these appear to cover the range of logical and feasible options?	Yes (i.e. given the scope of the NICE protocol)
4. Time horizon	
Is the time horizon of the analysis stated?	Yes
If so, is this justified in terms of the underlying disease and the effect of interventions?	Yes

continued

TABLE 66 *Appraisal of Gliadel® economic submission according to criteria of Sculpher* et al.[211] *(cont'd)*

Judgement criterion	Assessment
5. Cycle length (if relevant)	
If relevant, is the cycle length used in the model stated	Not applicable – not a Markov model
Is justification offered on the choice of cycle length? If so, does the justification relate to the disease process?	
6. Data identification	
Are the sources of parameter values in the model clearly stated?	Yes
Is reasonable empirical justification, from earlier iterations of the model, offered that these data are optimal?	Yes
For the first iteration of the model, has satisfactory justification been offered that data are based on a search of all the low-cost data sources (e.g. MEDLINE, DARE, Cochrane library)?	No – but not necessary here
Are ranges specified for parameters?	Yes (for PSA)
Is there evidence to suggest selective use of data?	Possibly: the selection of 0.8 as the utility value of symptom-free post-surgical survival may be optimistic, since it is partly based on values in the literature for similar-aged people in **average health** (i.e. does not reflect any side-effects of either cranial surgery, RT or the likely anxiety associated with living with a terminal disease). Nevertheless, our utility estimates for pre-progression/stable disease states, from the NHS VoHP, were also surprisingly high (0.80–0.88)
If some parameter estimates are based on elicitation of expert opinion, have the methods used for this purpose been adequately described (e.g. inclusion criteria, sample size, elicitation methods)?	Not applicable
Are the claims made about the model results tempered by the limitations of the data?	Not explicitly
7. Data incorporation	
For each parameter value, is there clear and reasonable justification of how data have been incorporated into the model?	Yes (NB very few parameters in the model)
Has a probabilistic sensitivity analysis been undertaken?	Yes
If so, do the distributions in parameter values reflect second order uncertainty?	Yes [except the distribution for sampling values of symptom-free utility, which is crudely assumed to be normally distributed about 0.8, with 3 standard deviations from 0.6 to 0.8 and 0.8 to 1.0 (constrained to 8.5)]
Have appropriate distributions been selected for each parameter?	Yes
Have interval rates been translated into transition probabilities using the appropriate formula?	Not applicable (Not a Markov model)
If appropriate, has a half-cycle correction been applied to adjust time-related estimate in the model?	Not applicable (Not a Markov model)
8. Internal consistency (i.e. does the model work in the way it is intended to work)	
Is there a statement about the tests of internal consistency that were undertaken?	No – but the calculations from this simple model have been checked to be accurate

continued

TABLE 66 *Appraisal of Gliadel® economic submission according to criteria of Sculpher* et al.[211] *(cont'd)*

Judgement criterion	Assessment
9. External consistency	
Are any relevant studies and/or models identified by the analyst for purpose of comparison?	Not applicable – the model's inputs use best available evidence and lead directly to the outputs; there are no other models or data sources against which to check or 'calibrate' the results of the model
Have any comparisons of the outputs of the model with independent external sources been reported?	Not applicable – see above
If so, are the conclusions justified? Have discrepancies been investigated and explained?	The conclusions are reasonably justified, except that the direct costs of healthcare in added months of life are not included in the analysis

Appendix 11

Critical appraisal of TMZ economic submission

Critical appraisals are set out in *Table 67*

TABLE 67 *Appraisal of TMZ economic submission according to NICE criteria*

Aspect of method	NICE methodological requirement	Compliance of submission?
The need for a reference case	Submissions to NICE should include an analysis of results generated using these reference case methods Inclusion of additional analyses if these are justified and clearly distinguished from the reference case Failure to meet the reference case requirements should be clearly specified and justified and the implications quantified (as far as possible)	**[Confidential information removed]**
Defining the decision problem	Estimating the clinical and cost-effectiveness should begin with a clear statement of the decision problem, in terms of: • technologies being compared • the relevant patient group(s) This statement should be consistent with the Institute's scope for the appraisal	**[Confidential information removed]**
Perspective	For outcomes, "include all direct health effects whether for patients or, where relevant, other individuals (principally carers)" For costs, an NHS and PSS perspective should be adopted	**[Confidential information removed]**
Type of economic evaluation	Cost-effectiveness analysis = the appropriate form of evaluation Health effects should be expressed in QALYs	**[Confidential information removed]**
Time horizon	Horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies compared	**[Confidential information removed]**

continued

TABLE 67 *Appraisal of TMZ economic submission according to NICE criteria (cont'd)*

Aspect of method	NICE methodological requirement	Compliance of submission?
Synthesis of evidence on outcomes	The analysis of clinical effectiveness should consider the: • range of typical patients • normal clinical circumstances • clinically relevant outcomes • comparison with relevant comparators The analysis should include measures of both relative and absolute effectiveness, appropriate measures of uncertainty and data from all relevant studies Any systematic review of outcomes should therefore: • describe the process of identifying relevant studies • describe study selection and data extraction methods • describe any critical appraisal tools used • identify probable treatment effect modifiers Meta-analysis (statistically pooled estimates of outcomes) is appropriate where there are sufficient relevant and valid data that use measures of outcome that are comparable	**[Confidential information removed]**
Valuing health effects	Health effects should be valued as QALYs: as quantified using "a standardised and validated (non-disease-specific) instrument" for measuring health-related QoL In turn, "the value of changes in patients' health-related QoL (i.e. utilities) should be based on public preferences elicited using a choice-based method" Evidence should be presented with any data taken from the literature identified systematically	**[Confidential information removed]**
Evidence on costs	Costs should relate to resources that are under the control of the NHS and PSS, and where differential effects on costs between the technologies being compared are possible These resources should be valued using the prices relevant to the NHS and PSS. (Where the actual price paid differs from the public list price, the public list price should be used; sensitivity analysis should assess the implications of variations from this price) The Institute should be made aware of any situations where a taking broader perspective – that is, documenting differential impact on non-NHS or non-PSS costs – is justified	**[Confidential information removed]**

continued

TABLE 67 *Appraisal of TMZ economic submission according to NICE criteria (cont'd)*

Aspect of method	NICE methodological requirement	Compliance of submission?
Discounting	For the reference case, an annual discount rate should be used of 1.5% for costs and 6% for effects (10th wave advice)	**[Confidential information removed]**
	When results are potentially sensitive to the discount rate used, sensitivity analysis should vary the rate between 0 and 6%	
Modelling methods	The models should "follow accepted guidelines", including full documentation and justification of structural assumptions and data inputs	**[Confidential information removed]**
	Also, probabilistic sensitivity analysis should be conducted on models to reflect the combined implications of uncertainty in parameters	
Presentation: data values used and their sources	All data used to estimate clinical and cost-effectiveness should be presented in tabular form and include details of data sources	**[Confidential information removed]**
	For continuous variables, mean values should be presented and used	
	For all variables, measures of precision should be detailed	
	For probabilistic sensitivity analyses, the distributions used to characterise the uncertainty in input parameters should be defined and justified	
Presentation: expected CE results	The expected value of each component of cost and expected total costs should be presented	Yes
	Expected QALYs for each option compared in the analysis should be presented	**[Confidential information removed]**
	ICERs should be calculated and presented as appropriate (i.e. using standard decision rules)	
Presentation: parameter uncertainty in the CEA	Probabilistic sensitivity analysis should be carried out	**[Confidential information removed]**
	Confidence elipses and scatter plots on the CE plane, and CEACs are the most appropriate ways of presenting this decision uncertainty	

continued

TABLE 67 *Appraisal of TMZ economic submission according to NICE criteria (cont'd)*

Aspect of method	NICE methodological requirement	Compliance of submission?
Presentation: other forms of uncertainty	For example, uncertainty about: the choice of studies included in any meta-analysis; the structural assumptions in the model Each alternative analysis should present separate probabilistic results	**[Confidential information removed]**
Presentation: analyses of patient subgroups	Where appropriate,[a] there should be separate estimates of clinical and cost-effectiveness for each relevant[a] patient subgroup For example, a 'per-protocol' (trial) subgroup analysis may be valid in addition to the ITT analysis of clinical effectiveness	**[Confidential information removed]**
Reflecting equity considerations in CEA	In the reference case, an additional QALY should receive the same weight regardless of the other characteristics of the individuals receiving the health benefit	Not applicable – QALYs not used

[a] Where capacity to benefit from treatment and/or costs are likely to differ (based on clear clinical justification, or biological plausibility).

Appendix 12

Weibull curve fitting in the economic model

Tables 68–70 and *Figure 41* show the estimates of all model parameters for overall survival times and the adjusted R^2 values and CIs for each fitted line for overall survival times.

TABLE 68 *Weibull parameter estimates for overall survival curves*

Treatment arm	Log λ (95% CI)	γ (95% CI)	Adjusted R^2
TMZ control	–7.469 (–7.748, –7.190)	1.794 (1.722, 1.866)	0.991
TMZ treatment (≤20 months)	–7.418 (–7.587, –7.249)	1.688 (1.731, 1.644)	0.997
TMZ treatment (>20 months)	–3.630 (–4.729, –2.531)	0.841 (0.609, 1.072)	0.988
BCNU-W placebo (≤21 months)	–8.599 (–8.828, –8.370)	2.089 (2.148, 2.030)	0.985
BCNU-W treatment (≤23 months)	–7.823 (–8.007, –7.638)	1.833 (1.880, 1.786)	0.988
Linear parameter estimates	**Alpha (95% CI)**	**Beta (95% CI)**	
BCNU-W placebo (>21 months)	0.213 (0.181, 0.246)	–0.0012 (–0.0015, –0.0010)	0.934
BCNU-W treatment (>23 months)	0.300 (0.273, 0.327)	–0.0013 (–0.0015, –0.0012)	0.967

TABLE 69 *Comparison of median overall survival reported in RCTs and fitted Weibull median overall survival*

	Median survival (weeks)		
Treatment arm	Trial	Predicted	Error (%)
BCNU-W placebo	51.04	51.92	1.72
BCNU-W treatment	60.72	58.52	3.62
TMZ control	52.43	52.38	0.09
TMZ treatment	63.26	65.21	3.09

TABLE 70 *Weibull parameter estimates for progression-free survival (TMZ only)*

Treatment arm	Log λ (95% CI)	γ (95% CI)	Adjusted R^2
TMZ control	–4.315 (–4.604, –4.026)	1.311 (1.229, 1.393)	0.983
TMZ treatment (≤12 months)	–4.908 (–5.228, –4.589)	1.308 (1.214, 1.402)	0.981
TMZ treatment (>12 months)	–3.145 (–3.890, –2.401)	0.861 (0.690, 1.032)	0.937

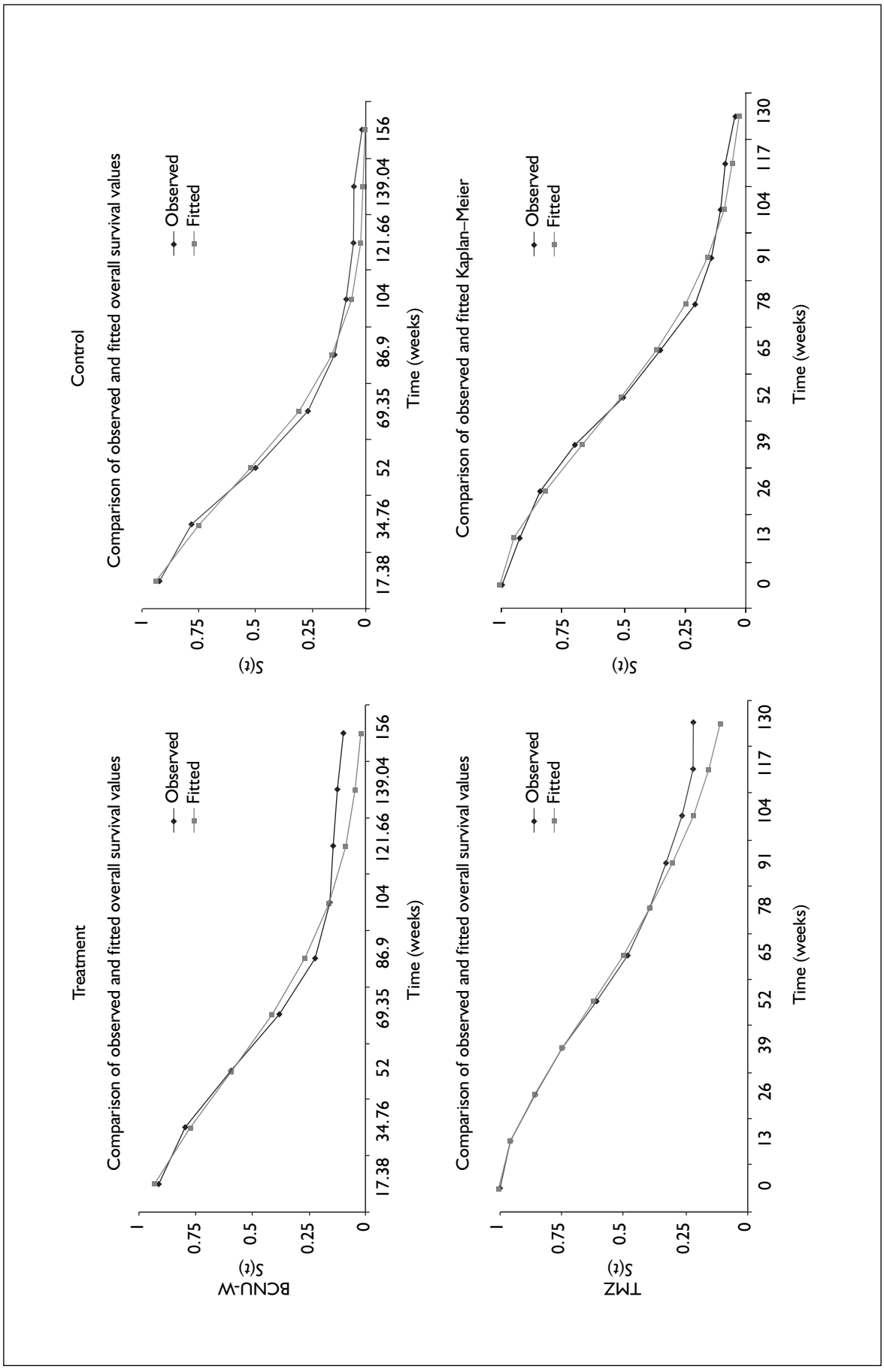

FIGURE 41 *Observed trial data and fitted curves used in the model* (Continued on next page.)

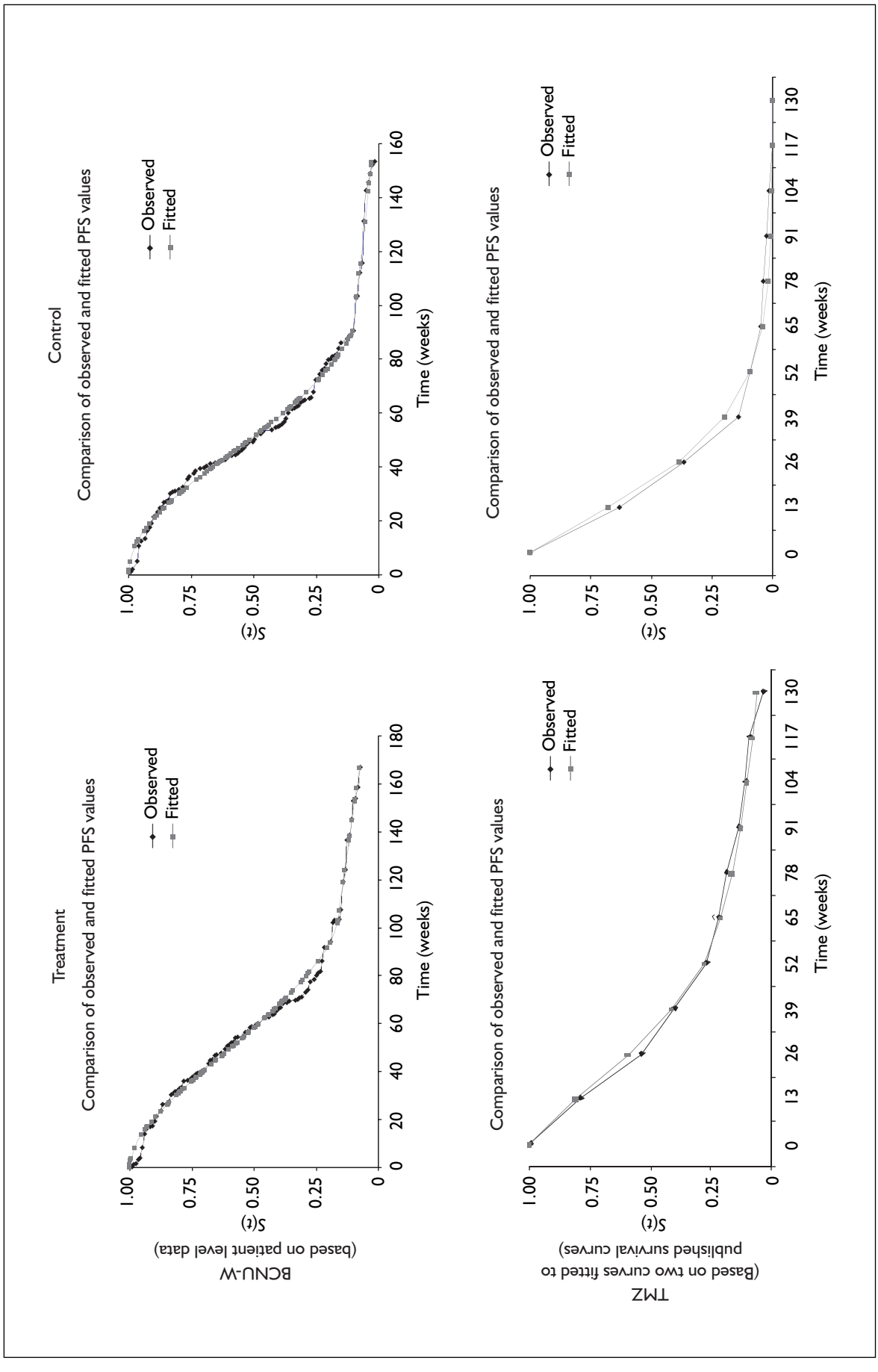

FIGURE 41 *(Cont'd) Observed trial data and fitted curves used in the model*

Appendix 13

Time-dependent transition probabilities used in the model

Time-dependent transition probabilities used in the model

The formula used to generate time-dependent transitional probabilities derived from Weibull approximations to published curves[216] is:

$$tp(t) = 1 - \exp\{\lambda(t-1)^{\gamma} - \lambda t^{\gamma}\}$$

where t relates to the current cycle number in the cohort simulation and lamda and gamma corresponding to the relevant values in *Tables 12*(*a*) and (*d*).

The formula used to generate time-dependent transitional probabilities derived from linear approximations to patient level data is

$$tp(t) = 1 - \frac{S(t)}{S(t-1)}$$

Where values for $S(t)$ and $S(t-1)$ are generated using the generic linear equation

$$S(t) = \alpha + \beta \times t$$

Alpha and Beta values used are those presented in *Tables 12*(*b*).

TABLE 71 *Time-dependent transition probabilities used in modelling the TMZ control arm*

Transition description	Parameter name	Value	Source
Any state that is not surgery or postoperative recovery to death	TPTP_*_DTH	1 – *P*(*overall survival*), where P(overall survival) is calculated using equations above	Weibull curve approximation to data presented in Stupp *et al*. 2005[181]
Remain in radiotherapy state	TPTP_RAD_RAD	1 – TPTP_RAD_DTH-TPTP_RDO_PRG, where TPTP_RAD_DTH is as calculated above.	Weibull curve approximation to data presented in Stupp *et al*. 2005[181]
Remain in stable state	TPTP_STB_STB	(1 – TPTP_STB_DTH-*P*(*progression*), where *both probabilities are* calculated using relevant equations above	Weibull curve approximations to data presented in Stupp *et al*. 2005[181]
Remain in progressive state	TPTP_PRG_PRG	1 – TPTP_PRG_DTH, where TPTP_PRG_DTH is as calculated above	Weibull curve approximation to data presented in Stupp *et al*. 2005[181]
Stable to progressive	TPTP_STB_PRG	*P*(progression free survival) – TPTP_STB_DTH, where *both probabilities are* calculated using relevant equations above	Weibull curve approximations to data presented in Stupp *et al*. 2005[181]

TABLE 72 *Time-dependent transition probabilities used in modelling the TMZ treatment arm*

Transition description	Parameter name	Value	Source
Any state that is not surgery or postoperative recovery to death	TPTM_*_DTH	1 – *P*(*overall survival*), where *P*(overall survival) is calculated using equations above	Weibull curve approximation to data presented in Stupp *et al*. 2005[181]
Remain in radiotherapy state	TPTM_RAD_RAD	1 – TPTM_RAD_DTH - TPTM_RDO_PRG, where TPTM_RAD_DTH is as calculated above.	Weibull curve approximation to data presented in Stupp *et al*. 2005[181]
Remain in stable state	TPTM_STB_STB	(1 – TPTM_STB_DTH- *P*(*progression*), where *both probabilities are* calculated using relevant equations above	Weibull curve approximations to data presented in Stupp *et al*. 2005[181]
Remain in progressive state	TPTM_PRG_PRG	1 – TPTM_PRG_DTH, where TPTM_PRG_DTH is as calculated above	Weibull curve approximation to data presented in Stupp *et al*. 2005[181]
Stable to progressive	TPTM_STB_PRG	*P*(progression free survival) – TPTM_STB_DTH, where *both probabilities are* calculated using relevant equations above	Weibull curve approximations to data presented in Stupp *et al*. 2005[181]

TABLE 73 *Time-dependent transition probabilities used in modelling the BCNU-W placebo arm*

Transition description	Parameter name	Value	Source
Any state that is not surgery or postoperative recovery to death	TPGP_*_DTH	1 – *P*(Overall survival), where P(overall survival) is calculated using relevant equations above	Weibull curve approximation to patient level data supplied by Link Pharmaceuticals
Remain in radiotherapy state	TPGP_RAD_RAD	1 – *TPGP_RAD_DTH*- TPGP_RDO_PRG, where *TPGP_RAD_DTH*) is as calculated above.	Weibull curve approximation to patient level data supplied by Link Pharmaceuticals
Remain in stable state	TPGP_STB_STB	1 – ((1 + ζ) × TPGP_STB_DTH), where TPGP_STB_DTH is as calculated above	Weibull curve approximation to patient level data supplied by Link Pharmaceuticals ζ derived using data presented in Westphal *et al*. 2003[151]
Stable to progressive	TPGP_STB_PRG	ζ × TPGP_STB_DTH, where TPGP_STB_DTH is as calculated above	Weibull curve approximation to patient level data supplied by Link Pharmaceuticals. ζ derived using data presented in Westphal *et al*. 2003[151]
Remain in progressive state	TPGP_PRG_PRG	1 – TPGP_PRG_DTH, where TPGP_PRG_DTH is as calculated above	Weibull curve approximation to patient level data supplied by Link Pharmaceuticals

TABLE 74 *Time-dependent transition probabilities used in modelling the BCNU-W treatment arm*

Transition description	Parameter name	Value	Source
Any state that is not surgery or postoperative recovery to death	TPGM_*_DTH	1 – *P*(Overall survival), where P(overall survival) is calculated using relevant equations above	Weibull curve approximation to patient level data supplied by Link Pharmaceuticals
Remain in radiotherapy state	TPGM_RAD_RAD	1 – *TPGM_RAD_DTH*-TPGM_RDO_PRG, where *TPGM_RAD_DTH*) is as calculated above	Weibull curve approximation to patient level data supplied by Link Pharmaceuticals
Remain in stable state	TPGM_STB_STB	1 – ((1+ζ) × TPGM_STB_DTH), where TPGM_STB_DTH is as calculated above	Weibull curve approximation to patient level data supplied by Link Pharmaceuticals ζ derived using data presented in Westphal *et al*. 2003[151]
Stable to progressive	TPGM_STB_PRG	ζ × TPGM_STB_DTH, where TPGM_STB_DTH is as calculated above	Weibull curve approximation to patient level data supplied by Link Pharmaceuticals ζ derived using data presented in Westphal *et al*. 2003[151]
Remain in progressive state	TPGM_PRG_PRG	1 – TPGM_PRG_DTH, where TPGM_PRG_DTH is as calculated above	Weibull curve approximation to patient level data supplied by Link Pharmaceuticals

Appendix 14

Scenarios used to elicit health state utility values

Health state scenario for stable malignant glioma

This scenario is derived from a QoL questionnaire in which the following statements were used to indicate the severity of various aspects of the condition:

- not at all
- a little
- a lot
- very much.

1. You have a mild headache and you often feel tired and drowsy.
2. Sometimes you feel nauseated but you don't actually vomit very often. You may occasionally lose your appetite.
3. You hardly ever have seizures.
4. Your vision is very occasionally slightly blurred and you may have a little difficulty reading.
5. You sometimes feel a little weak on one side of your body and have a little trouble with coordination but you do not need help with eating, dressing, washing and going to the toilet.
6. You hardly ever have trouble controlling your bladder.
7. You have no difficulty forming words but sometimes find it difficult to make yourself understood.
8. You sometimes have difficulty concentrating and sometimes forget things.
9. You feel a little irritable and are a little anxious and depressed about the future.

Health state scenario for stable malignant glioma during radiotherapy

This scenario describes a medical condition plus a specific treatment. The scenario is outlined below with some additional features due to the treatment.

This scenario is derived from outcome measures in which the following statements were used to indicate the severity of various aspects of the condition:

- not at all
- a little
- a lot
- very much.

1. You have a mild headache and you often feel tired and drowsy.
2. Sometimes you feel nauseated but you don't actually vomit very often. You may occasionally lose your appetite.
3. You hardly ever have seizures.
4. Your vision is very occasionally slightly blurred and you may have a little difficulty reading.
5. You sometimes feel a little weak on one side of your body and have a little trouble with coordination but you do not need help with eating, dressing, washing and going to the toilet.
6. You hardly ever have trouble controlling your bladder.
7. You have no difficulty forming words but sometimes find it difficult to make yourself understood.
8. You sometimes have difficulty concentrating and sometimes forget things.
9. You feel a little irritable and are a little anxious and depressed about the future.

Additional features due to treatment:

10. You lose your hair and your skin feels itchy.
11. You have difficulty sleeping.

Health state scenario for stable malignant glioma during radiotherapy and treatment with temozolomide

This scenario describes a medical condition plus a specific treatment. The scenario is outlined below with some additional features due to the treatment.

This scenario is derived from outcome measures in which the following statements were used to indicate the severity of various aspects of the condition:

- not at all

- a little
- a lot
- very much.

1. You have a mild headache and feel very tired and drowsy most of the time.
2. You usually feel nauseated and you vomit 2–5 times a day. You have poor appetite.
3. You hardly ever have seizures.
4. Your vision is very occasionally slightly blurred and you may have a little difficulty reading.
5. You sometimes feel a little weak on one side of your body and have a little trouble with coordination but you do not need help with eating, dressing, washing and going to the toilet.
6. You hardly ever have trouble controlling your bladder.
7. You have no difficulty forming words but sometimes find it difficult to make yourself understood.
8. You sometimes have difficulty concentrating and sometimes forget things.
9. You feel a little irritable and are a little anxious and depressed about the future.

Additional features due to treatment:

10. You lose your hair and your skin feels very itchy sometimes with a rash.
11. You have difficulty sleeping.
12. You are very susceptible to infections and sometimes have to be admitted to hospital for treatment.

Health state scenario for stable malignant glioma during radiotherapy and treatment with carmustine implants

This scenario describes a medical condition plus a specific treatment. The scenario is outlined below with some additional features due to the treatment.

This scenario is derived from outcome measures in which the following statements were used to indicate the severity of various aspects of the condition:

- not at all
- a little
- a lot
- very much.

1. You have a bad headache and you feel tired and drowsy.
2. Sometimes you feel nauseated but you don't actually vomit very often You may occasionally lose your appetite.
3. You often have seizures.
4. Your vision is blurred a lot of the time and you have great difficulty reading.
5. You sometimes feel a little weak on one side of your body and have a little trouble with coordination but you do not need help with eating, dressing, washing and going to the toilet.
6. You hardly ever have trouble controlling your bladder.
7. You have no difficulty forming words but sometimes find it difficult to make yourself understood.
8. You sometimes have difficulty concentrating and sometimes forget things.
9. You feel a little irritable and are a little anxious and depressed about the future.

Additional features due to treatment:

10. You lose your hair and your skin feels itchy.
11. You have difficulty sleeping.

Health state scenario for stable malignant glioma during treatment with temozolomide (after the end of radiotherapy and before any progression)

This scenario describes a medical condition plus a specific treatment. The scenario is outlined below with some additional features due to the treatment.

This scenario is derived from outcome measures in which the following statements were used to indicate the severity of various aspects of the condition:

- not at all
- a little
- a lot
- very much.

1. You have a mild headache and feel very tired and drowsy most of the time.
2. You usually feel nauseated and you vomit 2–5 times a day. You have poor appetite.
3. You hardly ever have seizures.
4. Your vision is very occasionally slightly blurred and you may have a little difficulty reading.
5. You sometimes feel a little weak on one side of your body and have a little trouble with

coordination but you do not need help with eating, dressing, washing and going to the toilet.
6. You hardly ever have trouble controlling your bladder.
7. You have no difficulty forming words but sometimes find it difficult to make yourself understood.
8. You sometimes have difficulty concentrating and sometimes forget things.
9. You feel a little irritable and quite anxious and are a little depressed about the future.

Additional features due to treatment:
10. Your skin feels very itchy sometimes with a rash.
11. You are very susceptible to infections and sometimes have to be admitted to hospital for treatment.

Health state scenario for progressive malignant glioma

This scenario is derived from outcome measures in which the following statements were used to indicate the severity of various aspects of the condition:

- not at all
- a little
- a lot
- very much.

1. You have a headache and you often feel tired and drowsy.
2. Sometimes you feel nauseated but you don't actually vomit very often. You may occasionally lose your appetite.
3. You occasionally have seizures.
4. Your vision is sometimes slightly blurred and you may have a little difficulty reading.
5. You sometimes feel weak on one side of your body and have a little trouble with coordination. You sometimes need help with eating, dressing, washing and going to the toilet.
6. Sometimes you have trouble controlling your bladder.
7. Sometimes you have difficulty forming words and find it difficult to make yourself understood.
8. You often have difficulty concentrating and sometimes forget things.
9. You sometimes feel irritable and are anxious and depressed about the future.

Health state scenario for progressive malignant glioma with severe motor function impairment

This scenario is derived from outcome measures in which the following statements were used to indicate the severity of various aspects of the condition:

- not at all
- a little
- a lot
- very much.

1. You have a mild headache and you often feel tired and drowsy.
2. Sometimes you feel nauseated but you don't actually vomit very often. You may occasionally lose your appetite.
3. You hardly ever have seizures.
4. Your vision is very occasionally slightly blurred and you may have a little difficulty reading.
5. You are very weak on one side of your body and have great difficulty with coordination such that you nearly always need help with eating, dressing, washing and going to the toilet.
6. You hardly ever have trouble controlling your bladder.
7. You have no difficulty forming words but sometimes find it difficult to make yourself understood.
8. You sometimes have difficulty concentrating and sometimes forget things.
9. You sometimes feel a little irritable and are a little anxious and depressed about the future.

Health state scenario for progressive malignant glioma with severe visual function impairment

This scenario is derived from outcome measures in which the following statements were used to indicate the severity of various aspects of the condition:

- not at all
- a little
- a lot
- very much.

1. You have a mild headache and you often feel tired and drowsy.
2. Sometimes you feel nauseated but you don't actually vomit very often. You may occasionally lose your appetite.

3. You hardly ever have seizures.
4. Your vision is always very blurred such that you are unable to read.
5. You sometimes feel a little weak on one side of your body and have a little trouble with coordination but you do not need help with eating, dressing, washing and going to the toilet.
6. You hardly ever have trouble controlling your bladder.
7. You have no difficulty forming words but sometimes find it difficult to make yourself understood.
8. You sometimes have difficulty concentrating and sometimes forget things.
9. You sometimes feel a little irritable and are a little anxious and depressed about the future.

Health state scenario for progressive malignant glioma with severe communication impairment

This scenario is derived from outcome measures in which the following statements were used to indicate the severity of various aspects of the condition:

- not at all
- a little
- a lot
- very much.

1. You have a mild headache and you often feel tired and drowsy.
2. Sometimes you feel nauseated but don't actually vomit very often and you may occasionally lose your appetite. You hardly ever have trouble controlling your bladder.
3. You hardly ever have seizures.
4. Your vision is very occasionally slightly blurred and you may have a little difficulty reading.
5. You sometimes feel a little weak on one side of your body and have a little trouble with coordination but you do not need help with eating, dressing, washing and going to the toilet.
6. You have great difficulty forming words and are unable to make yourself understood.
7. You sometimes have difficulty concentrating and sometimes forget things.
8. You sometimes feel a little irritable and quite anxious and are a little depressed about the future.

Appendix 15

Domains used and excluded for health state scenarios

The domains used and excluded are given in *Tables 75* and *76*.

TABLE 75 *Domains used for health state scenarios*

Scenario domain	Health-related QoL questionnaire domains included	Statement
Cognitive	Cognitive function	You have difficulty concentrating and remembering things
Emotion	Emotional function Future uncertainty	You feel irritable and anxious and are depressed about the future
Pain/tiredness	Pain Headache Fatigue Drowsiness	You have a headache and you feel tired and drowsy
Constitution	Nausea/vomiting Loss of appetite	You feel sick and vomit and you have lost your appetite
Bladder control	Bladder control	You have difficulty controlling your bladder
Visual	Visual disorder	Your vision is blurred and you have difficulty reading
Motor	Motor dysfunction Physical function Weak legs	You feel weak on one side of your body, have trouble with coordination and need help with eating, dressing, washing and going to the toilet
Communication	Communication deficit	You have difficulty speaking and find it difficult to express yourself to others
Seizures	Seizures	You have seizures

TABLE 76 *Domains omitted from health state scenarios*

Domain	Rationale
Role function	These questions seemed to reflect judgements by patients about the impact of their condition on their life and it seemed more appropriate to let the VoHP evaluate this
Social function	These questions seemed to reflect judgements by patients about the impact of their condition on their life and it seemed more appropriate to let the VoHP evaluate this
Global QoL	These questions seemed to reflect judgements by patients about the impact of their condition on their life and it seemed more appropriate to let the VoHP evaluate this
Dyspnoea	Not specifically relevant to brain tumours
Insomnia	Relevant to RT and included in that scenario
Constipation	Not specific to brain tumours and only small difference with general population
Diarrhoea	Not specific to brain tumours and only small difference with general population
Financial difficulty	Not specific to brain tumours
Hair loss	Relevant to RT and included in that scenario

Appendix 16

QoL scores for recently diagnosed and recurrent high-grade gliomas

	Recently diagnosed		Recurrent	
	QLQ-C30 score	**QoL weighting**	**QLQ-C30 score**	**QoL weighting**
Physical function	86.8	86.8	63.8	63.8
Role function	76.8	76.8	58.6	58.6
Emotional function	78.5	78.5	72.0	72.0
Cognitive function	78.9	78.9	66.7	66.7
Social function	72.9	72.9	62.8	62.8
Global QoL	69.1	69.1	60.8	60.8
Fatigue	30.9	69.9	37.3	62.7
Pain	15.4	84.6	15.1	84.9
Nausea/vomiting	9.3	90.7	6.8	93.2
Dyspnoea	10.0	90.0	13.5	86.5
Insomnia	22.0	78.0	19.0	81.0
Appetite loss	15.4	84.6	16.4	83.6
Constipation	9.8	90.2	16.7	83.3
Diarrhoea	5.7	94.3	10.1	90.9
Financial difficulties	24.4	75.6	36.5	63.5
Future uncertainty	22.9	77.1	28.8	71.2
Visual disorder	8.9	91.1	16.3	83.7
Motor dysfunction	13.0	87.0	26.7	73.3
Communication deficit	15.2	84.8	28.7	71.3
Headaches	15.4	84.6	19.4	80.6
Seizures	2.4	97.6	9.0	91.0
Drowsiness	31.7	68.3	38.0	62.0
Hair loss	21.1	78.9	14.8	85.2
Itching	11.4	88.6	13.5	86.5
Weak legs	4.1	95.9	12.5	87.5
Bladder control	4.1	95.9	17.2	82.8
Total for QoL weighting		**2170.7**		**1989.4**
Relative QoL weighting (%)		**83.5**		**76.5**

Appendix 17

Additional data in support of cost estimations

Drug name	Standard daily dose and prescription length	No. of treatments		Cost per treatment (£)	Cost/weeks (£)[a]	
		RT-only	RT + TMZ		RT-only	RT + TMZ
Dexamethasone Prednisone Bactrim Pentamidine inhalations Phenytoin Carbamazepin Valproic acid Clobazam Granisetron (antiemetic) Total	**[Confidential information removed]**					

Source: **[Confidential information removed]**.

[a] Cost per patient per week calculated by dividing the per drug total cost by: (i) the number of patients in each trial arm in the economic subanalysis group (n = 110 in RT only arm; n = 113 in RT + TMZ arm), and then (ii) by the mean number of weeks before disease progression (27 weeks in RT-only arm; 38 weeks in RT + TMZ arm).

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