The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma

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To provide a rapid review of the effectiveness and cost-effectiveness of temozolomide in the treatment of primary malignant brain tumours (anaplastic astrocytoma [AA] and glioblastoma multiforme [GBM]).

Background
Brain tumours make up approximately 1.5% of all malignant neoplasms in adults in England and Wales. About 50 - 60% of brain tumours are malignant gliomas (approximate incidence rate 3 to 4 per 100,000 per year), most of which are astrocytomas (AA) or glioblastoma multiform (GBM).

AA and GBM are the highest grades of astrocytoma and are not considered curable. Patients can suffer from a range of symptoms and impairments that can have a profound effect on quality of life, as well as their ability to work and to care for themselves.

Following diagnosis and primary treatment (usually with surgery, radiation, and corticosteroids), most patients will experience a tumour recurrence. Subsequent treatment options are limited and palliative. In the UK, approximately 30% of people with GBM or AA currently receive chemotherapy on relapse. Median survival time from initial diagnosis for AA is 27-36 months and approximately 11-12 months for GBM, although mean survival from diagnosis may be as low as 13 months and 7 months respectively. The average cost of treatment is approximately £11,900 per patient at a cost to the NHS in the region of £25 million per annum.

Methods
An extensive literature search was conducted using databases including the Cochrane Library, Medline, Embase, Cancerlit, Toxline, ISI Web of Science, BIOSIS, and PreMedline. Searches were conducted using the generic and trade names for the drug to locate all available clinical trials involving the drug and its adverse effects. The primary inclusion criteria were that the study should evaluate temozolomide in malignant glioma patients, include more than 45 patients, and include effectiveness and / or quality of life outcome measures. The quality of included studies was assessed using two quality assessment tools: the scale developed by Jadad was used to assess RCTs, and all studies were also assessed using a shortened version of a checklist developed for an epidemiological review.

Two reviewers independently assessed studies for inclusion, extracted data from the studies and evaluated the quality of each included study. Disagreements were resolved through discussion.

Because of the paucity of data, a narrative rather than a statistical synthesis was undertaken.

Results
Quantity and quality of available evidence
Nine full reports of seven studies were identified for inclusion, one randomised controlled trial (RCT) and six uncontrolled studies (one of which was available only in abstract format).

The RCT was a multi-centre, open label study of temozolomide versus procarbazine, that did not report the method of randomisation used and was neither single nor double-blinded. The comparator chosen is not commonly used in the UK, limiting the generalisability of the trial results. The remaining studies suffer from all of the biases inherent in non-comparative studies, further limiting the conclusions that can be drawn. Furthermore, most of the included studies applied performance status and life expectancy criteria such that they may have recruited somewhat healthier patients than would be considered eligible in routine practice.

Effectiveness of temozolomide
Although the quality of the available evidence is relatively poor, glomas do appear to show some response to temozolomide. The main benefit in patients with GBM, demonstrated in one RCT and one relatively large uncontrolled study, is an increase (13%) in the estimated proportion of patients remaining progression-free at six months and a significant increase in median progression-free survival of approximately four weeks. No significant overall survival advantage was found in comparison to procarbazine.

For patients with AA, one large uncontrolled study suggests some improvement in both progression-free survival and possibly in survival. The magnitude of any benefit in AA is difficult to quantify due to the lack of a within study comparison of temozolomide with an alternative treatment regimen.

Subgroup analyses provide some suggestion of better outcomes in patients who have not received any prior chemotherapy, although patient numbers were small. Since adjuvant chemotherapy is not commonly used in the UK, these results may be more applicable to the UK population, but require confirmation in large RCTs.

TMZ appears to involve few serious adverse effects. Vomiting appears to be well controlled by prophylactic anti-emetic regimens. Some clinicians believe that toxicity, particularly myelosuppression, is more predictable with TMZ and this has been noted as one of the advantages of this drug over others, however, empirical evidence is limited.

Quality of life
One of the major claims of benefit from temozolomide is that conferred on health-related quality of life. There is some evidence that quality of life is improved from recurrence until the point of disease progression for patients with GBM or AA.

Cost-effectiveness and cost-utility
On the basis of current evidence, which suggests only an increase in progression-free survival, the cost per progression-free week gained lies between £700 and £1000 for AA and GBM respectively. If a moderate impact on quality of life alongside a moderate increase in PFS is assumed, the cost per quality-adjusted life year (QALY) gained for patients with either GBM or AA is around £40,000 (for a QALY gain of 0.09 and 0.20 respectively).

Limitations of the analyses
The weaknesses of the primary studies seriously affect the strength of the conclusions that can be drawn about the effectiveness and cost-effectiveness of temozolomide. Only one RCT is available, the remainder of the evidence to date comes from relatively small uncontrolled studies. Most of the studies were conducted in patients with a relatively favourable prognosis

compared to those who might be eligible to receive temozolomide in routine care and the RCT did not use a comparator commonly used in the UK. These factors limit the generalisability of the results to UK practice.

These factors also impact on the reliability of the results of the economic analyses. In the first instance, the most appropriate analysis for a UK scenario is to compare temozolomide to a current standard treatment such as PCV. Although it was possible to obtain cost estimates for these two regimens, there are no effectiveness data available that directly compare these two treatment options. Therefore, alternative sources of data were used to approximate the results that might be seen with PCV.

Secondly, no reliable utility data were available. An estimate of the utility experienced at recurrence was provided by studies that used psychometric questionnaires to assess quality of life. The accuracy of this estimate may be questioned, but it did at least allow some exploration of the effect of temozolomide on quality of life while progression-free, and the resulting impact on the cost-utility of the treatment.

Because there was a further lack of data on utilities experienced following progression of disease, the deterioration in quality of life during this phase of disease was assumed to be linear. In practice, it may be more likely that the utility curve would dip sharply and then level off, in which case the assumptions made are likely to have over-estimated the value of life following progression and any hypothesised increase in survival.

Finally, only the direct costs of treatment at recurrence were considered. No data were available on the cost of treatment at the end of life, and any potential impact on such costs from the use of temozolomide. It may be that temozolomide introduces some cost savings by shortening the period of time from progression to death, but this was not possible to evaluate.

Conclusions

In summary, there is some indication of benefit from temozolomide, at a cost per QALY gained of around £40,000. However, the evidence is currently too weak for firm conclusions to be drawn.

The incidence of malignant glioma is relatively low and the overall budgetary impact for the NHS as a whole is in the order of £4 million per annum.

The true effectiveness of temozolomide for recurrent glioma will only be determined by large RCTs comparing temozolomide to best alternative care in a wider population of patients (i.e. not limited to those with favourable prognosis), possibly focusing on those who have not received any prior chemotherapy.

ABBREVIATIONS

AA	anaplastic astrocytoma
AO	anaplastic oligodendroglioma
AOA	anaplastic oligoastrocytoma or mixed glioma
BCM20	Brain Cancer Module (consisting of 20 questions)
BCNU	carmustine (a nitrosourea) – a chemotherapy agent
BNF	British National Formulary
CCNU	lomustine (a nitrosourea) – a chemotherapy agent
CER	cost-effectiveness ratio (see definitions of terms)
cGy	centiGray (a unit of radiation)
CI	confidence interval
CR	complete response
EMEA	European Agency for the Evaluation of Medicinal Products
EORTC	European Organisation for Research and Treatment of Cancer
GBM	glioblastoma multiforme
HRQL	health-related quality of life
KPS	Karnofsky performance status (see definitions of terms)
LY	life year
LYG	life year gained
mo	months
MR	minor response
MRI	magnetic resonance imaging
NNT	number needed to treat (see definitions of terms)
PCV	procarbazine, CCNU & vincristine
PFS	progression free survival
PR	partial response (see definitions of terms)
Procarb	procarbazine
pts	patients
QALY	quality adjusted life year (see definitions of terms)
QLQ-C30	Quality of Life Questionnaire – Cancer (30 questions)
qol	quality of life
RCT	randomised controlled trial
RT	radiotherapy
SD	stable disease (see definitions of terms)
TMZ	temozolomide
UKCCCR	United Kingdom Co-ordinating Committee on Cancer Research
WHO	World Health Organisation
wk	weeks
yr	year

DEFINITIONS OF TERMS

Complete response (CR)	A measure of tumour response. Defined as the disappearance of all enhancing tumour in neuroimaging.
Cost-effectiveness ratio (CER)	The incremental cost of producing an extra unit of a given outcome, e.g. incremental cost per life year gained.
Effect size	As defined in[1]: "Effect sizes were calculated by dividing the standard deviation of the mean of the baseline completion score by the mean of the second, third, and so on, completion."
Hazard ratio	A measure of the relative effect of treatments. Used to estimate the difference in survival between two groups across the entire study period.
Kaplan-Meier	A method of calculating survival curves where censored observations are expected. Censored observations occur either where a patient drops out before completion of the study or where a patient has not experienced the event of interest (e.g. death) at the time of the analysis.
Karnofsky Performance Status	A scale for assessing the clinical status of patients. See Appendix 8 for the scale.
Logrank test	The most common method of comparing groups of survival times. Where the logrank test is significant (usually $p < 0.05$) there is some evidence to suggest a difference between two groups. Note that the logrank test is solely a hypothesis test – it provides no direct information of the size of any between-group difference.
Number needed to treat (NNT)	The number of patients who need to be treated to prevent one given outcome. It is the inverse of the absolute risk difference.
Objective response (OR)	Complete response or partial response (see definitions elsewhere in list).
Open label	A clinical trial in which the investigator is aware of the intervention being given to any given participant (random allocation may or may not be used).
Partial response (PR)	A measure of tumour response. Defined as a 50% or more reduction in the sums of the products of the largest perpendicular diameters of contrast enhancement for all

	measurable lesions or an assessment of “definitely better” for all non-measurable lesions
Performance status	A clinician’s assessment of the clinical status of a patient. Can be assessed using scales such as the Karnofsky performance status scale or the WHO scale
Progressive disease (PD)	A measure of disease progression. Defined as a 25% or greater increase in size of the product of the largest perpendicular diameters of contrast enhancement for any measurable lesions or an assessment of “definitely worse” for any non-measurable lesions or any new tumour on MRI scans.
Progression free survival (PFS)	Survival without objective growth of tumour. It represents how long patients survive with improved or stable disease status.
Quality-adjusted life year (QALY)	An outcome measure that combines quantity and quality of life in a single index and should reflect preferences (utility values) for the associated health states. A QALY is calculated by the duration spent in a health state (in years) weighted by the preference for that state (utility).
Stable disease (SD)	A measure of disease status. Comprises all other situations not defined as complete response, partial response or progressive disease.
Survival	Length of time patients survive from initiation of treatment or proportion of patients surviving at a given time point
Toxicity grades	A common measure of toxicity in which higher grades refer to more toxicity. For full criteria of Common Toxicity Criteria for particular adverse events refer to http://ctep.info.nih.gov/CTC3/
Utility	A measure of preference for a given health state. Perfect health corresponds to a weighting of 1.0 and states equivalent to death are weighted 0.
WHO status	A scale for assessing the clinical status of patients. See Appendix 8 for the scale

AIM OF THE REVIEW

To provide a rapid review of the effectiveness and cost-effectiveness of temozolomide in the treatment of primary malignant brain tumours (anaplastic astrocytoma [AA] and glioblastoma multiforme [GBM]).

1 BACKGROUND

1.1 Description of underlying health problem – Brain Cancer

Brain tumours make up approximately 1.5% of all malignant neoplasms in adults in England and Wales.[2] Incidence figures for England and Wales are provided in table 1. Brain cancer is slightly more common in men than in women (1.2:1.0).[3] There is a slight peak in incidence in early childhood and the brain is the most common site for solid tumours in childhood.[3] Incidence also rises in later adulthood with a major peak around age 70-74 with incidences of approximately 20-25/100,000.[3]

There are many different types of brain cancers, generally presumed to arise from different cell types. Gliomas, most of which are astrocytomas, make up the majority of brain tumours. Although there are different schemes for grading brain tumours, four grades of astrocytoma can be distinguished, with higher grades being more aggressive.[4] Grades III and IV glioma usually refer to anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM) respectively.[4] Oligodendrogliomas, e.g., anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA) are not astrocytomas, but also vary in aggressiveness and can be difficult to distinguish from astrocytomas.[5]

Table 1 Incidence of brain cancers[a]

Approximate number of new cases per annum	Brain cancer incidence[6] 7/100,000	Glioma[I] incidence 3-4/100,000	AA[II] incidence 1-1.6/100,000	GBM [III] incidence 1.2-2/100,000	AO [IV] incidence 0.2-0.6/100,000
England (pop. 49.8 million [V])	3486	1494 - 1992	498 - 797	598 - 996	100 - 299
Wales (pop. 2.9 million [V])	203	87 - 116	29 - 46	35 – 58	6 - 17
Health Authority (pop. 500,000)	35	17 - 21	5 – 7	7 - 10	1 - 3

[I] 50 to 60% of malignant brain tumours
[II] 30-35% of gliomas
[III] 40-50% of gliomas
[IV] 5-15% of gliomas
[V] mid-1999 population estimates from ONS website (http://www.statistics.gov.uk/popest_mid99.asp)

In 1998 there were 3177 deaths from brain tumours in the UK, representing 2% of all cancer deaths.[3] Approximately 29% of adult patients with brain cancer survive for one year and

a Incidence figures reported are consistent with those reported in data from the Information and Statistics Division, Common Services Agency, National Health Service in Scotland where the combined incidence of GBM and AA was 2.7 / 100,000. However, some reports from the U.S. estimate combined incidence of GBM and AA at 5-8 / 100,000. [26]

approximately 13% survive for five years.[7] Although brain tumours account for less than 2% of primary tumours, they result in 7% of years of life lost from cancer before age 70.[3]

AA and GBM carry a particularly poor prognosis; they spread by expansion and infiltration and are not considered curable. The prognosis for high-grade gliomas is affected by age, histology (i.e., AA v GBM), and performance status (see definition of terms).[8;9] Older patients, those with poorer performance status, and those with higher grade tumours have a poorer prognosis. Age is also related to tumour histology: GBM patients are on average approximately 10 years older than AA patients. However, age may also be an independent prognostic factor for survival.[4]

Patients with malignant glioma can suffer from a range of symptoms and impairments. Some symptoms may be general whereas others may be specific to the area of brain where the tumour is located. General symptoms include headache, anorexia, nausea, vomiting, seizures, drowsiness, personality changes, and cognitive slowing. More focal symptoms could include difficulties with hearing, speech, ambulation, dexterity, visual difficulties, and mood disturbances.[4;10;11] These symptoms can have a profound effect on the quality of life of these patients as well as their ability to work and to care for themselves.

Following diagnosis and primary treatment, most patients will experience a tumour recurrence. Once a tumour has recurred, treatment options are limited and palliative. Although there are no recent population-based survival data for England and Wales, some authors suggest that median survival time from initial diagnosis for AA is 27 – 36 months,[4;9]and approximately 11-12 months[3;4]for GBM. Data for Scotland (based on over 800 cases diagnosed between 1992 and 1997) show that mean survival from diagnosis is as low as 13 months for AA and seven months for GBM[b].

1.2 Current service provision

Patients with high-grade gliomas are usually treated with surgery, radiation, and corticosteroids. Some patients with particularly poor prognoses are treated with corticosteroids or are managed with supportive care alone. Others, perhaps a quarter, would be recommended for palliative radiotherapy and approximately half would receive more aggressive radical radiotherapy. Among those treated with radical radiotherapy perhaps half would receive chemotherapy on relapse.

1.2.1 Treatment modalities

Surgery

Surgery is undertaken for three purposes: to obtain the diagnosis (i.e. to determine tumour histology), to relieve symptoms (e.g. to reduce effects of intracranial pressure), and to contribute to survival.[3] Although the relation between the amount of tumour excised and outcome[12] remains unclear, many believe that a major reduction in tumour size does prolong survival, particularly in younger, healthier patients.[9;12] However, conclusive evidence for the benefit of surgery is unavailable.

Surgery to excise the tumour is sometimes not possible because of the tumour location. Even when the tumour is accessible, excision can rarely be complete because of the infiltrative

b data from Information and Statistics Division, Common Services Agency, National Health Service in Scotland

nature of the tumours and because they are often located in cognitively vital brain areas (e.g., those responsible for language).[4] Tumours tend to recur at the site of the original tumour.

Radiotherapy
Radiotherapy (RT) is generally standard treatment. Randomised studies have shown that it enhances survival,[13;14]although some have suggested that in patients presenting with poor performance status there may be little benefit.[15] Considerable research has been conducted on optimal radiation doses and results suggest that a dose of 6000 cGy increases survival over a dose of 4500 cGy.[4;16] Additional research is evaluating other methods of timing and targeting radiation.

Chemotherapy
A broad range of chemotherapy agents may be used in an attempt to prevent or retard the growth of tumour cells, to kill tumour cells, or to radiosensitize tumours. Commonly used agents include the chloroethyl nitrosoureas, epipodophyllotoxins, and platinum compounds.[3]

Steroids
Corticosteroids (usually dexamethasone) are given to control the effects of raised intracranial pressure and to reduce neurological deficits by reducing tumour-induced oedema.[4]

1.2.2 Treatment stages

Initial treatment
The first line of treatment is usually surgery with the aim of major tumour debulking, shortly followed by radiotherapy.

The use of chemotherapy as an adjuvant treatment is more equivocal. Single studies, such as a large, multicentre RCT by the MRC Brain Tumour Working Party,[17] have found no benefit from the addition of chemotherapy (PCV - procarbazine, CCNU and vincristine) to a standard radiotherapy regimen in patients with high-grade gliomas. However, a recent meta-analysis by the MRC reported a 5% increase in two-year survival for RT plus chemotherapy compared to RT alone.[18] There has also been some suggestion that particular subgroups of patients may benefit -- perhaps as many as 25% of patients[4;17;19] -- but the factors that might identify those patients *a priori* have yet to be clearly identified.[19]

Adjuvant chemotherapy is becoming more common in the UK, but is currently not considered standard care.

Recurrence
Most patients with malignant glioma will suffer a recurrence of the tumour after receiving initial treatment.

Some patients will undergo additional surgery, again with the aim of complete resection.

Although stereotactic radiotherapy is sometimes used as adjuvant treatment, it is more often used after recurrence and is only appropriate for a small subset of patients (depending on tumour size and location).

Chemotherapy at recurrence usually consists of some agent(s) not previously administered.

In the UK, a single agent nitrosourea (e.g., CCNU or BCNU) or a combination therapy such as PCV (procarbazine, CCNU, and vincristine) is often used.[3] Procarbazine alone is sometimes used in the US, but is not standard therapy in the UK.

Two studies have been identified that provide some indication as to the effectiveness of current chemotherapy treatment following tumour recurrence. One[9] combines the results of eight consecutive chemotherapy studies in recurrent malignant glioma; the other[20]examined a range of treatments for recurrent malignant glioma including four chemotherapy RCTs. The results of these studies, where possible subdivided according to tumour histology, are summarised in Table 2. The outcome measures used are explained in the Definitions of Terms.

Table 2 Effectiveness of current treatments for recurrent malignant glioma

Study	Objective response	6 month progression-free survival	Survival	Other outcomes
Wong, *et al*, 1999[9] Combined 8 Phase II CT trials *n*=458, 375 analysed	1 CR, 9% PR, 5% MR, 25% SD CR+PR: GBM: 6% AA : 14% MR+SD: GBM : 27% AA : 34%	21% (95% CI: 17, 26%) GBM: 15% (95% CI: 10, 19%) AA: 31% (95% CI: 24, 39%)	median 30 wk (95%CI: 26, 35 wk) GBM: 25 wk AA: 47 wk 6 mo survival: 55% 1 yr survival: 32% 5 yr survival: 10%	median PFS: 10 wk (95% CI: 9, 11 wk) GBM: 9 wk AA: 13 wk 1 yr PFS = 12% 5 yr PFS = 4%
Huncharek, *et al*, 1998[20] Systematic review of treatment in recurrent high-grade astrocytoma *n*=1415, 347 in 4 CT RCTs			median 28 wk mean 31.5 +/- 13.4 4 CT RCTs: median 25 wk mean 26.2 +/- 3.1	Time to progression: median 14 wk mean 15.4 wk

CT – chemotherapy; CR – complete response; PR – partial response; MR – minor response; SD – stable disease. MR defined as decrease in tumour size by less than 50% with stable or decreasing corticosteroid dose

The results of these studies provide a baseline against which to evaluate the effectiveness of temozolomide. Although they provide the best available information about the effectiveness of chemotherapy treatments in recurrent malignant glioma, they are not ideal for comparison with temozolomide studies. For instance, many of the patients included in the Wong, *et al*[9] analysis had suffered more than one tumour recurrence, whereas many of those in the TMZ studies were at first recurrence. Therefore, the possible poorer prognosis of those in the Wong analysis may inflate the apparent effectiveness of TMZ.

1.2.3 Patterns of care and estimated costs of treatment

The economic impact of malignant glioma is disproportionate to its incidence. Two studies have been conducted in the UK to examine the patterns of resource use of glioma patients. One study aimed to identify the direct hospital costs of treating 236 patients with biopsy proven malignant glioma at a neuro-oncology clinic.[21] The other[22]assessed the clinical

outcomes, resource use and cost of care for 102 patients with high grade glioma treated at two specialist centres.

Across both studies, all patients bar one underwent some form of surgery during the initial treatment phase. Between 66%[21] and 99%[22] of patients underwent radiotherapy and approximately 30% underwent chemotherapy (PCV or BCNU) on relapse.[21;22] No patients in either study appear to have received adjuvant chemotherapy. Mean length of inpatient stay per patient was around 40 days.[22] This corresponds well with Scottish data on 818 cases of AA and GBM which found a mean number of hospital admissions per patient of 4.6, with a mean length of stay of 10.3 days per admission[c]. Latif *et al* broke down hospital admissions according to main treatment received: mean lengths of stay were eight days following surgery, 14 days for radical radiotherapy, and seven days for palliative radiotherapy.[21]

The total costs of care ranged from £1978 to £26,980 per patient in one study,[21] and averaged £11,900 in the other.[22] The largest components of overall costs in the latter study[22]were ward costs (£7185), surgery (£1292), radiotherapy (£1167), ITU costs (£799), out-patient costs (£611), imaging (£494) and community care costs (£456). A similar pattern was demonstrated by Latif *et al*.[21]

These studies generally support the thesis that up to 75% of the direct costs of treating malignant glioma are incurred during the initial treatment period.[23] Given the short life expectancy of glioma patients (often less than one year), the total cost of treating 1,500 to 2,000 new cases each year, using an average cost per patient of £11,900 is approximately £20 to 25 million.

1.3 Description of new intervention -- Temozolomide

1.3.1 Licensed Indications

The chemotherapy drug temozolomide (trade Temodal®) was licensed by the EMEA (20 Jan, 1999) for the treatment of patients with malignant glioma, such as AA and or GBM, showing recurrence or progression after standard therapy.[24] TMZ is an alkylating antitumour agent that is administered orally in the form of hard capsules and can therefore be administered by patients at home.

TMZ is rapidly absorbed and shows good tissue distribution, including some penetration across the blood-brain barrier.[25] It is converted to the active compound monomethyl triazenoimidazole carboxamide (MTIC) under physiological conditions.[25;26] TMZ is generally administered in cycles of five days per 28-day cycle at a dose of 200 mg/m^2 per day[24] (although there have been small trials with continuous treatment). For patients who had prior chemotherapy treatment is generally started at 150 mg/m^2 per day. TMZ is continued until there is unacceptable toxicity or further disease progression.

1.3.2 Contraindications

TMZ should not be taken by patients who have a hypersensitivity to its components or to dacarbazine. TMZ is also contraindicated in women who are pregnant or breast-feeding.

c data from Information and Statistics Division, Common Services Agency, National Health Service in Scotland

Approximately one in 20 patients' bone marrow is sensitive to TMZ.[25] Dose reductions are indicated in these patients. Myelosuppression is assessed before each cycle of therapy. Little cumulative toxicity has been noted for the drug and myelosuppression occurs on a predictable time course.[25]

1.3.3 Costs

The cost of the drug itself according to the *British National Formulary*[27] would be approximately £1175 per five-day course (assuming a daily dose of 340 mg – see Appendix 9 for computation). The median number of cycles reported in the studies reviewed ranged from three to seven courses, corresponding to a cost per patient of approximately £3525 to £8225.

1.3.4 Degree of diffusion

Discussion with experts suggests that TMZ is not currently widely funded in the UK and is not widely used, particularly outside the context of clinical trials.

2 EFFECTIVENESS OF TEMOZOLOMIDE FOR MALIGNANT GLIOMA

2.1 Methods[d]

The *a priori* methods used for the rapid review are outlined in the research protocol (see Appendix 1).

2.1.1 Objectives

The objective of the review was to evaluate temozolomide for its licensed indications, in comparison to standard alternative chemotherapy or against best standard care, in terms of both survival and quality of life.

Unfortunately there has only been a limited amount of research evaluating temozolomide and alternative treatment options. In the one randomised controlled trial (RCT) identified, TMZ was compared to "non-standard" chemotherapy.

2.1.2 Inclusion Criteria

The primary inclusion criteria were that the study should evaluate temozolomide in malignant glioma patients, include more than 50 patients, and include effectiveness and / or quality of life outcome measures. The sample size criterion was later revised down to include studies with a minimum of 45 patients as two studies were found with nearly 50 patients and all other studies had considerably smaller patient numbers.

Due to the anticipated lack of data on temozolomide, randomised, non-randomised and uncontrolled studies were eligible for inclusion in the review.

2.1.3 Literature Search

Appendix 2 provides details of the literature search, including databases and search terms used. Briefly, searches for the drug name (both generic and trade) were conducted on the Cochrane Library, Medline, Embase, Cancerlit, Toxline, ISI Web of Science, BIOSIS, and

d According to the explicit Quality Standards agreed by InterTASC.

PreMedline. Searches were conducted to locate all clinical trials involving the drug and its adverse effects. Having determined that sufficient data on adverse effects were available in studies of malignant glioma, studies were then excluded if they were in another condition, were pharmacokinetic studies, were reviews or commentaries or were too small. Additional searches focused on natural history, prognosis, and quality of life in malignant glioma.

Abstracts from studies identified by the search strategy were initially screened by two reviewers prior to requesting full text articles. Disagreements were resolved in discussion with a third reviewer.

2.1.4 Data Extraction

Two reviewers performed the data extraction of included studies. Any discrepancies were resolved through discussion. Summary tables of the data extracted from each included study are provided in appendices 4 and 5.

2.1.5 Quality Assessment

The quality of included studies was assessed using two quality assessment tools. For RCTs, the quality assessment scale developed by Jadad *et al*[28] was used (see Appendix 3). All studies were also assessed using a shortened version of a checklist developed by Spitzer, *et al* for an epidemiological review of smoking.[29] The checklist was modified to include the items of central relevance to the particular kind of studies being evaluated (see Appendix 3). In addition, guidance notes for internal interpretation of the checklist were developed to ensure equivalent interpretation of the checklist items between the evaluators.

Two reviewers independently evaluated the quality of each included study. Disagreements on evaluations were resolved through discussion. Results of quality evaluations are discussed narratively and detailed summaries for each effectiveness study are provided in Appendix 4.

2.1.6 Data synthesis

Preliminary searches of the literature on temozolomide indicated that very few relevant studies were available on the drug. In addition, there are very few comparisons of TMZ with any other treatment. Because of the paucity and heterogeneity of data, the data have been synthesised in a narrative rather than a statistical manner.

2.2 Results

2.2.1 Quantity of research available

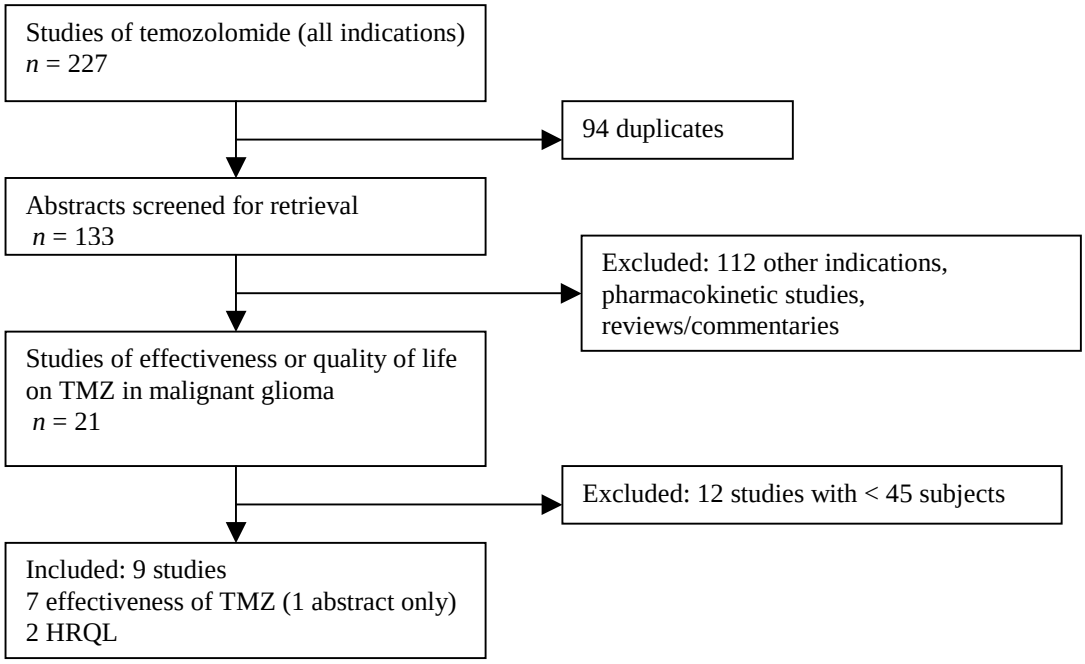
Eight full reports of six studies were identified for inclusion in the review, two of which are unpublished at the time of writing.[5;30] Six studies primarily reported effectiveness data for TMZ in patients with glioma. Three of these[30-32] also investigated health-related quality of life (HRQL) outcomes that were reported in more detail in two further papers.[1;33] One additional report of TMZ effectiveness was available in abstract only at the time of writing and because full details cannot be evaluated, it will be mentioned only briefly.[34] Figure 1 provides an overview of the primary search and inclusion process for TMZ effectiveness studies. See Appendix 2 for more detailed description of the overall search strategy.

Twelve studies of TMZ in recurrent malignant glioma were excluded because the numbers of patients included was less than 45 (range 11-41).[35-46] Data on the use of TMZ in 27 newly

diagnosed patients provided by one of the included studies[47] was also excluded due to sample size.

Although TMZ is licensed for use in children as young as three years old, no studies meeting our inclusion criteria using TMZ in paediatric populations were available.

Figure 1 Flow diagram of TMZ effectiveness search results



2.2.2 Description of included effectiveness studies

Table 3 provides details of the included studies. Only one RCT was identified (a). The remaining studies (b – g) are single group studies.

Patients

Detailed patient inclusion criteria are only available from full reports. Therefore, patient descriptions are based on the six full reports of effectiveness studies that are available. All patients were adults >18 years old with histologically confirmed recurrent malignant glioma. In three studies, patients had to be at first tumour recurrence.[30-32] In the remainder, whether patients had had more than one recurrence was not clear. In four studies patients were required to have a Karnofsky performance status (KPS) ≥ 70,[30-32] or performance status on the World Health Organisation scale of ≤ 3[48] (see Appendix 8 for scales). A further study required a KPS ≥ 60.[5] In five studies patients were required to have a life expectancy ≥ 12 weeks.[5;30-32;48] The remaining study for which a full report was available did not apply inclusion criteria other than appropriate diagnosis.[47]

In one study all but one patient had received previous chemotherapy.[5] Among the other studies that reported the number of chemotherapy-naïve patients the proportion ranged from 32% to 71%. Additional details of inclusion and exclusion criteria for included studies can be found in Appendix 4.

Intervention
Except where noted, dosage of TMZ was the same in all studies. In patients who had not received prior chemotherapy, the dose was 200 mg/m^2/day for five days in each 28-day cycle. In patients who had received prior chemotherapy, the initial dose was reduced to 150 mg/m^2/day with the dose escalating to 200 mg/m^2/day after the first cycle if haematology results were satisfactory. The RCT used procarbazine at a dosage of 150 mg/m^2/day for 28 consecutive days in each 56-day cycle.

Table 3 Included Studies

Histology Trial	**Design**	**No. Patients**	**Outcomes assessed**
GBM			
a) Yung, *et al*, 2000[31]	RCT	*n* = 225 TMZ = 112 procarb = 113	TMZ / procarb effectiveness adverse events HRQL (also reported in Osoba, *et al*[1])
b) Brada, *et al*, submitted for publication[30]	single group	*n* = 138	TMZ effectiveness adverse events HRQL (also reported in Osoba, *et al*[1])
AA or AOA			
c) Yung, *et al*, 1999[32]	single group	*n* = 162	TMZ effectiveness adverse events HRQL (also reported in Osoba, *et al*[33])
AO or AOA			
d) Chinot, *et al*, submitted for publication[5]	single group	*n* = 48	TMZ effectiveness adverse events
Mixed Histologies			
e) Bower, *et al*, 1997[48]	single group	*n* = 116	TMZ effectiveness adverse events
f) Newlands, *et al*, 1996[47]	single group	*n* = 48	TMZ effectiveness adverse events
g) Spagnolli, *et al*, 2000[34] (abstract only)	single group	*n* = 62	TMZ effectiveness adverse events

2.2.3 Quality of included effectiveness studies

Quality assessments for each included study can be found on the summary tables in Appendix 4.

RCT
The included RCT was a multi-centre, open label study that did not report the method of randomisation used. There is no assurance that the method of randomisation used was appropriate, although there does not appear to be substantial differences in baseline characteristics between the groups. TMZ patients on average had a shorter time from diagnosis to recurrence than those receiving procarbazine. This difference was considered in the analyses and was not found to have affected the results. It might reasonably be assumed that any bias introduced by a shorter time to recurrence would lead to poorer outcomes in the TMZ group rather than augmenting any potential benefit from TMZ.

The open-label design means that the study was not double-blind. Therefore, it is possible that clinical judgements and patients' self-reports of quality of life were affected by knowledge of the treatments being given.

The use of procarbazine as the comparator is problematic for the generalisability of this trial to UK practice. It was chosen as the comparator because it is orally administered and it is one of the few options available to patients who have recurrent glioma, particularly if they have had previous nitrosourea therapy. However, it is not commonly used alone in the UK, but instead is often used in combination therapy (PCV: procarbazine [in lower doses than used alone in the cited study], CCNU and vincristine). Therefore, the RCT results are not directly applicable to those UK patients with recurrence who would be considered for chemotherapy.

Quality concerns for all included studies
None of the studies give any assurance that clinicians and patients were blinded to the treatments that were being given (and indeed this would not be possible in an uncontrolled study). This knowledge is likely to have affected the subjective assessments of clinical status and the patients' self-reports of their quality of life.

The method of recruiting subjects affects the generalisability of results. Only one study reported the method used to recruit subjects (recruiting consecutive patients). This may have led to some bias in the recruitment process, such that the patients enrolled are not representative of the population of patients with high-grade recurrent glioma. This potential for bias is further compounded by the entry criteria described in section 2.2.2. The performance status and life expectancy criteria will have led to somewhat healthier patients being selected for inclusion, such that results from these studies are likely to be more favourable than would be found in a more representative patient population.

However, not all patients are considered for chemotherapy at recurrence, and it is possible that those who might be considered for such treatment may have higher than average performance status scores and/or life expectancy. On the other hand, a wider range of patients may in practice be considered 'fit' for chemotherapy, not least because it may be difficult to deny very ill people the chance of treatment even when the intent is palliative.

2.2.4 Outcome Measures

The outcome measures and factors that may affect their interpretation are described below. More detailed discussion of factors that affect various outcome measures[49] and how the included studies addressed these factors can be found in Appendix 6.

Objective Response
The objective response measure gives some idea as to whether the drug is having an effect on tumour growth. In aggressive tumours in which recurrence has taken place, even a relatively low response rate may be considered important. In addition, stable disease (i.e. no improvement in tumour status, but no major progression of disease) is an often reported outcome although the clinical importance of this distinction is debated.

Criteria for measuring objective response (i.e., effects on tumour) were similar in all studies. These criteria are defined in the Definitions of Terms. Variations from and refinements to these descriptions are noted on the data extraction tables found in Appendix 4.

Measurement of objective response does not involve a specific length of follow-up. In all included studies objective response was assessed by a combination of clinical assessment of neurological status and by neuroimaging. In all cases except one[47], the neurological status examinations were conducted monthly and neuroimaging was conducted every two months. An objective response was declared when changes in status and tumour scans (as defined for each study in Appendix 4) occurred across evaluations at least one month apart. Therefore, objective response is a measure of a defined change in tumour status at any point after the initiation of treatment.

Progression[e]
Two measures of progression were commonly included: six-month progression free survival (PFS) and median progression free survival. Six-month progression free survival is a measure of how many patients survive without further tumour progression for six months following the initiation of treatment. In this extremely aggressive disease, it is important to evaluate how many patients may achieve a period of improvement or stability in disease. For this reason, six-month progression free survival was considered one of the primary outcomes in most of the effectiveness studies.

Median progression free survival is also reported in some studies.

Survival[f]
Survival was considered in all studies. This is a measure of the time that patients survive from the initiation of the treatment.

In reports of times to progression or survival, the starting point is an important consideration. Although not all the studies reported the start date, those that did reported it as the date of initiation of treatment. For both median progression free survival and survival there was no specified length of follow-up. Measures of progression and survival also depend on the timing of the baseline and follow-up evaluations. The point at which recurrence is detected and further treatment is initiated will affect the estimates of PFS and survival. Furthermore, when imaging is being performed more regularly than in clinical practice, initial recurrence may be detected earlier producing longer estimates of survival. Likewise, however, additional progression after recurrence and the initiation of chemotherapy may also occur earlier than in routine practice, thereby underestimating progression-free survival. Therefore, the results for both PFS and survival may not be directly generalisable to clinical practice.

Health-related quality of life (HRQL)
HRQL is a measure of how patients assess their own functioning. The objective response measure discussed above generally includes an assessment of clinicians' judgements of how patients are performing in daily life, but the HRQL is a self-report measure. The measures used in the included studies focus on how people are functioning in their daily life and what

e Several of the studies estimated PFS and/or survival times using the Kaplan-Meier method, which allows estimation when there are censored observations. A censored observation is one that cannot be measured precisely but is known to be beyond some limit, e.g. when patients drop out of a trial or when they are still alive at the time of the analysis. Results based on Kaplan-Meier estimates are noted on the summary tables included in Appendix 4.
f See footnote e

symptoms they are experiencing, and are discussed in detail in Appendix 6. Seven quality of life domains were selected *a priori* in the included reports as being of particular interest: global quality of life, role functioning, social functioning, visual disorder, motor dysfunction, communication deficit, and drowsiness. These domains were selected by the trialists, on the recommendation of a panel of brain tumour experts, in order to decrease the possibility of finding statistically significant associations by chance alone.

Given the extremely poor prognosis for malignant gliomas, it is important to consider not only effects of treatment on tumour growth and the length of survival, but also effects on the quality of life during survival.

2.2.5 Assessment of effectiveness

Results are summarised according to type of malignant glioma and outcome measures assessed. The primary results from the included effectiveness studies are summarised in Table 4 (results from one abstract are not shown). Detailed results from each of these studies can be found in Appendix 4.

For ease of comparison all survival times that were initially reported in months are reported here in weeks[g]. All results have been rounded to one decimal point.

A summary of HRQL results is shown in Table 5 and more detailed summaries of the two HRQL reports are given in Appendix 5. A more detailed narrative summary of the HRQL results is provided in Appendix 7. It should be noted that the HRQL results are reported as a within-subject change from baseline and not as the difference in effect between groups.

Table 4 Summary of Effectiveness Results

Study	Objective Response			6 month PFS	Survival	Other outcomes
GBM						
Yung, *et al*[31] RCT *n*= 225	CR TMZ 0% procarb 0%	PR 5.4% 5.3%	SD 40.2 % 27.4 %	TMZ =21% (95%CI: 13, 29%) procarb = 8% (95%CI: 3, 14%)	6 month survival: TMZ: 60% (95%CI: 51, 70%) procarb: 44% (95%CI: 35, 53%) TMZ 6 wk median survival advantage, NS	median PFS: TMZ=12.4 wk procarb=8.32 wk HRQL (see Osoba, *et al*, 2000[1])
Brada, *et al*[30] single group *n* = 138	CR 1%	PR 7%	SD 43%	19% (95%CI: 12, 26%)	median 23.4 wk 6 mo survival: 46%	median PFS 9.1 wk HRQL (see Osoba, *et al*, 2000[1])
AA or AOA						
Yung, *et al*[32] single group *n* = 162	CR 8%	PR 27%	SD 27%	46% (95% CI: 38,54%)	median 59 wk	median PFS: 23.5 wk HRQL (see Osoba, *et al*, 2000[33])
AO or AOA						
Chinot, *et al*[5] single group *n* = 48	CR 16.7%	PR 27.1 %	SD 39.6 %	50.5%	median 43.4 wk	median PFS: 29 wk
Mixed Histologies						

g Survival and progression free survival times that were reported in months were converted to weeks using the following formula: (number of months x 30.4 days) / 7.

Bower, *et al*[48] single group *n* =116 (results from 103 eligible)	OR 11%	SD 47%	22% (95% CI: 14,31%)	median 25.2 wk (95% CI: 20,30.4 wk)	median response duration for those with OR = 20 wk
Newlands, *et al*[47] single group *n* = 48	25% OR			In recurrent disease: 1 yr survival = 22% (95% CI: 12,36%)	

CR – complete response; PR – partial response; SD – stable disease; OR – objective response; procarb - procarbazine; NS – Not statistically significant

2.2.5.1 GBM:

Objective Response:
Overall response rates in the RCT were higher for TMZ, though the difference only just reached conventional statistical significance levels (p=0.049).[31] The number of patients with a partial response was virtually identical in the two groups (5.4% TMZ, 5.3% procarbazine), but the proportion of patients with stable disease was 40.2% with TMZ and 27.4% with procarbazine. There were no complete responses.

In one single group study, CR was reported in 1% of patients.[30] The proportion of objective response was 8% in one study[30] and 11% in another.[48] Stable disease was reported in 43% of patients in one study.[30]

Six-month progression free survival:
In the RCT[31] Kaplan-Meier estimates of progression-free survival at six months indicate a higher estimated proportion of patients surviving in the TMZ group (21%, 95% CI: 13,29%) compared to the procarbazine group (8%, 95% CI: 3,14%). Note however that this is a comparison of estimated survival proportions at one single time point (six months), as opposed to a comparison of the total survival experience of the two groups. Although theoretically possible, no statistical comparison of the two proportions was presented.

Using these data, the number needed to treat (NNT) to achieve an extra progression-free patient at six months is 8 (95% CI: 5, 23).

The logrank test (see definition of terms) across the whole data set indicated that there may have been meaningful differences in PFS across the groups (P = 0.008).[31] The hazard ratio[h] (the preferred method of deriving an estimate of survival differences) also indicated that progression-free survival was higher in the TMZ group (hazard ratio = 1.54, indicating an estimated increase in PFS in the TMZ group to 154% of that for procarbazine). No confidence intervals were provided to support the claimed statistical significance of this result.

For the 72 patients who were chemotherapy-naïve, the estimated proportion progression-free at six months was 22% in the TMZ group (95% CI: 8, 35%) and 7% in the procarbazine group (95% CI: 0, 16%).[50] These estimates suffer from the same caveats described above, and again no statistical comparison of the two proportions was presented.

In one single-group study, six-month progression free survival was 19% (95% CI: 12, 26%).[30]

Median Progression Free Survival:
In the RCT estimated median PFS was 12.4 weeks for TMZ compared with 8.3 weeks in the procarbazine group.[31]The 95% confidence interval for the difference in median survival was not presented.

The logrank test for the whole data set again indicated that there may be significant differences in median progression-free survival between the groups (P = 0.006).[31] The hazard

h The hazard ratios presented are assumed to apply to the complete study period (as is the norm), as opposed to only the first six months.

ratio for the difference in median PFS was 1.47 (95% CI: 1.11, 1.95), indicating that TMZ was associated with an estimated significant increase in median PFS to 147% of that for procarbazine.[50]

In the chemotherapy-naïve subgroup, median PFS was 17 weeks in the TMZ group and 8.3 weeks in the procarbazine group.[50] The hazard ratio for the difference in median PFS was again significant (hazard ratio = 1.98 [95% CI: 1.19, 3.29]), although the confidence intervals were wide.

In one single-group study, median PFS was 9.1 weeks.[30] Median PFS for a subgroup of patients who had not had chemotherapy previously (n = 98) was 9.6 weeks.

Data for an additional outcome, "neurological failure," was provided by the company. Neurological failure is assessed by the evaluation of neurological/clinical symptoms and is more subjective than evaluations of MRI scans. Median time to neurological failure on TMZ was 18.2 weeks and on procarbazine was 15.2 weeks (p = 0.035). Six month response rates using this measure were 38% for TMZ (95% CI: 27, 48%) and 26% for procarbazine (95% CI: 15, 37%), p = 0.03.[50]

Survival:
In the RCT, Kaplan-Meier estimates of median survival at six months indicate an increased estimated survival proportion in the TMZ group (60%, 95% CI: 51,70%) compared to the procarbazine group (44%, 95% CI: 35,53%).[31] This is again a comparison of estimated survival proportions at a single time point (six months), as opposed to a comparison of the total survival experience of the two groups.

The NNT to prevent one extra death within six months is 7 (95% CI: 4,41).

The logrank test for the whole data set also indicated that there may have been meaningful differences in overall survival across the groups (p = 0.019).[31] The hazard ratio for survival at six months was 1.44, indicating that TMZ is associated with an estimated increase in survival to 144% of that for PCB (no confidence intervals provided).

Data from the company indicate the median survival was 31.9 weeks for temozolomide and 24.6 weeks for procarbazine (difference 7.3 weeks or 1.7 months).[50] The published paper reported a difference in median survival of 1.5 months. Both were stated not to be statistically significant (no data presented).

The logrank test also suggests that there were no meaningful differences in median survival duration between the groups (p = 0.330).[31]

For chemotherapy-naïve patients in the trial, survival in the TMZ group was 32.7 weeks and in the procarbazine group was 23.2 weeks. The hazard ratio was 1.684 (95% CI: 1.03, 2.75).[50]

In one single-group study, the median survival time was 23.4 weeks.[30] Among patients who had not had previous chemotherapy median survival time was 23 weeks.

HRQL:

In the RCT,[1] those patients on TMZ who remained progression free at six months showed improvements in five of seven pre-selected quality of life domains (Table 5). Only improvements in drowsiness and social functioning had an effect size > 0.2[i] (0.56 and 0.27, respectively) and only the improvement in drowsiness reached statistical significance. In contrast, those patients who had been on procarbazine reported diminished HRQL in all seven pre-selected domains independent of whether there had been progression or not (except global quality of life in those who were progression free at six months in whom there was no change).

Table 5 Summary of HRQL Results

Histological group and Study	Significant changes from baseline to 6 months	Global Quality of Life	Role Function	Social Function	Comm. Disord.	Visual Disorder	Motor Dysfunc-tion	Drowsi-ness
GBM Osoba, *et al* 2000[1]	Without progression:	+ TMZu			+ TMZu			+TMZ + TMZu
	With Progression:	- TMZ - TMZu	- TMZ - procarb - TMZu	-TMZ	-procarb	- TMZu	- TMZ - procarb - TMZu	- procarb - TMZu
AA or AOA Osoba, *et al* 2000[33]	Without progression:	+		+				
	With Progression:	-	-	-		-		-

TMZ - patients randomised to TMZ; Procarb - patients randomised to Procarbazine; TMZu - patients in single group study of TMZ; Comm. Disord. - Communication disorder

Table 5 shows the statistically significant changes between baseline (start of treatment) and six months later in pre-selected HRQL domains. Changes in those patients who remained progression-free for six months are shown in rows labelled "without progression." Changes in HRQL status in patients who had experienced disease progression within six months are shown in rows labelled "with progression." Results for patients with GBM are based on the RCT and one uncontrolled trial of temozolomide, therefore three sets of results are presented in the table: temozolomide patients treated in the RCT (labelled TMZ); procarbazine patients treated in the RCT (labelled procarb); and temozolomide patients treated in the uncontrolled study (labelled TMZu). Positive changes in HRQL are preceded by + signs whereas negative changes are preceded by – signs.

In the single group study,[1] HRQL in the 22 patients who remained progression free at six months improved from baseline in all seven pre-selected domains. Effect sizes were all 0.20 or greater (range: 0.2 to 0.48). However, only improvements in global quality of life, communication deficit and drowsiness achieved statistical significance.

Progression of disease tended to lead to deterioration in HRQL scores across all groups, regardless of treatment. However in TMZ groups there were improvements from baseline in the weeks preceding progression.

i The magnitude of changes (effect size) was computed by "dividing the standard deviation of the mean of the baseline completion score by the mean of the second, third, and so on completion. [1]Effect sizes of 0.2 – 0.5 are considered small. Effect sizes between 0.5 and .08 are moderate and > 0.8 are large.

Interim Summary -- GBM:
Results from the RCT provide the most reliable data. In this trial more patients on TMZ than procarbazine had six months free of disease progression. Median progression free survival was approximately four weeks longer on TMZ than procarbazine.

Results from the single group studies must be interpreted cautiously because there is no controlled comparison within the study. There is little to suggest that TMZ in these studies produced improved progression free survival or survival.

Generally, quality of life for patients on TMZ prior to progression was improved whereas quality of life was diminished for patients on procarbazine.

2.2.5.2 AA:

Only one single-group study was available that considered the effects of TMZ exclusively in AA.[32] Another[48] that included mixed histology patients also reported some results for AA separately.

Objective Response:
CR was reported in 8% of patients.[32] Objective response (combined complete and partial responses) was reported in 35% of these patients. Stable disease was reported in 27%. Another study of patients with mixed histologies reported an objective response in 10% of patients with AA.[48]

Six-month progression free survival:
Six-month progression free survival was 46% (95% CI: 38,54%).[32] For the subgroup of patients who had not had prior chemotherapy (n = 65) six-month PFS was 50% (95% CI: 38,63%).

Median progression free survival:
Median PFS was 23.5 weeks.[32] Median PFS for patients who had not had previous chemotherapy was 26.9 weeks.

Survival:
Median survival time was 59 weeks.[32] Median survival for chemotherapy-naïve patients was 49.9 weeks.

HRQL:
Among patients who were progression free at six months, scores improved from baseline in all seven pre-selected domains[33] (
Table 5). The effect sizes were > 0.2 for global quality of life (0.33) and social functioning (0.45), both of which were statistically significant.

HRQL scores at progression were at or below baseline. In the weeks preceding progression scores in most domains had been better than at baseline although gradually declining as progression neared. It should be noted that the same subjects did not consistently provide data at all time points.

Interim Summary – AA:

The results from studies of TMZ in AA should be considered cautiously because the studies were single group studies that do not provide a controlled comparison with an alternative treatment.

Objective response was somewhat higher in TMZ than in previous chemotherapy studies.[9;20] However, in the two studies reporting objective response, there was a large disparity in the proportion of patients reported to have achieved an objective response.

Six-month progression free survival, median PFS and survival in the TMZ study were all greater than in the AA group from the Wong *et al* report[9] summarised in section 1.2.2. However, as previously noted the TMZ patients may have had better prognoses than those in the Wong *et al* analysis.[9]

Quality of life prior to progression generally improved on TMZ, but deteriorated at progression.

2.2.5.3 AO and AOA

One study was available reporting results of TMZ in a single group of patients with AO (anaplastic oligodendroglioma) or AOA (mixed glioma).[5] All but one of these patients had received prior treatment with PCV chemotherapy.

Objective Response:
CR was reported in 16.7%. Objective response (CR+PR) was reported in 43.8% of patients with a further 39.6% with stable disease.

Six-month Progression free survival:
Six month progression free survival was 50.5%.

Median PFS:
Median PFS was 29 weeks.

Survival:
Median survival time was 43.4 weeks.

Interim Summary – AO or AOA:
One study suggests that effects of TMZ may be substantial in patients with AO or AOA. Relatively large proportions of patients achieved objective response and six month PFS although survival may not have been affected. However, these results must be interpreted with extreme caution as there is no appropriate comparison available.

2.2.5.4 Mixed Histologies:

Two full studies and one abstract reported on results of TMZ in single groups of patients with mixed histologies including GBM, AA and AOA.[34;47;48]

Objective Response:
The objective response rate ranged from 11% to 25%. In the two full reports, a further 47% and 38% were reported to have stable disease or "no change" in disease, respectively.[47;48] Similar results were reported in an abstract reporting objective response in 21% of patients and stable disease in 37%.[34]

In the Bower, *et al* study[48] 65 patients had not had previous chemotherapy. An objective response was seen in 15% of these patients (95% CI: 6, 24%).

Six-month Progression free survival:
One study reported six-month progression free survival of 22% (95%CI: 14, 31%).[48]

Survival:
In the one study reporting survival, the median was 25.2 weeks.[48]

Interim Summary – Mixed Histologies:
Because these studies are single group studies and a good comparison is not available, no strong conclusions can be drawn. Bearing in mind the limitations of comparing the TMZ results with the chemotherapy summary studies reported earlier, there appear to be no improvements in the proportions of patients with six-month progression-free survival or in survival. Further caution is required in the interpretation of results from mixed histological groups because of the effect of histology on outcomes.

2.2.6 Adverse effects of TMZ

Table 6 provides a summary of adverse events from included studies (except for one abstract); further detail is provided in Appendix 4.

Myelosuppression is the most serious adverse effect and is dose limiting. However, myelosuppression does not appear to be cumulative and is relatively easily treated. For those studies reporting percentages of patients rather than number of episodes, between 6% and 10% of patients suffered grade 3 or 4 thrombocytopenia, 2%-4% suffered grade 3 or 4 neutropenia, 1%-4.5% suffered grade 3 or 4 leukopenia, and 1% suffered grade 3 or 4 anaemia.

Table 6 Summary of adverse events

Study	**Adverse Events (grade 3 or 4 toxicity)**				
	Thrombo-cytopenia	**Neutro-penia**	**Leukopenia**	**Anaemia**	**Other (> 5%)**
GBM					
Yung, *et al*[31]	TMZ: 7% procarb: 4%	TMZ: 4% procarb: 3%	TMZ: 1% procarb: 0%	TMZ: 1% procarb: 2%	
Brada, *et al*[30]	10%	4.5%	7%		
AA or AOA					
Yung, *et al*[32]	6%	2%	2%	1%	asthenia; headache; nausea; vomiting
AO or AOA					
Chinot, *et al*[5]	6.4%				
Mixed histology (# episodes)					
Bower, *et al*[48] *n* =101 evaluable patients	13	5	6	1	lymphopenia (59); nausea, vomiting, lethargy (all >20 episodes)

Newlands, *et al*[47] (data for all 75 pts - incls 27 pre-recurrence)	7		5	3	lymphopenia (41)

procarb = procarbazine

A wide range of other grade 3 or 4 adverse effects were noted, but generally occurred in small proportions of the patients. Grades 3 or 4 adverse effects that occurred in more than 5% of patients in any study were asthenia (6%), headache (6%), nausea (10%), and vomiting (6%). These effects were all noted in the Yung, *et al* study[32] and occurred in fewer patients in other studies. All of the studies routinely included anti-emetics,[5;47;48] or allowed their use as needed[30-32] and noted that vomiting was generally well controlled by them. Additional grade 3 or 4 effects were: fatigue, fever, peripheral oedema, convulsions, dizziness, somnolence, abdominal pain, anorexia, constipation, diarrhoea, pruritis, confusion, hemiparesis, paresis, pulmonary infection and rash.

In the RCT comparing TMZ with procarbazine, the myelosuppressive effects were similar for both drugs, but nausea, vomiting, and fatigue were noted more often in the procarbazine group. Although similar proportions of patients suffered adverse events, these proportions are affected by the number of cycles administered and length of treatment: over 90% of patients on TMZ were treated for more than one cycle whereas only 33% of patients were treated with more than one cycle of procarbazine. The overall toxicity of TMZ does appear to be less.

Overall, TMZ appears to involve few serious adverse effects. Haematological effects can be assessed with laboratory tests. Some adverse effects are controllable (e.g., vomiting).

3. ECONOMIC ANALYSIS OF TEMOZOLOMIDE FOR MALIGNANT GLIOMA

3.1. Methods

A simple cost utility model was used to evaluate the cost-effectiveness of temozolomide in comparison to best alternative care.

All parameters used in the model (effectiveness, quality of life and costs) were varied in a sensitivity analysis. It should be noted that a ‘best case’ outlook was adopted: i.e. the assumption that, if anything, temozolomide may provide additional benefit over and above existing care. This assumption is based on the best available evidence, but the quality of that evidence is variable it is possible that TMZ provides no real benefit over and above existing treatment options. We have not explored in this section the possibility that TMZ produces worse outcomes than usual care.

AA is known to have a somewhat better prognosis than GBM, and as there was also some indication from the literature review that AA may be more chemosensitive than GBM, separate analyses according to these histological subtypes were performed. Economic analyses for the oligodendrogliomas (AO and AOA), were not performed due to lack of data.

3.1.1. Estimation of net benefits

3.1.1.1. Effectiveness estimates

The estimates of effectiveness used in the model were identified from the literature review in section 2.

The body of literature on the use of temozolomide in malignant glioma is very small and consists largely of uncontrolled studies, limiting the strength of any conclusions that can be drawn. However, evidence to date, though inconclusive, suggests that temozolomide leads to small increases in progression-free survival (PFS) for both GBM and AA patients and has little or no impact on survival, particularly in GBM. The side-effect profile of temozolomide appears to be favourable and there is no evidence that it produces worse outcomes than best alternative care.

Problems with the data used should be noted:

1. the effectiveness estimates provided in the studies are median as opposed mean data. This may result in an over-estimation of survival times, and is also problematic when combining these data with mean costs.
2. usual care for patients eligible for temozolomide in the UK most often consists of one of three chemotherapy regimens: PCV, BCNU, or CCNU. No data are available on the effectiveness of these regimens and so alternative sources of data have been used on the assumption that a reasonable picture of the outcomes of care will be provided.

GBM

Data from the Yung *et al* RCT[31] of temozolomide versus procarbazine was used to provide the PFS estimates for both groups. Only the *difference* in survival was provided by the trial, so the survival rate from the combined analysis of alternative chemotherapy treatments by Wong *et al*[9] was used to estimate the survival rate for GBM patients not treated with temozolomide (Table 7). As discussed earlier (section 1.2.2), the patients in these trials may have had a poorer prognosis than those in the TMZ trials, potentially inflating the effectiveness of TMZ.

Standard practice is to vary effectiveness estimates within the 95% confidence intervals provided by the trial data. In this case, the necessary data were not provided by the trial, and given the paucity of the available data only a limited sensitivity analysis was undertaken with a relatively narrow range of values.

Table 7 GBM survival estimates [a]

	Glioblastoma Multiforme (GBM)			
	No Tem	Tem	Difference	Range tested
Progression-free survival (weeks)	8	12	4 [b]	0, 8
Survival (weeks)	25 [c]	31 [c]	6 [d]	0

[a] data from RCT by Yung *et al*[31]
[b] p = 0.006
[c] not provided by RCT, survival for patients not receiving TMZ obtained from Wong *et al* [9]
[d] not significant

Given the small but significant result obtained for PFS, the increased benefit was varied from 0 to 8 weeks.

The non-significant result for survival suggested that any potential benefit from temozolomide was likely to be limited, and was likely to be less than six weeks. This was supported by the review of uncontrolled studies, and therefore only one alternative value for survival was tested in the sensitivity analysis, 0 weeks.

AA

For patients with AA, the progression-free survival and survival rates for temozolomide were provided by the Yung *et al*[32]uncontrolled study. Effectiveness data (PFS and survival) for the comparator group were again taken from the Wong *et al*[9] combined analysis of alternative chemotherapy treatments. Although this does not provide a valid within-study comparison, it does provide some estimates by which to evaluate the *potential* benefit from temozolomide.

Table 8 AA survival estimates

	Anaplastic Astrocytoma (AA)			
	No Tem	Tem	Difference	Range tested
Progression-free survival (weeks)	13 [a]	24 [b]	11	0, 22
Survival (weeks)	47 [a]	59 [b]	12	0

[a] data from Wong *et al*[9]

[b] data from Yung *et al* uncontrolled study[32]

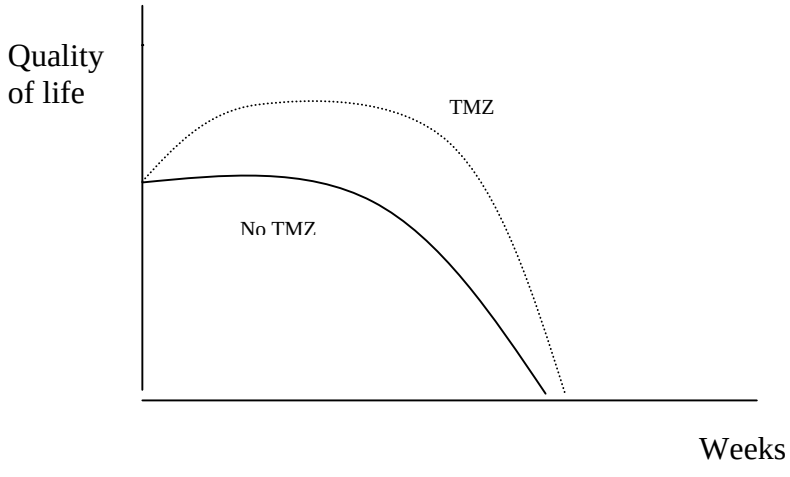
Again, the range of values tested in the sensitivity analyses were relatively narrow (Table 8), due to the paucity of the available data.

3.1.1.2. Estimation of utilities

The utility estimates used in the model were derived from the literature.

Two studies (discussed in section 2.2.5) were included that used psychometric instruments (EORTC QLQ-C30) to assess the quality of life of patents receiving temozolomide. These indicate that temozolomide may have a significant impact on quality of life of patients with both AA and GBM until the point of disease progression, when there is a rapid deterioration across all quality of life domains. It is therefore possible that the main benefit from temozolomide lies in the improvement in quality of life (see Figure 2).

Figure 2 Potential impact of temozolomide on quality of life



No studies were identified that provided a single index of quality of life (utility) either for patients receiving temozolomide, or for patients with malignant glioma (which could have provided baseline values). However, there is a global quality of life question included on the EORTC QLQ-C30 that asks patients "how would you rate your overall quality of life during the past week?" with anchors of "very poor" to "excellent". When these responses are converted to a scale of zero to one, thereby treating the question as a rating scale, responses have been shown to correlate highly with utilities obtained from EuroQol and simple quality of life rating scales.[51]

Table 9 Responses to global quality of life question

	Mean score at baseline	Standard deviation	Effect size at 6 months*
GBM (uncontrolled)[1] Temozolomide	55.5	23.2	Progression-free (n=22): 0.48 With progression (n=87): -0.24
GBM (RCT)[1] Temozolomide Procarbazine	63.0 58.6	20.6 22.9	Progression-free (n=19): -0.14 With progression (n=70): -0.27 Progression-free (n=7): 0 With progression (n=83): -0.45
AA (uncontrolled)[33] Temozolomide	61.4	22.5	Progression-free (n=63): 0.33 With progression (n=45): -0.32

* measure of the change in score from baseline to 6 months

Both of the temozolomide studies using the EORTC QLQ-C30 provided baseline scores (and standard deviations) in response to this question, thereby providing utilities for people with AA and GBM at recurrence (
Table 9). Neither of the studies provided data on the responses to this question over time, however, the effect sizes after six months generally indicate that people who remained progression free experienced a positive effect on quality of life, whilst those who had progressed experienced a deterioration.

Table 10 Utility values for GBM and AA and range tested

	GBM	AA
Average score on global qol item [a]	59.0	61.4
Corresponding utility at recurrence	0.60 [b]	0.60 [b]
Alternative utilities tested	0.80, 1.0	0.80, 1.0

[a] Global quality of life item included in the EORTC QLQ-C30 scale for assessment of quality of life
[b] The same baseline utility was used for AA and GBM as the average scores were so similar

The utility values at recurrence have been used to provide an estimate of quality of life without treatment with temozolomide (Table 10). Because the data on what happens to quality of life are not particularly robust, three possible scenarios were examined. These were that, compared to usual care, TMZ:

1) returns quality of life to perfect health until disease progression
2) has only a moderate impact on quality of life until disease progression

3) has no impact on quality of life, i.e. quality of life is maintained at baseline until disease progression

A 'worst case' scenario, in which quality of life deteriorates from baseline to progression was not examined as the literature review provided insufficient data to evaluate such a scenario.

No data on quality of life or utility values following progression of disease were available, therefore the deterioration in utility following progression was assumed to be linear.

3.1.1.3. Estimation of life years gained and quality-adjusted life years gained

The effectiveness of temozolomide in terms of progression-free survival and survival were used to estimate the number of progression-free weeks gained (PFWG) and life years gained (LYG). Utility estimates were added to produce estimates of the number of quality-adjusted life years (QALYs) gained. The utility curves for an increase in PFS, survival and utility as a result of temozolomide treatment are shown in Appendix 10.

3.1.2. Estimation of net costs[j]

Only direct costs relating to incremental cost of temozolomide administration and follow-up have been considered. The costs for the comparator are based on the PCV regimen, as it is a commonly used therapy in the UK. Costs incurred at the end of life, following progression of disease have been excluded due to lack of data.

The cost per cycle of each regimen using baseline costs is given in Table 11. The calculation of the individual cost components, data sources used, and range of costs tested are provided in Appendix 9. The cost of MRI could not be calculated per cycle since MRI scans are given at baseline, following two treatment cycles and at six months follow-up. This cost has therefore been calculated per course of treatment, according to length of progression-free survival.

Table 11 Cost per cycle of treatment

	PCV	**TMZ**
Chemotherapy costs	£106	£1,176
Anti-emetics (granisetron)	£73	£110
Out-patient visits	£300	£200
Total cost per cycle	**£480**	**£1,488**

The main factor influencing the incremental cost is the period of progression-free survival, as chemotherapy is administered until the point of disease progression. The incremental costs of temozolomide for each of the estimates of PFS tested in the model are given in Table 12.

Table 12 Incremental cost of temozolomide (TMZ) for GBM and AA

	GBM			**AA**		
Progression-free survival (wks) (TMZ)[a]	8	12	16	13	24	35
Cycles of TMZ [b]	2	3	4	3.25	6	8.75
Cost per course of TMZ [c]	**£2,975**	**£4,463**	**£5,950**	**£4,834**	**£8,925**	**£13,016**
Number of MRI scans (TMZ) [d]	2	2	2	2	3	3
Cost of MRI (TMZ)	£444	£444	£444	£444	£666	£666

j Costs are rounded to the nearest whole pound in calculations and in tables.

Cycles of PCV [e]	1.33	1.33	1.33	2.17	2.17	2.17
Cost per course of PCV [c]	**£640**	**£640**	**£640**	**£1,040**	**£1,040**	**£1,040**
Number of MRI scans (PCV) [d]	1	1	1	2	2	2
Cost of MRI (PCV)	£222	£222	£222	£444	£444	£444
Incremental cost of TMZ [f]	**£2,557**	**£4,044**	**£5,532**	**£3,794**	**£7,607**	**£11,396**

a PFS estimates tested in the model
b based on cycle length of 4 weeks
c number of cycles multiplied by cost per cycle (Table 11)
d MRI scans administered at baseline, following 2 cycles of treatment and at 6 months follow-up
e based on cycle length of 6 weeks and PFS of 8 and 13 weeks for GBM and AA respectively
f cost per course of TMZ and cost of MRI minus cost per course of PCV and cost of MRI

Given the high incremental cost of temozolomide, the impact of variations in other costs was very small, therefore only the results using these baseline costs are presented (further data available from the authors).

3.1.3. Discounting

Due to the very short timeframe of the analysis (survival generally under one year), no discounting of costs or benefits has been undertaken.

3.2. Results – Glioblastoma Multiforme (GBM)

Data were combined to provide both cost-effectiveness and cost-utility analyses. The main results are discussed in the following sections, and the full results are provided in Appendix 11.

3.2.1. Cost-effectiveness analyses

The cost-effectiveness analyses were undertaken in two ways. As the literature review indicated little or no increase in survival from temozolomide, the cost per progression-free week gained was calculated. However, in the event of a survival advantage from temozolomide the cost per life year gained was also estimated.

3.2.1.1. Cost per progression-free week gained

Two estimates of the gain in progression-free survival were used: four weeks and eight weeks. The incremental costs per progression-free week gained were £1011 and £691 respectively.

3.2.1.2. Cost per life year gained

Only one estimate of increased survival was tested in the model. A six week gain in survival is equivalent to a gain of 0.12 life years (Appendix 11).

The cost per life year gained depends on the length of progression-free survival. A four week gain in PFS combined with a 6 week gain in survival provides a cost per life year gained of £35,051. Gains in PFS of 0 and 8 weeks with a 6 week survival gain produce costs per LYG of £22,159 and £47,943 respectively.

3.2.2. Cost-utility (QALYs gained): baseline analysis

The impact of temozolomide on quality of life has a significant impact on the cost-effectiveness ratios produced.

The most likely scenario suggested from the literature review was that temozolomide produces a modest increase in progression-free survival, has no effect (or no significant effect) on survival and to some extent improves quality of life while patients remain progression-free. This provided data for the baseline analysis (Table 13). This scenario involved an increase in progression-free survival of 4 weeks and an increase in utility of 0.2 resulting in a cost per QALY of £42,920.

Table 12 also outlines more extreme scenarios. If quality of life is not improved while progression-free, an additional 0.02 QALYS are gained at a cost of £175,256 per extra QALY.[k] At the opposite extreme, if quality of life were to be returned to a state of perfect health by temozolomide, 0.17 QALYs are gained at a cost of £24,454 per QALY. The true value is likely to lie somewhere between £42,920 and £175,256 per QALY gained.

Table 13 Results of GBM baseline analysis

	Increase in PFS only		
Increase in PFS / Increase in survival (wks)	4 / 0	4 / 0	4 / 0
Increase in utility from TMZ while progression-free	0.40	0.20	0
QALYs gained	0.17	0.09	0.02
Cost/QALY gained	£24,454	£42,920	£175,256

The extent of the increase in PFS does not make a great deal of difference to the cost/QALY estimates because the longer the PFS, the more cycles of TMZ administered and the higher the costs incurred (see Appendix 11).

3.2.3. Cost-utility (QALYs gained): sensitivity analyses

Several scenarios were explored in the sensitivity analyses, the most relevant of which are presented in Table 14.

The CERs obtained are largely influenced by:

- the utility gained from temozolomide
- the length of progression-free survival (which determines the incremental costs)

Table 14 Results of GBM sensitivity analyses

	Increase in PFS and survival			**Increase in survival only**			**No increase in PFS or survival**		
Increase in PFS/ survival (wks)	4 / 6	4 / 6	4 / 6	0 / 6	0 / 6	0 / 6	0 / 0	0 / 0	0 / 0
Increase in utility [a]	0.40	0.20	0	0.40	0.20	0	0.40	0.20	0
QALYs gained	0.22	0.14	0.06	0.17	0.10	0.03	0.11	0.06	0
Cost/QALY gained	£18,130	£28,809	£70,102	£15,109	£25,086	£73,865	£22,924	£45,847	∞ [b]

[a] while progression-free

[b] No incremental benefit from TMZ, i.e. no increase in progression-free survival, overall survival or utility

k cost per QALY gained can be calculated because of the assumption of linear decline in utility following progression.

Table 14 demonstrates the influence of the utility assumptions on the CERs. When quality of life is returned to perfect health (increase of 0.40), the costs/QALY gained lie between £15,109 and £22,924, regardless of the increases in PFS and survival. However, when temozolomide does not improve quality of life over that from standard care, the costs/QALY gained lie at over £70,000[l].

Larger increases in PFS (eight weeks) increased the costs per QALY gained, ranging from £19,976 to £119,857, as more costs are incurred the longer the progression-free period (Appendix 11).

Repeating the analyses using alternative cost estimates for the anti-emetic regimen used, the cost of an out-patient attendance, and the cost of an MRI, also made little difference to the CERs (data not shown).

3.3. Results - Anaplastic Astrocytoma (AA)

The same analyses were conducted for patents with AA, using effectiveness and cost data to reflect the longer progression-free survival and survival of these patients compared to those with GBM (Appendix 12). The costs per progression-free week gained and cost per life year gained from temozolomide were estimated.

3.3.1. Cost-effectiveness analyses

3.3.1.1. Cost per progression-free week gained

Two estimates of the gain in progression-free survival were used: 11 weeks and 22 weeks. The incremental costs per progression-free week gained were £737 and £554 respectively.

3.3.1.2. Cost per life year gained

Only one estimate of increased survival was tested in the model. A 12 week gain in survival is equivalent to a gain of 0.23 life years (Appendix 12).

The cost per life year gained depends on the length of progression-free survival. An 11 week gain in PFS combined with a 12 week gain in survival provides a cost per life year gained of £35,129. Gains in PFS of zero and 22 weeks with a 12 week survival gain produce costs per LYG of £16,441 and £52,856 respectively.

3.3.2. Cost-utility (QALYs gained): baseline analysis

The baseline analysis for AA was also based around the assumptions that temozolomide produces a modest increase in progression-free survival, has no (or no significant effect) on survival and to some extent improves quality of life while patients remain progression-free. This most likely scenario involved an increase in progression-free survival of 11 weeks and an increase in utility of 0.2 resulting in a cost per QALY of £40,534.

Under more extreme scenarios, the number of QALYs gained ranges from 0.06 at a cost of £127,743 per extra QALY[m], to 0.34 at a cost of £24,089 per extra QALY. These outcomes are

l see footnote k
m see footnote k

produced by assuming that quality of life is either not improved at all while progression-free or is returned to perfect health, respectively.

Table 15 Results of AA baseline analysis

	Increase in PFS only		
Increase in PFS / Increase in survival (wks)	11 / 0	11 / 0	11 / 0
Increase in utility from TMZ while progression-free	0.40	0.20	0
QALYs gained	0.34	0.20	0.06
Cost/QALY gained	£24,089	£40,534	£127,743

3.3.3. Cost-utility (QALYs gained): sensitivity analyses

Table 16 presents the results of some of the sensitivity analyses. The influence of the utility assumptions made can again be clearly seen. If quality of life is returned to perfect health, the cost/QALY gained is between £12,487 to £20,132. If temozolomide does not improve quality of life over standard care while progression-free, the costs/QALY rise to over £50,000.

When the analyses were repeated for a 22 week increase in PFS, there was little difference in the number of QALYs gained or cost/QALY gained (Appendix 12).

The impact of using alternative cost estimates for the anti-emetic regimen used, the cost of an out-patient attendance, and the cost of an MRI, were also examined; little impact on the CERs was found (data not shown).

Table 16 Results of AA sensitivity analyses

	Increase in PFS and survival			Increase in survival only			No increase in PFS or survival		
Increase in PFS/survival (wks)	11 / 12	11 / 12	11 / 12	0 / 12	0 / 12	0 / 12	0 / 0	0 / 0	0 / 0
Increase in utility [a]	0.40	0.20	0	0.40	0.20	0	0.40	0.20	0
QALYs gained	0.45	0.29	0.13	0.30	0.19	0.07	0.19	0.09	~
Cost/QALY gained	£17,938	£27,734	£61,095	£12,487	£20,340	54,804	£20,132	£40,264	∞ [b]

[a] while progression-free
[b] No incremental benefit from TMZ, i.e. no increase in progression-free survival, overall survival or utility

4. IMPLICATIONS FOR OTHER PARTIES

The impact of a diagnosis of malignant glioma on families and carers is likely to be considerable. A wide range of symptoms may be experienced many of which can be severely debilitating. The disease is almost always fatal and life expectancy following diagnosis can be less than one year. In all, the disease causes significant distress to both patients and carers.

Patients are unlikely to be able to continue with their normal daily activities for any length of time following diagnosis, and are likely to receive a significant amount of care at home from carers and community services. Patients spend an average of only 40 days in hospital throughout the course of the disease. Bloor *et al*[22] found a moderate amount of community service use by patients, including home visits by hospice care teams, GPs, Macmillan nurses and district nurses, at an average cost of £456 per patient. If TMZ lengthens only progression-free survival, then these costs may only be postponed. However, if TMZ also increases overall survival, i.e. increases the length of time spent at the end of life, more costs

may be incurred. There are no data available on the impact of TMZ on costs associated with final deterioration.

The indirect costs of glioma (from loss of productivity) are likely to be substantial, as are direct costs to patients and carers.

5. FACTORS RELEVANT TO THE NHS

Cancer has been identified as one of the Government priority areas for health. The recent NHS Cancer Plan[52] emphasises the 'postcode lottery of care' whereby patients in different parts of the country receive varying quality and types of treatment. This is particularly relevant to the use of TMZ in malignant glioma as current provision seems to be inconsistent across health authorities.

There is already considerable ongoing and proposed research concerning TMZ. The new National Cancer Research Institute may play an important role in identifying where research is most needed and where it is most likely to contribute to progress both in cancer research as a whole and within individual cancers.

Although there is some suggestion of higher one-year survival of brain tumours among affluent groups, five year-survival across England and Wales does not appear to be affected by deprivation.[2] There is no suggestion of socio-economic differences in incidence from malignant gliomas, however people with brain cancer are clearly disadvantaged due to the nature of their disease. Survival rates are extremely poor, current treatments are not curative, and few palliative care options are available.

6. DISCUSSION

Main Results

Evidence for the effectiveness of temozolomide for recurrent malignant glioma comes mainly from three phase II clinical studies, including only one RCT, conducted in patients with GBM and AA (the two most common types of glioma). Several other small, uncontrolled studies have also been conducted in a somewhat wider population of glioma patients (including AO, AOA).

Evidence to date indicates that glial tumours do have some response to temozolomide. This response is closely related to tumour histology: patients with AA experience a larger response compared to those with GBM.

The main benefit in patients with GBM, demonstrated in one RCT and one relatively large uncontrolled study, is an increase (13%) in the estimated proportion of patients remaining progression-free at six months and a significant increase in median progression-free survival of approximately four weeks. However, there was no significant survival advantage in comparison to an alternative chemotherapy regimen.

For patients with AA, one large uncontrolled study suggests favourable progression-free survival and possibly survival. The magnitude of any benefit in AA is difficult to quantify due to the lack of a within study comparison of temozolomide with an alternative treatment regimen.

Some subgroup analyses have been conducted in patients who have not received any prior chemotherapy in the expectation that such patients might respond differently to TMZ. The number of patients eligible for analysis is small, however, there is some suggestion of better median PFS. Since adjuvant chemotherapy is not commonly used in the UK, these subgroup analyses may be more applicable to the UK population, but require confirmation in larger RCTs.

TMZ appears to involve few serious adverse effects. Vomiting appears to be well controlled by prophylactic anti-emetic regimens. Some clinicians believe that toxicity, particularly myelosuppression, is more predictable with TMZ and this has been noted as one of the advantages of this drug over others. Nitrosoureas seem to be less predictable in myelosuppression and they can produce cumulative myelosuppression that can require delay or discontinuation of these agents, and may prevent subsequent treatment with alternative agents. It should be noted, however, that there is disagreement about the toxicity of TMZ among clinicians and little empirical evidence is available.

On the basis of current evidence, which suggests only a moderate increase in progression-free survival, the cost per progression-free week gained is around £1000 for GBM and £700 for AA. If this were to be combined with some increase in survival, the cost per life year gained is would lie at around £30,000 (for a life year gain of 0.12 for GBM and 0.23 for AA).

However, one of the major claims of benefit from TMZ is that conferred on health-related quality of life. Evidence to date indicates that TMZ does improve HRQL from recurrence until at or near disease progression for patients with GBM or AA, and appears to confer considerably better quality of life than procarbazine. Given the cognitive impairments that can be associated with brain tumours these improvements may be quite important in the daily functioning of patients and in their relationships with family and friends.

If a relatively moderate impact on quality of life alongside a moderate increase in PFS is assumed, the cost per QALY gained from TMZ for patients with either GBM or AA is likely to lie at around £40,000 (for a QALY gain of 0.09 and 0.20 respectively). When these assumptions are combined with some increase in survival, the cost/QALY gained drops to just under £30,000 for both histological subgroups. This latter value should be interpreted in the light of the desirability of an increase in the length of time spent at the end of life when the quality of life experienced may be extremely poor. On the other hand, it can be argued that time spent at the end of life should be weighted more highly than at any other time.

Current direct costs of treating malignant glioma in the UK are something in the region of £25 million per annum. Approximately 30% of patients have been considered for chemotherapy in the past, if this proportion were to be maintained, then around 600 patients per year could be eligible to receive temozolomide. The incremental cost of the drug varies according to tumour type and impact on PFS. Assuming a moderate impact on PFS, if 300 patients with GBM and 300 with AA received temozolomide at recurrence, the annual incremental cost to the NHS would be in the order of £4 million per annum.

Assumptions, limitations and uncertainties

The implications drawn from both the review of effectiveness and from the economic analyses should be treated with a great deal of caution, both due to limitations in the evidence available to date and the assumptions made in the economic model.

Limitations in the evidence

1. Only one controlled trial is available. This trial was conducted only in patients with GBM, did not use a comparator that is commonly used in the UK, and was not powered to detect a clinically significant difference in outcomes. Furthermore, limited details of the methods used in the trial, including methods of randomisation, were available. For all other types of glioma (including AA), only data from uncontrolled studies are available. Although an attempt was made to compare the results of the uncontrolled trials to the results of trials of other forms of treatment for malignant glioma, such comparisons are fraught with difficulties and cannot provide solid evidence about the effectiveness of an intervention. Furthermore, the patients included in the studies used for comparison probably had a poorer prognosis than those in the TMZ studies. The comparison between these results and the TMZ studies may suggest more favourable effectiveness for TMZ than would be seen in practice.

2. Only median as opposed to mean data were available. This may lead to an over-estimation of survival if the results are skewed towards very short survival times.

3. Many of the outcome measures used are relatively subjective, particularly those used to evaluate tumour response. None of the studies reviewed (including the RCT) used single or double-blinding, largely due to the uncontrolled nature of the studies. It is possible that subjective clinical assessments and patient self-report of quality of life may have been affected by knowledge of the treatment, however in most studies radiological data were centrally reviewed and often by blind reviewers.

4. Measures of progression and survival depend importantly on the timing of the baseline and follow-up evaluations. The point at which recurrence is detected and further treatment is initiated will affect the estimates of PFS and survival. Furthermore, when imaging is being performed more regularly than in normal practice, initial recurrence may be detected earlier producing longer estimates of survival. Likewise, however, additional progression after recurrence may also be detected earlier than in routine practice, thereby underestimating progression-free survival. Therefore, the results for both PFS and survival may not be directly generalisable to clinical practice.

5. Finally, it is likely that the patients included in the studies reviewed are only a subset of those who may be eligible for chemotherapy in clinical practice, and may provide a more favourable picture of TMZ than might be seen in routine care. Most of the studies completed to date required patients to have relatively high performance status (KPS > 70) and life expectancy (at least 12 weeks). In practice, all patients considered sufficiently fit are likely to undergo some form of chemotherapy (sometimes because it is unacceptable to patients and/or relatives to do nothing).

Assumptions made in the economic model

The economic analysis relies to a large extent on the available effectiveness data and therefore suffers from all the above caveats. In addition, several assumptions were required that further reduce confidence in the results.

1. There are no data directly comparing TMZ to widely used treatments used in the UK such as CCNU or PCV. In the absence of such data, for patients with GBM, the analysis relied on effectiveness data for procarbazine produced by the included RCT, and for those with AA, on the results of a summary of trials of chemotherapy. These data can only be assumed to provide an indication of the *potential* cost-effectiveness of temozolomide. Because of the caveats already discussed, the economic evaluations may be based on slightly overestimated PFS and / or survival values. Sensitivity analyses have been included to allow consideration of this possibility.

2. Limited data are available on the quality of life of patients with recurrent glioma. Three of the studies reviewed administered psychometric questionnaires to patients, the results of which give a general picture of quality of life, but do not provide reliable utility estimates for use in a cost-utility analysis. On the basis of a single study which found a good correlation between the responses to a global quality of life question, an estimate of the utility experienced at recurrence was obtained. Whether the baseline utility used is accurate may be questionable, however it did at least allow some exploration of the effect of temozolomide on quality of life while progression-free, and the resulting impact on the cost-utility of the treatment.

3. There was a further lack of data on utilities experienced *following* progression of disease, therefore the deterioration in quality of life during this phase of disease was assumed to be linear. In practice, it is more likely that the utility curve would dip sharply and then level off, such that the assumptions made are likely to have over-estimated the value of life following progression and any hypothesised increase in survival.

4. Finally, no indirect costs were considered and only the direct costs of treatment at recurrence were included. No data were available on the cost of treatment at the end of life, and any potential impact on such costs from the use of temozolomide. It may be that temozolomide may introduce some cost savings by shortening the period from progression to death (increasing PFS without impacting on survival), but this was not possible to evaluate.

Need for further research

Considerable research on TMZ is ongoing. Much of the research is similar in design to that reviewed here – single group studies of TMZ effectiveness and toxicity in relatively small patient groups. There are also studies considering different dosing regimes for the drug as well as combining TMZ with other drugs or treatments that may potentiate its effects. There are trials ongoing in children and in other histological subgroups.

However, the most pressing need is for adequately powered RCTs of TMZ for recurrent glioma compared to best alternative care such as PCV, in a wider population of patients (i.e. not limited to those with best prognosis), focusing on those who have not received any prior chemotherapy. Because malignant glioma is relatively uncommon, multi-centre trials recruiting a large proportion of eligible patients will be necessary.

There is also a need for research to be conducted in children. However, such research requires different considerations as the distribution of types and locations of tumour vary between children and adults.[3]

In addition, ongoing research may point to needed research into TMZ as adjuvant therapy, or offered in different doses, etc.

Some of these research needs may be fulfilled by current ongoing or planned trials:

- an RCT of TMZ versus standard nitrosourea-based chemotherapy (PCV) in chemotherapy-naïve patients with recurrent AA and GBM at first relapse is in development by the Clinical Trials Unit of the Medical Research Council (MRC) in collaboration with the UKCCCR Brain Tumour Group. The trial aims to recruit patients with a wider spectrum of disease, and will not be confined only to patients with favourable prognosis. If the full application is successful, the trial is expected to launch in summer 2001 and accrual of patients would require approximately three years.
- an RCT sponsored by the EORTC and the National Cancer Institute of Canada comparing RT with concomitant TMZ with RT followed by TMZ in patients with GBM is underway. The newly opened study (July, 2000) will recruit 520 patients across Europe and Canada, but will likely take several years to complete.
- An RCT sponsored by the U.S. National Cancer Institute and the Radiation Therapy Oncology Group has been funded to compare TMZ against carmustine against TMZ plus carmustine in patients with AA. All chemotherapy regimens will be administered concurrently with RT. A preliminary trial will determine whether the combined treatment produces unacceptable toxicity. The recently opened study is recruiting in the U.S. and Canada and it is expected that patient accrual of 570 patients will last four years.

7. CONCLUSIONS

On the basis of the available evidence, TMZ does demonstrate some effectiveness in recurrent malignant glioma. Appropriate comparisons of TMZ with other chemotherapy regimens are generally lacking. The available data suggest that the effects of TMZ are modest with regard to extending progression-free survival and survival, but similar results have been reported in several studies. Effects on HRQL also appear reliable. The adverse effects of the drug are not usually severe. There are suggestions that TMZ may produce fewer adverse effects and be easier to administer than other possible treatments.

Assuming modest effectiveness gains for TMZ, the cost per QALY gained from temozolomide is likely to be approximately £40,000. The incidence of malignant glioma is relatively low and the overall budgetary impact for the NHS as a whole is in the order of £4 million per annum.

Appropriate RCTs comparing TMZ with other alternative therapies need to be conducted in order to draw firm conclusions about the effectiveness of TMZ.

REFERENCES

1. Osoba D, Brada M, Yung WK, Prados M. Health-related quality of life in patients treated with temozolomide versus procarbazine for recurrent glioblastoma multiforme. *J Clin Oncol* 2000;18(7):1481-91.

2. Cancer Survival Trends in England and Wales 1971-1995. 2000.

3. Rampling R. CRC CancerStats: Brain. *CRC CancerStats* 2000.

4. Chamberlain MC, Kormanik PA. Practical guidelines for the treatment of malignant gliomas. *West J Med* 1998;168(2):114-20.

5. Chinot, O., Honore, S., Dufour, H., Barrie, M., Figarella-Branger, D., Muracciole, M., Braguer, D., Martin, P. M., and Grisoli, F. Safety and efficacy of temozolomide in patients with recurrent anaplastic oligodendroglioma following standard radiotherapy and chemotherapy. Submitted for publication . 2000.

6. Office for National Statistics. Health Statistics Quarterly. [Autumn]. 2000. London, The Stationery Office. National Statistics.

7. Office for National Statistics. Health Statistics Quarterly. [Summer]. 2000. London, The Stationery Office. National Statistics.

8. Curran-WJ J, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ *et al*. Recursive partitioning analysis of prognostic factors in three radiation therapy oncology group malignant glioma trials. *J Natl Cancer Inst* 1993;85:704-10.

9. Wong ET, Hess KR, Gleason MJ, Jaeckle KA, Kyritsis AP, Prados MD *et al*. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol* 1999;17(8):2572-8.

10. Whitton AC, Rhydderch H, Furlong W, Feeny D, Barr RD. Self-reported comprehensive health status of adult brain tumor patients using the health utilities index. *Cancer* 1997;80(2):258-65.

11. Osoba D, Brada M, Prados M, Yung WKA. Effects of Disease Burden on Health-Related Quality of Life in Patients with Malignant Gliomas. *Neuro-oncology* 2000;2(4).

12. Quigley MR, Maroon JC. The relationship between survival and the extent of the resection in patients with supratentorial malignant gliomas. *Neurosurgery* 1991;29(3):385-8.

13. Walker MD, Alexander E, Hunt WE, MacCarty CS, Mahaley MS, Mealey J *et al*. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. *J Neurosurg* 1978;49:333-43.

14. Kristiansen K, Hagen S, Kollevold T, Torvik A, Holme I, Nesbakken R *et al*. Combined modality therapy of operated astorcytomas grade III and IV. Confirmation

of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicentre trial of the Scandinavian Glioblastoma study group. *Cancer* 1981;47(4):649-52.

15. Davies E, Clarke C, Hopkins A. Malignant cerebral glioma--I: Survival, disability, and morbidity after radiotherapy. *BMJ* 1996;313(7071):1507-12.

16. Blomgren H. Brain tumors. *Acta Oncol* 1996;35 Suppl 7:16-21.

17. MRC Brain Tumour Working Party. Randomised trial of procarbazine, CCNU and vincristine in the adjuvant treatment of high grade astrocytoma - a Medical Research Council Trial. Submitted for publication. 2000.

18. Stewart LA, Burdett S, Souhami RL. Chemotherapy in high-grade glioma: A meta-analysis using individual patient data from randomized clinical trials (RCTs). *Proc Annu Meet Am Soc Clin Oncol* 2000;650.

19. DeAngelis LM, Burger PC, Green SB, Cairncross JG. Malignant glioma: who benefits from adjuvant chemotherapy? *Ann Neurol* 1998;44(4):691-5.

20. Huncharek M, Muscat J. Treatment of recurrent high grade astrocytoma; results of a systematic review of 1,415 patients. *Anticancer Res* 1998;18(2B):1303-11.

21. Latif AZ, Signorini D, Gregor A, Whittle IR. The costs of managing patients with malignant glioma at a neuro-oncology clinic. *Br J Neurosurg* 1998;12(2):118-22.

22. Bloor K, Drummond MF, Brada M, Rampling R. High grade gliomas: clinical outcomes, resource use and cost of care. University of York: Centre for Health Economics (memo); 1998.

23. Silverstein MD, Cascino TL, Harmsen WS. High-grade astrocytomas: resource use, clinical outcomes and cost of care. *Mayo Clinic Proc* 1996;71:936-44.

24. The European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products European Public Assessment Report (EPAR): Temodal. 20-1-1999.

25. Newlands ES, Stevens MFG, Wedge SR, Wheelhouse RT, Brock C. Temozolomide: A review of its discovery, chemical properties, pre-clinical development and clinical trials. *Cancer Treat Rev* 1997;23(1):35-61.

26. Friedman HS, Kerby T, Calvert H. Temozolomide and treatment of malignant glioma. *Clin Cancer Res* 2000;6(7):2585-97.

27. *British National Formulary*. London: BMJ Books, 2000.

28. Jadad A, Moore A, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996;17(1):1-12.

29. Spitzer WO, Lawrence V, Dales R, Hill G, Archer MC, Clarck P *et al*. Links between passive smoking and disease; A best-evidence synthesis. *Clin Invest Med* 1990;13(1):17-42.

30. Brada, M, Hoang-Xuan, K, Rampling, R, DietrichP-Y., Dirix, LY, Macdonald, D, Heimans, JJ, Zonnenberg, BA, Bravo-Marques, JM, Henriksson, R, Stupp, R, Yue, N, Bruner, J, Dugan, M, Rao, S, and Zaknoen, S. Multicenter phase II trial of temozolomide in patients with glioblastoma mulforme at first relapse. Submitted for publication . 2000.

31. Yung WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD *et al*. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer* 2000;83(5):588-93.

32. Yung WKA, Prados MD, Yaya TR, Rosenfeld SS, Brada M, Friedman HS *et al*. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. *J Clin Oncol* 1999;17(9):2762-71.

33. Osoba D, Brada M, Yung WKA, Prados M. Health-related quality of life in patients with anaplastic astrocytoma during treatment with temozolomide. *Eur J of Cancer* 2000;36:1788-95.

34. Spagnolli F, Boni C, Gagliardi R, Tassinari D, Carapella C, Pace Andrea *et al*. Temozolomide as second line chemotherapy in the treatment of recurrent malignant gliomas. *Proc Annu Meet Am Soc Clin Oncol* 2000;653.

35. Honore' S, Chinot O, Guise S, Dufour H, Grisoli F, Braguer D. Temozolomide (Temodal registered) in malignant glioma second line chemotherapy. *J Pharm Clin* 1999;18:18-9.

36. Janinis J, Efstathiou E, Panopoulos C, Samantas E, Aravantinos G, Christodoulou C *et al*. Phase II study of temozolomide in patients with relapsing high grade glioma and poor performance status. *Med Oncol* 2000;17(2):106-10.

37. Lashford LS, Pearson AD, Thiesse P, Jasparn T, Vassal G, Dugan M *et al*. Efficacy of Temodal in diffuse, intrinsic brain stem gliomas (BSG). *Proc Annu Meet Am Soc Clin Oncol* 1998;17.

38. 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. *Eur J Cancer Part A Gen Top* 1993;29(7):940-2.

39. Paulsen F, Hoffmann W, Becker G, Belka C, Weinmann M, Classen J *et al*. Chemotherapy in the treatment of recurrent glioblastoma multiforme: Ifosfamide versus temozolomide. *J Cancer Res Clin Oncol* 1999;125(7):411-8.

40. Spagnolli F, Boni C, Gagliardi R, Ravaioli A, Tassinari D, Carapella C *et al*. Activity of Temozolomide in Recurrent Malignant Gliomas: A Phase II Study. (Meeting abstract). *Proc Annu Meet Am Soc Clin Oncol* 1999;18:A590.

41. Stupp R, Maeder P, Pica A, Wurm R, Hungerbuhler Hp, Villemure G *et al*. Improved outcome with chemotherapy with temozolomide for recurrent glioblastoma (GBM) and anaplastic astorcytoma (AA). *Neurooncol* 1998;39:151.

42. 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(12):3851-7.

43. Viviers L, Brada M, Hines F, Britton J, Abson C, Ashley S. A Phase II Trial of primary chemotherapy with temozolomide in patients with low-grade cerebral gliomas. *Proc Annu Meet Am Soc Clin Oncol* 2000.

44. Brandes AA, Ermani M, Pasetto L, Amista P, Scienza R, Sotti G *et al*. Temozolomide (TMZ) in high grade gliomas (HGG) at second relapse: a Phase II study. *Proc Annu Meet Am Soc Clin Oncol* 2000.

45. Stupp R, Kraljevic SO, Dietrich P-Y, Pica A, Maillard I, Maeder P *et al*. Promising survival with concomitant and adjuvant temozolomide (TMZ) for newly diagnosed glioblastoma multiforme (GBM). *Proc Annu Meet Am Soc Clin Oncol* 2000.

46. Friedman AH, Cokgor I, Edwards S, Rich JN, Quinn JA, Stewart B *et al*. Phase II treatment of anaplastic oligodendroglioma and low grade glioma with temozolomide. *Proc Annu Meet Am Soc Clin Oncol* 2000.

47. Newlands ES, O'Reilly SM, Glaser MG, Bower M, Evans H, Brock C *et al*. The Charing Cross Hospital experience with temozolomide in patients with gliomas. *Eur J Cancer Part A* 1996;32(13):2236-41.

48. Bower M, Newlands ES, Bleehen NM, Brada M, Begent RJ, Calvert H *et al*. Multicentre CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma. *Cancer Chemother Pharmacol* 1997;40:484-8.

49. Brada M, Yung WK. Clinical trial end points in malignant glioma: need for effective trial design strategy. *Semin Oncol* 2000;(3 Suppl 6):11-9.

50. Schering-Plough Ltd. Temozolomide in the treatment of malignant glioma in the United Kingdom. A submission to the National Institute for Clinical Excellence. 2000.

51. Norum J. Quality of life (QoL) measurement in economical analysis in cancer: A comparison of the EuroQol questionnaire, a simple QoL-scale and the global QoL measure of the EORTC QLQ-C30. *Oncol Rep* 1996;3(4):787-91.

52. Department of Health. The NHS Cancer Plan. London: Department of Health; 2000.

53. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365-76.

54. Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsu MA, Yung WKA *et al*. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res* 1996;5(1):139-50.

55. Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsu MA, Yung WKA *et al*. Effect of neurological dysfunction on health-related quality of life in patients with high-grade glioma. *J Neuro Oncol* 1997;34(3):263-78.

56. Osoba D. What has been learned from measuring health-related quality of life in clinical oncology. *Eur J Cancer* 1999;35(11):1565-70.

57. National Health Service in Scotland. Scottish Health Service Costs. Year ended 31st March 1999. Edinburgh: Information and Statistics Division; 2000.

APPENDIX 1

Rapid review methods from the research protocol

Research question

- What is the effectiveness and cost-effectiveness of temozolomide (Temodal) for the treatment of primary malignant brain tumours (anaplastic astrocytoma and glioblastoma multiforme)?

- This review will focus on the use of temozolomide for its licensed indications, in terms of *both* survival *and* quality of life. In addition, evidence relating to its use as first-line therapy (i.e. before tumour recurrence or progression has occurred) will be examined.

Inclusion criteria

- primary malignant gliomas (specifically anaplastic astrocytoma or glioblastoma multiforme)
- adults and children aged over 3
- temozolomide at any dose/regimen
- if insufficient data on side-effects is identified from the above studies, RCTs of temozolomide in other tumours (such as melanoma) with ≥ 50 patients and which report relevant treatment side-effect data will be included.

Study designs

- randomised controlled trials
- non-randomised studies with concurrent controls
- studies without concurrent controls with sample size ≥ 50 patients

Search Strategy

- Extensive electronic searches of the following databases will be conducted by, or in consultation with, an experienced information scientist, to identify both published and unpublished literature. These searches will aim to identify: existing systematic reviews and primary studies evaluating the effectiveness of temozolomide; relevant quality of life literature; and economic evaluations.
- Databases to be searched include:
  Cochrane Database of Systematic Reviews (CDSR); Database of Abstracts of Reviews of Effectiveness (DARE); HTA Database; MEDLINE; EMBASE; BIOSIS; CancerLit; TOXLINE; Cochrane Controlled Trials Register; Science Citation Index; National Research Register; CancerTrials – NCI trials in progress; UKCCCR Register of Cancer Trials
- Other search strategies to identify further useful citations that will be used include scanning the reference lists of all retrieved studies and contact with the authors of included studies.

Quality Criteria

- RCTs will be assessed using a modification of the Jadad scale.[28] This scale has been chosen as it is the closest approximation to a validated tool currently available. However, due to problems with the use of composite scales as quality markers, the items in the scale

will used in a checklist format, with the addition of an extra item (relating to allocation concealment).
- All studies providing effectiveness or side-effect data will be assessed using an alternative quality assessment tool, not specific to RCTs, such as that developed by Spitzer *et al*[29] for an epidemiological review. This provides a more detailed checklist which specifically addresses issues such as selection bias and allocation bias relevant to non-RCTs.

Review methods
- If more than one RCT is identified the use of quantitative synthesis of RCTs will be explored. Where this is not possible, a narrative synthesis of included studies will be undertaken.

Methods for estimating qualify of life, costs and cost-effectiveness and/or cost/QALY
- A literature search for studies relating to quality of life in patients receiving temozolomide will be undertaken. Studies using generic or disease-specific quality of life assessment scales will be reviewed. If no studies have used single composite measures of quality of life (i.e. utility values), an attempt will be made to identify methods of mapping existing measures onto a single index measure.
- Incremental costs will be identified by mapping out the pathways of care for patients receiving temozolomide and for those not receiving the drug. Incremental costs are likely to relate mainly to the cost of the drug, staff costs, length of stay, and any side-effect treatments.
- A cost-effectiveness model will be developed to estimate the incremental cost per life year gained. A cost-utility analysis will be conducted using utility measures identified as above. Where no such utilities have been identified, the results of the cost-effectiveness analysis (life years gained) will be assumed to approximate the minimum QALY gain (i.e. assume utility value of 1.00 for both treatment groups), and the use of alternative utility estimates will be explored in a sensitivity analysis.
- Sensitivity analyses will also be conducted around the effectiveness and cost estimates.

Application of review methods
- Data extraction will be undertaken independently by two reviewers, with arbitration by a third reviewer where necessary.
- Quality assessment will be undertaken independently by two reviewers, with arbitration by a third reviewer where necessary.

APPENDIX 2

Search Strategy

Primary searches focused on studies of the effectiveness and adverse effects of temozolomide. These searches were conducted on the following databases:

Cochrane Library	2000 Issue 3
Medline	1966 – 2000/08
Embase	1989 – 2000/06
CancerLit	Search 19 July, 2000
Toxline	Search 19 July, 2000
ISI Web of Science	Search 19 July, 2000
BIOSIS	Search 19 July, 2000
PreMedline	Search 19 July, 2000

These searches included free text terms: temozolomide, temoda*, temozol* and Mesh search terms chosen to include side effects, adverse effects, and all clinical trials in humans. Initial searches were not limited to trials in malignant glioma in order to include potentially relevant studies in other conditions for information on adverse effects.

Additional searches were conducted for quality of life in malignant glioma, prognostic factors in malignant glioma, and natural history of malignant glioma. Finally, searches were conducted that included names of quality of life measures and cost terms connected with malignant glioma.

These searches were conducted on the following databases:

Medline	1980 – 2000/08
Embase	1989 – 2000/06
ISI Web of Science	Search 27 July, 2000

Quality of life searches included free text terms quality, life, QALY*, qlq*, EORTC, BCM20, QLQ-C30, utility, brain cancer module, qol, hrqol, hrql as well as Mesh quality of life subheadings. Searches for information on glioma included Mesh terms “brain neoplasms” as well as free text terms glioma, glioblastoma multiforme, anaplastic astrocytoma, and brain cancer. Cost searches included Mesh economics terms as well as the free text terms cost, costs, costed, costly, costing, economic, pharmacoeconomic, price, pricing, temoda*, and temozol*, utilit*, health status, qol, hrqol, hrql, and qaly.

Reference lists of all full-text articles obtained were scanned for additional relevant articles. In addition, the authors of included studies were contacted to request any additional data or names of researchers who should be contacted for further information.

Across all searches 539 references of potential relevance were found. These included 227 articles describing studies of temozolomide as well as articles of relevance to history and prognosis of malignant glioma, quality of life in malignant glioma, etc. Titles and abstracts were evaluated by 2 reviewers and in discussion with a third reviewer full text versions were requested for 89 articles. Twenty-one of these included reports of effectiveness of TMZ in malignant glioma. Seven of these met our inclusion criteria for discussion of TMZ

effectiveness in malignant glioma. Two additional reports met our inclusion criteria including measurement of quality of life in malignant glioma while on TMZ treatment. This quality of life data had also been briefly reported in the effectiveness reports, but was reported more fully in the separate quality of life reports.

Complete search strategies available from the authors.

APPENDIX 3

Methods for assessing the quality of included studies

One RCT was included. The quality of the RCT was assessed using the Jadad scale[28]

Jadad scale:

Questions to assess the likelihood of bias

1. Is the study described as randomised (this includes the use of the words such as randomly, random and randomisation)?
2. Is the study described as double-blind?
3. Is there a description of withdrawals and drop-outs?

Scoring the items

Either give a score of 1 point for each 'yes' or 0 points for each 'no.' There are no in-between marks.

Give 1 additional point if:

For question 1, the method to generate the sequence of randomisation is described and it is appropriate (table of random numbers, computer-generated, etc.)

and / or

If, for question 2, the method of double-blinding is described and it is appropriate (identical placebo, active placebo, dummy, etc.)

Deduct 1 point if:

For question 1, the method to generate the sequence of randomisation is described and it is inappropriate (patients were allocated alternately or according to date of birth, hospital number, etc.)

and / or

For question 2, the study is described as double-blind but the method of blinding is inappropriate (e.g., comparison of table v injection with no double dummy).

Guidelines for assessment:

Randomisation

A method to generate the sequence of randomisation will be regarded as appropriate if it allows each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

Double-blinding

A study must be regarded as double-blind if the term 'double-blind' is used. The method will be regarded as appropriate is it is stated that neither the person doing the assessment nor the study participant could identify the intervention being assessed, or if, in the absence of such a statement, the use of active placebos, identical placebos, or dummies is mentioned.

Withdrawals and drop-outs

Participants who were included in the study but did not complete the observation period or were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the report of the study. If there is no statement on withdrawals, this item must be given 0 points.

Quality checklist adapted from Spitzer, *et al.*[29] with guidance notes:

In addition to the Jadad scale an assessment was used for all included studies that would be appropriate for single group, uncontrolled studies. These quality criteria were adapted from Spitzer, *et al.*[29] The original checklist was modified to include items of particular relevance.

1. Does the trial use proper random assignment?
   A study with proper random assignment would include multiple conditions with random assignment and would use an appropriate method for the assignment (e.g., random numbers table, computer generated, etc.) with allocation concealment.
2. Did the study use proper sampling?
   A study with proper sampling would allow for all patients to be equally likely to enter the study (e.g., patients selected consecutively or randomly sampled).
3. Was the sample size adequate?
   Proper sample size enables adequately precise estimates of priority variables found to be significant (e.g., can compute CI within relatively small range or relatively small SEM).
4. Were the criteria for definition or measurement of outcomes objective or verifiable?
   Good outcome measures would be defined by clear methods for measuring outcomes (i.e., an operational definition) that are public, verifiable and repeatable.
5. Were outcomes measured with blind assessment?
   In studies with blind assessment those evaluating outcomes are unaware of the treatment status of those being evaluated.
6. Were objective criteria used for the eligibility of subjects?
   Good eligibility criteria would use clear, public, verifiable characteristics that are applied for inclusion and exclusion.
7. Were attrition rates (%) provided?
   A study should report the number of patients who could not be contacted for outcome measures or later, e.g., drop-outs or withdrawals due to treatment toxicity.
8. Were groups under comparison comparable?
   Comparable groups show similar results across a reasonable range of baseline characteristics that could be expected to affect results.
9. Are the results generalizable?
   Generalizable results come from a sample population that is representative of the population to which results would be applied.

APPENDIX 4

Summary of TMZ Effectiveness Studies

Reference and Design	Intervention	Subjects	Outcome measures
Yung, *et al*, 2000[31] Multi-centre, international, open label, Phase II randomised trial of temozolomide v procarbazine in GBM at first relapse	Temozolomide (TMZ), oral admin. Chemotherapy naïve: 200mg/m^2/day for 5 days in 28-day cycle Prior chemotherapy: 150 mg/m^2/day for 5 days in 28-day cycle Procarbazine, oral admin. Chemotherapy naïve: 150 mg/m^2/day for 28 consec days in 56-day cycle. Prior chemotherapy: 125 mg/m^2/day in same cycle Treatment until unacceptable toxicity, disease progression or 2 years treatment completed.	*n* = 225 112 TMZ, 113 Procarb Adults age ≥ 18 Median age: TMZ = 52 (range 21-76) Procarb = 51 (range 21-74) Inclusion: • Histologically proven supratentorial glioblastoma multiforme (GBM) or gliosarcoma at first relapse. • Recurrence of progression evaluated by imaging. • Karnofsky performance scale (KPS) ≥ 70 • Life expectancy ≥ 12 weeks at entry • See comments Exclusion: (see comments)	Objective Response Six-month PFS* Median PFS Survival Adverse Events* HRQL (QLQ-C30[+3] and BCM20) * Primary Outcomes

Results

- **Objective Response**: TMZ: 5.4% PR, 40.2% SD; Procarb: 5.3% PR, 27.4% SD.
  Overall response (PR + SD) greater in TMZ, p = .049.
- **Six-month PFS**: TMZ = 21% (95%CI: 13,29), Procarb = 8% (95%CI: 3,14) hazard ratio, *n*=1.54, *p*=.008.
  In histologically eligible population: TMZ = 19% (95%CI: 11,27), PCB = 9% (95%CI: 3,14)
- **Median PFS**: TMZ = 12.4 weeks, Procarb = 8.32 weeks, *p*= .0063, hazard ratio of 1.47 (95%CI: 1.11,1.95).
- **Survival:** At 6 months 60% of TMZ surviving (95%CI: 51,70), 44% of Procarb surviving (95%CI: 35,53), hazard ratio = 1.44, p = .019.
  1.5 months longer in TMZ, but not statistically significant.
- **Adverse Events:** (% patients in days 1-56): Haematologic grade 3 or 4: thromocytopenia 7% in TMZ, 4% in Procarb; neutropenia 4% in TMZ, 3% in Procarb; anemia 1% in TMZ, 2% in Procarb; leukopenia 1% in TMZ, 0 in Procarb.
  No other adverse events of grade 3 or 4 in more than 5% of patients in either group.
  No evidence of cumulative myelotoxicity in TMZ.
  Dropouts due to adverse events: 3 in TMZ, 11 in Procarb.
- **HRQL**: Data reported in more detail in Osoba, *et al* 2000.[1] See Appendix 5.

Comments relevant to Subjects:

- Additional inclusion criteria: MRI scans timed relative to surgery and corticosteriod use to allow good imaging of tumour. Could have one prior course of chemo that must have contained a nitrosourea
- Exclusion criteria: >1 prior chemotherapy; previous chemotherapy with single-agent PCB or dacarbazine; chemotherapy (excluding vincristine, nitrosourea or mitomycin C) within 4 wk prior to study drug; vincristine within 2 wk prior to study drug; nitrosourea or mitomycin C within 6 wk prior to study drug; history of PCB-induced rash; previous interstitial radiotherapy or stereotactic radiosurgery; pregnancy; breastfeeding; toxicity from prior therapy; HIV positive; previous or concurrent solid tumour at other sites (except basal cell carcinoma)
- 91% of TMZ confirmed histologically eligible, 96% of procarbazine confirmed histologically eligible. Other histologies primarily anaplastic astrocytoma or anaplastic oligoastrocytoma
- 5 patients randomised but not treated

Comments Relevant to Outcomes:

- Monthly performance, clinical, neurological, and HRQL assessments. Tumour imaging every 2 months.
- See definitions of terms for objective response criteria plus the following refinements: scan results were to be found on consecutive MRI scans at least 1 month apart. CR required no corticosteroid use except for physiologic doses with stable or improved neurologic condition. PR required stable corticosteroid use for 7 days before each scan at the same dose administered at the previous scan or at a reduced dose with stable or improved neurologic condition.
- Neurologic exam based on changes in signs and symptoms graded from –2 (definitely worse) to +2 (definitely better)
- blinded central review of neuropathology and neuroradiology
- PFS measured from start date of treatment to event date or last evaluation.
- Survival measured from start date of treatment to date of death or the last evaluation.
- Kaplan-Meier method was used to estimate PFS and survival

Adverse Events:

- No specific information on use of antiemetics. Implied use as needed.

Attrition:

- 15 TMZ, 31 procarbazine discontinued for reasons other than progression
- Most procarbazine patients not treated for more than one cycle.
- At end of week 12, 56% of TMZ patients and 30% of procarbazine patients remained in study. Dropouts primarily due to progression or toxicity.

Quality Assessment for RCTs (Jadad Score[28]):

Question	**Score**
Was the study randomised?	1
Was the study described as double blind?	
Was there a description of withdrawals and dropouts?	
What proportion of sample (intervention and control groups separately withdrew or dropped out?	1

Quality Assessment (Revised from Spitzer, *et al*[29]):

	Yes	U/I/S*	No	DK/NR+	N/A	Comments
Proper Random Assignment				x		No method described
Proper Sampling				x		
Adequate Sample Size	x					
Objective Outcomes		x				Neuro status and scans subjective
Blind Assessment	x		x			Blinded central review of histology & scans; neuro assessment not blind
Objective eligibility criteria		x				Performance status and life expectancy subjective
Reported Attrition	x					
Comparability of Groups		x				TMZ shorter time to relapse
Generalizability		x				Performance status and life expectancy criteria may select pts with better prognosis

* U/I/S = uncertain / incomplete / substandard

\+ DK/NR = don't know / not reported

Reference and Design	Intervention	Subjects	Outcome measures
Brada, *et al*, submitted[30] Multi-centre, international, open label, uncontrolled phase II trial of temozolomide in glioblastoma multiforme	Temozolomide, oral admin. Chemotherapy naïve: 200 mg/m^2/day for 5 days in 28-day cycle Prior nitrosourea-containing chemotherapy: 150 mg/m^2/day for 5 days in 28-day cycle increasing to 200mg on successive cycles if no grade 3 or 4 hemotologic toxicity Max treatment = 1 year or until unacceptable toxicity and/or disease progression	*n* = 138 128 with GBM or GS (*n*=2) Adults age ≥ 18 Median age 54 (range 24-77) Inclusion: • Histologically proven supratentorial glioblastoma multiforme (GBM) at first relapse. Eligible histology also included gliosarcoma (GS) • Recurrence of progression evaluated by imaging • Recurrence > 12 wk following conventional radiation therapy and not more than one course of adjuvant nitrosourea-containing chemotherapy • Karnofsky performance scale (KPS) ≥ 70 • Life expectancy of > 12 weeks. Exclusion: (see comments)	Objective Response Six-month PFS* Median PFS Adverse Events* HRQL (QLQ-C30[+3] and BCM20) *Primary Outcomes

Results

- **Objective Response**: ITTgroup: 8% CR or PR, 43% SD
  In eligible histology group 8% CR or PR, 45% SD
- **Six-month PFS**: 19% (95%CI: 12,26)
  18% (95%CI: 11,24) in eligible-histology population
- **Median PFS**: 2.1 months
- **Survival:** Median 5.4 months
  6-month survival rate 46%
- **Adverse Events**: Haemotologic (grade 3 or 4): thrombocytopenia 10%, leukopenia, 7%, neutropenia, 4.5%.
  3 patients discontinued due to adverse events
  No other adverse events of grade 3 or 4 in more than 5% of patients
- **HRQL**: Data reported in more detail in Osoba, *et al* 2000.[1] See Appendix 5.
- A Cox regression analysis showed only time from initial diagnosis to first relapse predicted progression-free survival and survival

Comments relevant to subjects:

- Exclusion Criteria: Inadequate haemotologic laboratory values
- 6 patients did not receive TMZ

Comments relevant to outcomes:

- MRI performed at trial entry within 2 weeks before first TMZ treatment and after every second course of TMZ.
- Criteria for objective response described in definitions of terms
- Neurologic evaluation: definitely better (+2), possibly better (+1), unchanged (0), possibly worse (-1), definitely worse (-2)
- Scans centrally reviewed. Unclear whether reviewers aware of treatment.
- PFS measured from start of TMZ treatment
- Kaplan-Meier method used to estimate the progression-free survival and event-free survival at 6 months

Adverse Events:

- Adverse events on NCIC-CTC scale
- Prophylactic antiemetics allowed.

Quality Assessment (Revised from Spitzer, *et al*[29]):

	Yes	U/I/S*	No	DK/NR+	N/A	Comments
Proper Random Assigment					x	
Proper Sampling				x		
Adequate Sample Size	x					
Objective Outcomes		x				Neuro status and scans subjective
Blind Assessment			x	x		Neuro assessment not blind; status of scan reviews unknown
Objective eligibility criteria		x				Performance status and life expectancy subjective
Reported Attrition	x					
Comparability of Groups					x	
Generalizability		x				Performance status and life expectancy criteria may select pts with better prognosis

* U/I/S = uncertain / incomplete / substandard
+ DK/NR = don't know / not reported

Reference and Design	Intervention	Subjects	Outcome measures
Yung, *et al*, 1999[32] Multicentre, international, open label, uncontrolled, Phase II trial of temozolomide in AA or AOA	Temozolomide (TMZ), oral admin. Chemotherapy naïve: 200 mg/m^2/day for 5 days in 28-day cycle Prior chemotherapy: 150 mg/m^2/day for 5 days in 28-day cycle increasing to 200 mg on successive cycles if no grade 3 or 4 haemotologic toxicity Follow-up: 6 months Max treatment: 2 years	*n* = 162 111 with AA or AOA 19 with glioblastoma multiforme (GBM) Adults age ≥ 18 Median age 42 (range 19-76) Inclusion: • Histologically proven supratentorial anaplastic glioma (anaplastic astrocytoma[AA] or anaplastic mixed oligoastocytoma [AOA]) at first relapse • Recurrence or progression evaluated by imaging • Karnofsky performance scale (KPS) ≥ 70 • Life expectancy >12 weeks at entry Exclusion: (see comments)	Objective Response Six-month PFS* Median PFS Survival Adverse Events* HRQL (QLQ-C30[+3] and BCM20) *Primary Outcomes

Results

- **Objective Response**: ITT group: 8% CR, 27% PR, 27% SD
  AA+AOA group: 7% CR, 28% PR, 29% SD
- **6 month PFS**: 46% (95% CI = 38,54);
  48% in histologically confirmed AA+AOA group (95%CI = 39,58)
- **Median PFS**: 5.4 months group
  AA+AOA: 5.5 months
  Kaplan-Meier estimates: 24% progression free at 12 months
- **Survival**: 13.6 months, AA+AOA group = 14.5 months
  Kaplan-Meier estimates for 6 and 12 month survival: 75% (95%CI = 68,82) and 56% (95%CI = 48,64)
  Kaplan-Meier 6 month survival estimates: AA 78% (95%CI = 70,86), AOA 79% (95%CI: 57,100)
- **Adverse Events**: Hemotologic grade 3 or 4: thrombocytopenia = 6%, leukopenia = 2%, neutropenia = 2%, anemia = 1%. Other adverse events >5%: asthenia, headache, nausea, vomiting
  9 patients discontinued due to adverse effects (6 attributed to drug)
  Myelosuppression was noncumulative
- **HRQL**: Data reported in more detail in Osoba, *et al* 2000.[1] See Appendix 5.
- In Cox regressions of possible prognostic factors, only baseline KPS significantly predicted PFS and survival

Comments relevant to subjects:

- Exclusion Criteria: prior chemotherapy (other than with nitrosourea), inadequate haemotologic laboratory values
- 4 patients did not receive TMZ

Comments relevant to outcomes:

- See definitions of terms for criteria for objective response plus the following refinements: scan results were to be found on consecutive MRI scans at least 1 month apart, CR required no corticosteroid use except for physiologic doses with stable or improved neurologic condition. PR required stable corticosteroid use for 7 days before each scan at the same dose administered at the previous scan or at a reduced dose with stable or improved neurologic condition. Progressive disease required stable corticosteroid use for 7 days before each scan at the same dose administered at the time of the previous scan or at an increased dose without or without neurologic progression .
- Neurologic exam based on changes in signs and symptoms graded from –2 (definitely worse) to +2 (definitely better)
- Scans centrally reviewed by committee. Unclear whether reviewers were aware of treatment.

Adverse events:

- Prophylactic antiemetics allowed.

Quality Assessment (Revised from Spitzer, *et al*[29]):

	Yes	U/I/S*	No	DK/NR+	N/A	Comments
Proper Random Assigment					x	
Proper Sampling				x		
Adequate Sample Size	x					
Objective Outcomes		x				Neuro status and scans subjective
Blind Assessment			x	x		Neuro assessment not blind; status of scan reviews unknown
Objective eligibility criteria		x				Performance status and life expectancy subjective
Reported Attrition	x					
Comparability of Groups					x	
Generalizability		x				Performance status and life expectancy criteria may select pts with better prognosis

* U/I/S = uncertain / incomplete / substandard
+ DK/NR = don't know / not reported

Reference and Design	Intervention	Subjects	Outcome measures
Chinot, *et al*, submitted for publication [5] Open label, uncontrolled, single centre (France), Phase II trial of temozolomide in AO or AOA	Temozolomide (TMZ), oral admin. 150 mg/m^2/day for 5 days in 28-day cycle increasing to 200 mg on successive cycles if no grade 3 or 4 haemotologic toxicity Max treatment: 2 years	*n* = 48 39 with AO (anaplastic oligodendroglioma) 9 with AOA (anaplastic oligoastrocytoma) Adults age ≥ 18 Median age 41 Inclusion: • Histologically confirmed recurrent pure AO or AOA • At least 12 wk post-RT • Karnofsky performance scale (KPS) ≥ 60 • Life expectancy >12 weeks at entry • At least 1 contrast-enhancing lesion measurable by MRI Exclusion: (see comments)	Objective Response* Six-month PFS Median PFS Survival Adverse Events *Primary Outcomes
Results • **Objective Response**: 16.7% CR, 27.1% PR, 39.6% SD • **Six-month PFS**: 50.5% • **Median PFS**: 6.7 months (7.5 mo for those achieving OR; >11.5 mo for those achieving CR) Kaplan-Meier estimate: 25.4% progression free at 12 months • **Survival**: Median 10 months (>26 mo for those achieving CR) 6 month survival rate: 77.1% 12 month survival Rate: 45.8% • **Adverse Events:** Hemotologic grade 3 or 4: thrombocytopenia = 6.4% No patients discontinued due to treatment-related toxicity			

Comments relevant to subjects:

- Exclusion Criteria: more than 1 prior course of chemotherapy, chemotherapy or RT within 8 weeks prior, HIV positive, AIDS-related disease, inadequate recovery from prior toxicities, inadequate haemotologic laboratory values
- 47 patients received prior PCV chemotherapy
- Histology reviewed by single reviewer

Comments relevant to outcomes:

- Baseline assessments within 1 week prior to initiating TMZ. MRI every 2 cycles
- See definitions of terms for criteria for objective response plus the following refinements: scan results were to be found on consecutive MRI scans at least 1 month apart, CR required no corticosteroid use except for physiologic doses. PR ≥50% and <100% reduction in enhancing tumour volume on consecutive MRI scans with stable steroid use and stable or improved neurologic status. Progressive disease as in definition of terms or necessity of increasing steroids. All responses confirmed by another MRI 1 to 2 months later.
- No information about MRI scan reviews. Unclear whether reviewers were aware of treatment.
- PFS at 12 months and survival analysed by Kaplan-Meier method.
- Final follow-up: physical and neurologic examination, determination of performance status, haematologic evaluation, clinical chemistry assessment and MRI within 30 following last cycle and every 2 months thereafter.
- Median 6 cycles TMZ given

Adverse Events:

- Prophylactic antiemetics administered with TMZ.

Quality Assessment (Revised from Spitzer, *et al*[29]):

	Yes	U/I/S*	No	DK/NR+	N/A	Comments
Proper Random Assigment					x	
Proper Sampling				x		
Adequate Sample Size		x				
Objective Outcomes		x				Neuro status and scans subjective
Blind Assessment			x	x		Neuro assessment not blind; status of scan reviews unknown
Objective eligibility criteria		x				Performance status and life expectancy subjective
Reported Attrition	x					
Comparability of Groups					x	
Generalizability		x				Performance status and life expectancy criteria may select pts with better prognosis

* U/I/S = uncertain / incomplete / substandard
\+ DK/NR = don't know / not reported

Reference and Design	Intervention	Subjects	Outcome measures
Bower, *et al*, 1997 Multi-centre (UK), Uncontrolled Phase II	Temozolomide (TMZ) oral admin.: 750mg/m^2 divided as equally as possible over 5 days given every 28 days. If no grade 2 or greater myelosuppression on cycle 1, dose increased to 1000mg as above. See additional details in comments	*n* = 116, 103 eligible 1 dropout 1 loss to follow-up Median age = 44 (range 24-78) Inclusion: • Histologically confirmed supratentorial grade III or IV glioma and • imageable lesions that had progressed within past 2 months • continuing neurological impairment • World Health Organisation (WHO) performance status ≤ 3 • life expectancy > 3 months. Exclusion: (see comments)	Objective Response* Response Duration* Six-month PFS Survival Adverse Events* * Primary Outcomes
Results • **Objective Response**: 103 eligible patients (including 18 not evaluable for response):11%, 47% SD Objective response rate 3% (95%CI: 0,9) in 31 patients who had received prior chemotherapy (after surgery and radiation), 15% (95%CI: 6,24) in 65 patients who had received surgery and radiotherapy only Objective response 2/20 in AA, 8/73 in GBM and 1/9 in unclassified high-grade glioma • Median response duration for 11 patients achieving objective response: 4.6 months • **Six-month PFS**: 22% (95%CI: 14,31). • **Survival**: Median of eligible patients 5.8 months (95% CI: 4.6,7.0) • **Adverse Events** (episodes): Hemotological: lymphopenia 59, thrombocytopenia 13, neutrophils 5, leucopenia 6, anaemia 1. Other effects > 20 episodes: nausea, vomiting, lethargy			

Comments relevant to subjects:

- Exclusion Criteria: radiotherapy within past 10 weeks, or prior chemotherapy within past 4 weeks (6 weeks for nitrosoureas), inadequate bone marrow, hepatic or renal function, if on dexamethasone, no change in dose in prior 2 weeks.
- Declaration of 13 patients as ineligible may have affected results. Several were not suffering from target disease, but others seemed more ill (3 not on stable corticosteroids, 1 with WHO status of 4) or perhaps less ill (1 with no persisting neurological deficit, 1 with no evaluable disease at entry).
- 18 patients were "not evaluable for response"

Comments relevant to outcomes:

- Radiological evaluation prior to 1st and 3rd cycles of TMZ and after alternate cycles thereafter.
- Objective Response = improvement in one or more neurological symptoms sufficient to improve the neurological status by one grade on the MRC scale across 2 observations not less than 4 weeks apart, no deterioration or other neurological symptoms or signs and no new neurological deficits. Imaging criteria only used in association with clinical improvement.
- Stable Disease = neither improvement nor deterioration in neurological status over min of 8 weeks, irrespective of a radiological change in tumour size but without an increase in the corticosteroid dose except on days of TMZ admin when dose could be increased for prophylactic cover of cerebral oedema.
- Progressive Disease = deterioration of neurological status and/or an escalation in the corticosteroid dose
- MRC scale of neurological status: 0 = no neurological deficit; 1 = function adequate for useful work; 2 = moderate function impairment; 3 = major functional impairment; 4 = no useful function
- Survival calculated from first day of TMZ until death or date of last follow-up
- Duration of response from commencement of TMZ until documentation of progression

Adverse events:

- Prophylactic antiemetics with each course of temozolomide.
- Adverse events cannot be evaluated in terms of % of patients suffering as same events may have occurred in same patients more than once.

Quality Assessment (Revised from Spitzer, *et al*[29]):

	Yes	U/I/S*	No	DK/NR+	N/A	Comments
Proper Random Assigment					x	
Proper Sampling				x		
Adequate Sample Size	x					
Objective Outcomes		x				Neuro status and scans subjective
Blind Assessment			x	x		Clinical assessment not blind; status of scan reviews unknown
Objective eligibility criteria		x				Performance status and life expectancy subjective
Reported Attrition	x					
Comparability of Groups					x	
Generalizability		x				Performance status and life expectancy criteria may select pts with better prognosis

* U/I/S = uncertain / incomplete / substandard

\+ DK/NR = don't know / not reported

Reference and Design	Intervention	Subjects	Outcome measures
Newlands, *et al*, 1996 Consecutive cases of malignant glioma treated with temozolomide (TMZ)	Temozolomide (TMZ) oral admin. 150 mg/m^2/day for 5 days escalating if no significant myelosuppression on day 22 to 200 mg/m^2/day for 5 days at 4 week intervals. Treatment until progression in those responding	*n* = 48 consecutive patients with recurrent glioma treated at Charing Cross Hospital Median age (*n*=75): 46.6 (range 20-72) (27 patients with newly diagnosed disease were excluded) 2 treated in phase I study	Objective response Duration of response Survival (1 year)

Results

- **Objective Response:** 25% OR (see criteria in comments), 38% no change
- Duration of Response: Median 6.1 months (range 3.4 – 16.9 months)
- **Survival** (1 year): 22% (95%CI: 12,36)
- **Adverse Events** (episodes grades 3 or 4 [including newly diagnosed patients]): Haematologic: lymphopenia 4, leucopenia 5, platelets 1, anaemia 3
  No other grade 3 / 4 adverse events > 10 episodes

Comments relevant to outcomes:

- Scans at baseline (after 2 weeks stable dexamethasone dose), after 2 cycles of treatment, after 5-6 cycles and at any clinical indication of disease progression
- Objective Response = MRC neurological status scale improvement of 1 or more for minimum of 4 weeks with clear reduction in tumour mass on CT or MRI
- OR assessed at maximum neurological and CT/MRI improvement, usually 2 or 5 months after starting TMZ
- Scans reviewed by neuroradiologist blinded to treatment.
- Duration of response measured from start of therapy
- Number of TMZ courses median 7 (range 1-29)

Adverse events:

- Prophyactic antiemetics with each course of TMZ
- Adverse events cannot be evaluated in terms of % of patients suffering as same events may have occurred in same patients more than once

Quality Assessment (Revised from Spitzer, *et al*[29]):

	Yes	U/I/S*	No	DK/NR+	N/A	Comments
Proper Random Assigment					x	
Proper Sampling	x					Consecutive pts at Charing Cross Hospital
Adequate Sample Size		x				Fairly wide confidence intervals
Objective Outcomes		x				Neuro status and scans subjective
Blind Assessment	x		x			Reviews of scans blinded; neuro assessment not blind
Objective eligibility criteria	x					Only recurrent high-grade glioma required
Reported Attrition	x					
Comparability of Groups					x	
Generalizability		x				Patients from single centre may not be representative

* U/I/S = uncertain / incomplete / substandard
\+ DK/NR = don't know / not reported

APPENDIX 5

Summaries of HRQL Reports

Reference and Design	Intervention	Subjects	Outcome measures
Osoba, *et al*, 2000[1] HRQL results from Yung, *et al* [31]and Brada, *et al* [30]studies in GBM. See effectiveness summaries in Appendix 4.	Temozolomide (TMZ), oral admin. Chemotherapy naïve: 200 mg/m^2/day for 5 days in 28-day cycle Prior chemotherapy: 150 mg/m^2/day for 5 days in 28-day cycle Procarbazine, oral admin. Chemotherapy naïve: 150 mg/m^2/day for 28 consec days in 56-da cycle. Prior chemotherapy: 125 mg/m^2/day in same cycle 24 week follow-up	*n* = 109 in uncontrolled TMZ trial *n* = 89 in temozolomide arm of randomised trial *n* = 90 in PCB arm of randomised trial Adults age ≥ 18 Mean age in uncontrolled trial = 53.2 (range 24-77) Mean age in TMZ arm = 51.2 (range 21-72) Mean age in PCB arm of = 49.3 (range 23-73) Inclusion: • Histologically proven supratentorial high-grade glioma at first relapse with recurrence or progression confirmed by imaging • Karnofsky Performance Scale ≥ 70 Exclusions: (see comments)	Changes in HRQL (QLQ-C30 and BCM20) in 7 pre-selected domains* Effect of changes in disease status on HRQL* Proportion of patients with clinically signficant changes in HRQL Duration of HRQOL improvements *Primary Outcomes

Results

- **6 month HRQL change**: TMZ patients without progression (19 in RCT and 22 in single group study) associated with improved HRQL scores. Improvements significant in several domains including global QL in uncontrolled trial.
  TMZ patients with progression associated with reduced HRQL including significant declines in several domains including Global QL in both uncontrolled and randomised trials.
  PCB associated with declines in HRQL independent of disease progression although the declines only reached significance in the group with progression.
- **Effect of Progression**: HRQL scores improved or stable for TMZ patients up to progression when scores were dramatically worse.
  In PCB patients, HRQL scores generally worse than baseline throughout.
- **Proportion of patients with HRQL changes**: Among patients whose scores could improve, TMZ improvements ranged from 15% (Global QL in randomised TMZ group) to 40% (in communication deficit in randomised TMZ group) across domains.
  In the PCB group, improvement ranged from 14% (in drowsiness) to 24% (in visual disorder)
- **Duration of HRQL changes**: Medians varied from 11.3 weeks to 21.6 weeks in the TMZ groups and from 9.8 to 12.7 weeks in the PCB group. Changes were longest lasting in patients with complete response or partial response, a little shorter in those with stable disease, and shortest in those with progressive disease.

Comments

- Pre-selected HRQL domains were role functioning, social functioning, global QL, visual disorder, motor dysfunction, communication deficit and drowsiness
- Clinically significant change in HRQL defined as change of ≥10 (on scale of 0-100) lasting for at least two assessments 4 weeks apart
- Don't know when baseline evaluations taken in relation to assignment to treatment groups.
- Patients were in open-label studies so knowledge of treatment may have affected results
- Relatively large proportion of groups did not complete HRQL questionnaires (79% completed both baseline and at least one assessment on treatment)
- Due to high attrition (disease progression or death) the numbers of patients in groups is difficult or impossible to establish and often quite small.
- Much larger *n* in progression than progression free groups.

Reference and Design	Intervention	Subjects	Outcome measures
Osoba, *et al*, 2000[33] HRQL results from Yung, *et al* [32]study in AA. See effectiveness summary in Appendix 4.	Temozolomide (TMZ), oral admin. Chemotherapy naïve: 200 mg/m^2/day for 5 days in 28-day cycle Prior chemotherapy: 150 mg/m^2/day for 5 days in 28-day cycle Chemotherapy to be given for 1 year and could be continued longer in responding patients, if desired. 24 week follow-up	N = 162, 138 with both baseline and on-treatment evaluations Adults age ≥ 18 Mean age = 42.5 (range 19-76) Inclusion: • Histologically proven supratentorial astrocytoma at first relapse with recurrence or progression confirmed by imaging. • Karnofsky Performance Scale ≥ 70 • On stable dose of corticosteroid for at least 10 days before therapy • Life expectancy ≥ 12 weeks. Exclusion: (see comments)	Changes in HRQL (QLQ-C30[+3] and BCM20) in 7 pre-selected domains* Effect of changes in disease status on HRQL* Proportion of patients with clinically significant changes in HRQOL Duration of HRQOL improvements *Primary Outcomes

Results

- Baseline scores reflect considerable difficulties in role and social functioning, global QL, and motor dysfunction, communication deficit and drowsiness
- **6 month HRQL change**: patients without progression (*n* = 63) associated with maintenance or improved HRQL scores in all seven pre-selected domains. Improvements in social functioning and global QL were statistically significant, but small.
  Patients with progression reported statistically significant deterioration in 5 of 7 of the pre-selected domains
- **Effect of Progression**: HRQL scores were either at baseline or worse than baseline for the seven pre-selected domains
- Changes in HRQL prior to progression showed an initial improvement over baseline in most domains with a gradual decrease in scores as progression neared and deterioration below baseline scores at progression.
- **Proportion of patients with HRQOL changes**: Among patients whose scores could improve, proportion of HRQL responses ranged from 35% to 49% regardless of tumour response.
- **Duration of HRQL changes**: median varied from 12 weeks (for Global QL and drowsiness) to 20 weeks (for social functioning, motor dysfunction, and communication deficit). Duration of response tended to be longer in those with complete or partial tumour response, but were nearly as long in those with stable disease

Comments

- Pre-selected HRQL domains were role functioning, social functioning, global QL, visual disorder, motor dysfunction, communication deficit and drowsiness
- Clinically significant change in HRQL defined as change of ≥10 (on scale of 0-100) lasting for at least two assessments 4 weeks apart
- HRQL changes associated with progression at 6 months may have been underestimated as the last available HRQL scores were used prior to death or inability to complete the questionnaire rather than estimating a final score
- Patients are not unaware of treatment given

APPENDIX 6

Discussion of Outcome Measures

Objective Response:
All included studies evaluated objective response, although the criteria for response varied to some degree. These criteria were defined in the "Definitions of Terms" section. In all studies there was appropriately placed concern about evaluating response on the basis of imaging alone. Interpretation of radiological images of these tumours is apparently variable and dependent upon surgery, RT, and corticosteroid levels.[49] Baseline images were taken under stable corticosteroid doses for a minimum of three days prior to scan in all studies. In all included effectiveness studies scans were centrally reviewed, which should also minimise variation in their interpretation.

In addition, evaluations of objective response also required assessments of clinical status. Changes in clinical status are closely related to tumour status and are therefore used as additional evidence of treatment effects.[47] There is some concern about the clinical assessments, which are subjective in nature and not centrally reviewed. There is considerable variation in the assessment of clinical status using measures such as the Karnofsky performance status (KPS) or the MRC neurological status scale.[49] (See Appendix 8 for clinical status scales.) Variations in the use of such scales may be particularly problematic in multi-centre trials. Four of six included effectiveness trials were multi-centre trials and some variability in the results may be attributable to the use of subjective clinical status evaluations. In addition, in none of the studies were treating clinicians or patients unaware of the treatment that they were receiving. This knowledge may also affect subjective evaluations of clinical status.

One response category that is often reported is "stable disease." Because this outcome has been reported in several studies, it is included in our report. However, it should be noted that there is no consensus on how to measure this outcome and therefore it may be particularly unreliable.

Progression:
When considering progression as an outcome measure, it is important to consider how evidence of progression will be collected.[49] In all included studies clinical evaluations were conducted at regular intervals. More importantly, in four of six of the full reports assessed imaging scans were obtained at regular two month intervals (Yung, *et al*, 1999 did not specify) helping to assure that times to progression were not unduly affected by variable assessment methods. The use of a particular time at which to measure the proportion of progression-free survivors also aids in reducing variation in results due to different timing of assessment.

Survival:
It should be noted that survival is affected by tumour histology, age, and performance status.[9;49] Three studies considered the effectiveness of TMZ in patients with AA (and anaplastic oligodendroglioma),[32] GBM,[30;31] or AO & AOA[5]separately. However, two trials consisted of a mix of patients with AA and GBM.[47;48] The proportion of patients with each tumour grade would be expected to affect the outcomes. These trials included 71% and 77%

GBM patients respectively and 19% AA. These distributions include more than the usual fraction of patients with GBM and therefore results in these trials may be affected by the poorer prognosis of GBM. In addition, age affects survival and is related to tumour histology with GBM patients being approximately 10 years older than AA patients. Finally, performance status is related to survival.

The studies summarised here reported medians for progression free survival and for survival. It should be noted that medians may overestimate mean survival times, particularly in serious cancers in which a substantial number of patients may have very short survival times. Treatments that prolong life, but do not cure will produce medians that are overestimates of mean survival.

Health-related quality of life (HRQL):
The primary questionnaire used was developed by the European Organisation for Research and Treatment of Cancer QLQ-C30 (with version 2.0 scoring)[53] along with a specific questionnaire on brain cancer, the Brain Cancer Module, BCM20.[54] Both questionnaires focus on patients' self-report of their health-related quality of life (HRQL). Both questionnaires have been shown to have adequate validity and reliability, although the role functioning and cognitive functioning scales of the QLQ-C30 have shown some internal consistency problems.[53;55] The QLQ-C30 consists of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting) and a global health and quality of life scale along with several single-item symptom questions. The BCM20 contains five scales (emotional distress, future uncertainty, visual disorder, motor dysfunction, and communication deficit) along with seven, single-item symptom questions. After translating scores onto a scales of 0-100, it has been found that changes in these scales of 10 or more points were considered clinically significant and to be subjectively noticeable by patients.[56] It has been noted that baseline HRQL measures should be taken before randomisation and / or treatment to prevent knowledge of assignment or treatment to affect results. Although the reports are unclear in this regard, in none of the reported studies does this seem to be the case.

The HRQL questionnaires were administered at baseline prior to the start of chemotherapy and just before each subsequent chemotherapy cycle. The primary outcomes were changes from baseline in seven pre-selected HRQL domains (global QL, role functioning, social functioning, visual disorder, motor dysfunction, communication deficit, drowsiness). Additional data were reported, but in order to limit the possibility of claiming effects on the basis of chance, these additional data must be interpreted with caution and are not discussed here. HRQL changes were assessed at six months in those who remained progression free and at progression for all patients from whom data were available. The duration of HRQL improvements was also of interest along with the proportion of patients who achieved HRQL improvements.

Because the nature of high grade glioma means that many subjects will die or otherwise be unable to continue participation over time, these HRQL results are based primarily on comparisons between the baseline scores and on-treatment scores of the same subjects. In this way, each subject serves as his or her own control and attrition is less problematic. Nonetheless, it is true that in some evaluations there are very few patients surviving and in evaluations of effects of progression, for instance, the results are collected at different times for different subjects.

Questionnaire completion rates were considerably less than 100% creating some concern for whether the subjects completing questionnaires at both baseline and during treatment were representative or whether more ill patients may not have been included. The technique of considering changes in HRQL scores within subjects allays this concern somewhat. It is also of some concern that the studies in which HRQL data were obtained were open label studies. The knowledge of patients that they were on an experimental drug trial may have affected their evaluations. Finally, it should be noted that because there are often small numbers of subjects contributing to particular cells that statistical significance does not always coincide with what are considered clinically or subjectively significant changes in assessments.

APPENDIX 7

Detailed HRQL results

Baseline Scores:
In the Osoba, *et al* report of HRQL in GBM,[1] there were data from a single group study of TMZ as well as patients who were randomised to either TMZ or procarbazine. On a scale of 0-100 with higher scores reflecting better functioning, patients with GBM reported means for Global QL ranging from 55.5 to 63 across the three study groups.

Patients with AA[33] reported a mean Global QL of 61.4. These patients also reported the presence of symptoms, in particular motor dysfunction, communication deficit and drowsiness. The reporting of symptoms in these patients was significantly greater than in another group of newly diagnosed patients in motor dysfunction, communication deficit, weakness of both legs, and trouble controlling the bladder.[11] The baseline scores of these patients were found to be similar to those of patients with advanced ovarian and lung cancer and patients with metastatic heterogeneous cancers except that patients with recurrent brain cancer had worse cognitive functioning and less pain.[11] Comparison of the baseline HRQL of these patients with normal populations in Denmark and Norway demonstrate that scores in the patients are much lower than in the general population.[11]

Changes in HRQL from baseline to 6 months (or progression):
In the single group study of TMZ in GBM, HRQL in the 22 patients who remained progression free at six months demonstrated improvements from baseline in all seven pre-selected domains. Effect sizes were all greater than 0.20, which was considered clinically significant. However, only improvements in global QL, communication deficit and drowsiness achieved statistical significance. The HRQL results in the TMZ group from the RCT portion of the report were similar but slightly less unequivocal. Those patients on TMZ who remained progression free at six months showed improvements in five of the seven pre-selected domains. Only improvements in drowsiness and social functioning had an effect size > 0.2 and only the improvement in drowsiness reached statistical significance. By contrast, however, those patients who had been on procarbazine reported diminished HRQL in all 7 pre-selected domains independent of whether there had been progression or not (except Global QL in those who were six-month progression free in whom there was no change). The effect sizes of the changes were greater than 0.2 among those in whom there was not progression in all domains except Global QL. None of these changes reached statistical significance. For the patients on procarbazine in whom there had been progression within six months, effect sizes of negative changes at the 6 month assessment in all 7 pre-selected domains were greater than 0.2 with the exception of visual disorder. Changes in drowsiness, communication deficit, motor dysfunction, and role function reached statistical significance.

When comparing HRQL in TMZ and procarbazine there is a possibility that responses favouring TMZ are partially attributable to the shorter cycle length for TMZ (five days each 28 days v 28 days each 56 days).

In the Osoba, *et al* report of HRQL in AA there was a single group of patients treated with TMZ. At the six month assessment 63 (39%) of patients were progression free. For the seven pre-selected HRQL domains, scores improved from baseline in all domains in these

patients. The effect sizes were > 0.2 for global QL and social functioning, which also were statistically significant. In those patients whose disease had progressed, scores in all seven domains were worse than baseline with scores in global QL, drowsiness, visual disorder, social functioning, and role functioning being statistically poorer than baseline with effect sizes > 0.2.

Effect of Progression:
Generally, progression produced deterioration in HRQL scores. In the study of patients with GBM, the mean change in all pre-selected domain scores deteriorated below baseline levels with the exception of visual disorder in patients randomised to TMZ in the RCT portion of the study. In the weeks preceding progression there were improvements from baseline in the TMZ groups and the HRQL changes were relatively stable until four weeks prior to progression (although it should be noted that different subjects contributed data to the assessments at different time points). In general, the procarbazine group demonstrated poorer HRQL than at baseline across all assessments in most domains. The few improvements in HRQL in the procarbazine group were small in magnitude.

In the study of HRQL in AA, scores at progression were at or below baseline. In the weeks preceding progression scores in most domains had been better than at baseline although gradually declining as progression neared. (Again, it should be noted that the same subjects did not consistently provide data at all time points.)

Proportions of patients with clinically significant change in HRQL:
Previous work on these questionnaires suggests that patients subjectively notice changes of ≥ 10 on the scale of 0-100.[56] Therefore the proportion of patients experiencing changes of ≥10 were computed. In addition, only patients in whom this improvement lasted for ≥ eight weeks were counted. (These proportions were computed on patients in whom function scale scores were ≤ 90 and symptom scores were ≥ 10 at baseline in order that improvement would be possible.)

In the study of patients with GBM, the proportion of TMZ treated patients demonstrating improvement ranged from a low of 15% (for Global QL) to a high of 40% (for communication deficit). Proportions of improvement in the procarbazine group were lower ranging from 14% (for drowsiness) to 24% (for motor dysfunction).

In the study of patients with AA, the proportion of patients showing improvement ranged from a low of 35% (for visual disorder) to a high of 49% (for social functioning).

Duration of HRQL improvements:
Using the criteria outlined above for HRQL improvement, the duration of improved scores was computed for those showing improvement. (It should be noted that different patients contributed to different means and that *n*'s were relatively small, ranging from 11 to 29).

In the study of patients with GBM, durations of response were greater in patients receiving TMZ than in those receiving procarbazine, with the exception of improvements in visual disorder in which improvement in the procarbazine group was slightly longer. However, there were no statistical comparisons of these differences. The duration of HRQL response

was longest in patients achieving CR or PR in tumour response, somewhat shorter in those with stable disease, and shortest in those with progressive disease.

In the study of patients with AA, the median duration of HRQL response varied from 12 weeks (for global QL and drowsiness) to 20 weeks (for social functioning, motor dysfunction, and communication deficit).

Taken together, the quality of life results demonstrate that patients with recurrent malignant glioma have a diminished quality of life and are suffering from a number of debilitating symptoms. A reasonable proportion of patients who are treated with TMZ report improvements in quality of life measures that generally last until near progression. In comparison with procarbazine, TMZ seems to confer considerably better quality of life perhaps partly because current treatment regimens involve taking the drug on fewer days in addition to effects of TMZ on tumour growth. Quality of life improvements are more pronounced in patients who remain progression free. Large proportions of patients who have an objective response to TMZ demonstrate improvement in some domains of HRQL,[30] however, the absolute number of patients this includes is quite small.

APPENDIX 8

Performance Status Scales

Karnofsky Performance Status	World Health Organisation Status
100 Normal, no complaints: no evidence of disease	0 Fully active, able to carry on all predisease performance without restriction
90 Able to carry on normal activity; minor signs of symptoms of disease	
80 Normal activity with effort, some signs of symptoms of disease	1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
70 Cares for self but unable to carry on normal activity or to do work	
60 Requires occasional assistance but is able to care for most of personal needs	2 Ambulatory and capable of self care but unable to carry out any work activities. Up and about more than 50% of waking hours
50 Requires considerable assistance and frequent medical care	
40 Disabled; requires special care and assistance	3 Capable of only limited self care, confined to bed or chair more than 50% of waking hours
30 Severely disabled; hospitalisation is indicated although death is not imminent	
20 Very ill; hospitalisation and active supportive care necessary	4 Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
10 Moribund	
0 Dead	5 Dead

APPENDIX 9

Calculation of individual cost components[n]

A. CHEMOTHERAPY COSTS

All drug costs were obtained from the British National Formulary, No. 39, March 2000.

UNIT COSTS

Drug	Pack size	BNF Cost[27]	Cost per unit
Temozolomide	5 x 5 mg	£17.30	£3.46
	20 x 5 mg	£69.20	£3.46
	5 x 20 mg	£69.20	£13.84
	20 x 20 mg	£276.80	£13.84
	5 x 100 mg	£346.00	£69.20
	5 x 250 mg	£865.00	£173.00
CCNU (PoM)	20 x 40 mg	£171.35	£8.57
Procarbazine (PoM)	50 x 50 mg	£37.44	£0.75
Vincristine[a] (iv)	1 mg vial	£10.92	£10.92
	2 mg vial	£21.17	£21.17
	5 mg vial	£44.16	£44.16

[a] Non proprietary

A1. Temozolomide

COST PER CYCLE

	Recommended dose	Required dose per day*	Obtained from	Cost per day	Days per cycle	Cost per cycle
Temozolomide	200 mg/m^2	340 mg	3 x 100 mg 2 x 20 mg	£235.28	5	**£1,176**

A2. PCV

COST PER CYCLE

	Recommended dose	Required dose per day*	Obtained from	Cost per day	Days per cycle	Cost per cycle
CCNU	110 mg/m^2	187 mg	5 x 40 mg	£42.84	1	£42.84
Procarbazine	60 mg/m^2	102 mg	2 x 50 mg	£1.50	14	£20.97
Vincristine	1.4 mg/m^2	2.38 mg	1 x 2 mg**	£21.17	2	£42.34
Total cost per cycle						**£106**

* for average body surface area of 1.7 m^2

** maximum dose per day

B. ANTI-EMETIC COSTS

n Note that costs have been rounded to the nearest pound within calculations.

It was assumed that prophylactic anti-emetics would be given to every patient for five days in the temozolomide group and for 3 days following administration of CCNU.

UNIT COSTS

Drug		BNF Cost[27]	Cost per unit
Granisetron	10 x 1 mg	£91.43	£9.14
	5 x 2 mg	£91.43	£18.29
Metoclopramide	28 x 10 mg	£2.60	£0.09

Granisetron was used for all analyses presented in Section 3. The use of metoclopramide as a cheaper alternative was evaluated in a sensitivity analysis.

B1. Granisetron

	Recommended daily dose	Obtained from	Cost per day	Days per cycle	Cost per cycle
Granisetron	1-2 mg pre treatment	1 x 2 mg	£18.29	1	£18.29
	2 mg	2 x 1 mg	£18.29	5 3	£91.43 £54.86
				Total cost per cycle of TMZ **Total cost per cycle of PCV**	**£110** **£73**

B2. Metoclopramide

	Recommended daily dose	Obtained from	Cost per day	Days per cycle	Cost per cycle
Meto-clopramide	3 x 10 mg	3 x 10 mg	£0.28	5 3	£1.39 £0.84
				Total cost per cycle of TMZ **Total cost per cycle of PCV**	**£1.39** **£0.84**

C. OUTPATIENT VISITS[o]

Temozolomide is administered orally and requires two hospital visits per cycle:

- on day one, for provision of five days of temozolomide capsules
- on day 22, for full blood count

PCV is a combination of drugs that are administered both orally and intravenously, requiring three hospital visits per cycle.

- on day one, for oral administration of CCNU
- on day eight, for intravenous administration of vincristine, and provision of 14 day course of procarbazine
- on day 29, for intravenous administration of vincristine

o These contacts have been classed as outpatient visits but will vary in intensity. For instance, some blood count data may be obtained through GP visits. The latter two visits for PCV administration are considered to be minor out-patient attendances, however no costs were available distinguish between resource use at full outpatient visits and minor visits.

The cost of an outpatient attendance was obtained from the NHS in Scotland Cost Book, 1999.[57] The cost used is the mean cost across all hospitals in Scotland. Although the cost may be higher then those in England and Wales, it is the most reliable cost available. Discussions with the Finance department at Southampton General Hospital confirm that it is a reasonable estimation of the cost of an outpatient attendance. They estimate the costs of an outpatient attendance at £86 for a neurology visit, £159 for neuro-surgery, £54 for clinical oncology, and £333 for medical oncology. The latter cost includes the cost of drugs administered during these visits.

C1. Outpatient attendance costs

	Temozolomide	**PCV**
Full visits per cycle	2	1
Minor visits per cycle	0	2
Cost per attendance	£100	£100
Cost per cycle	**£200**	**£300**

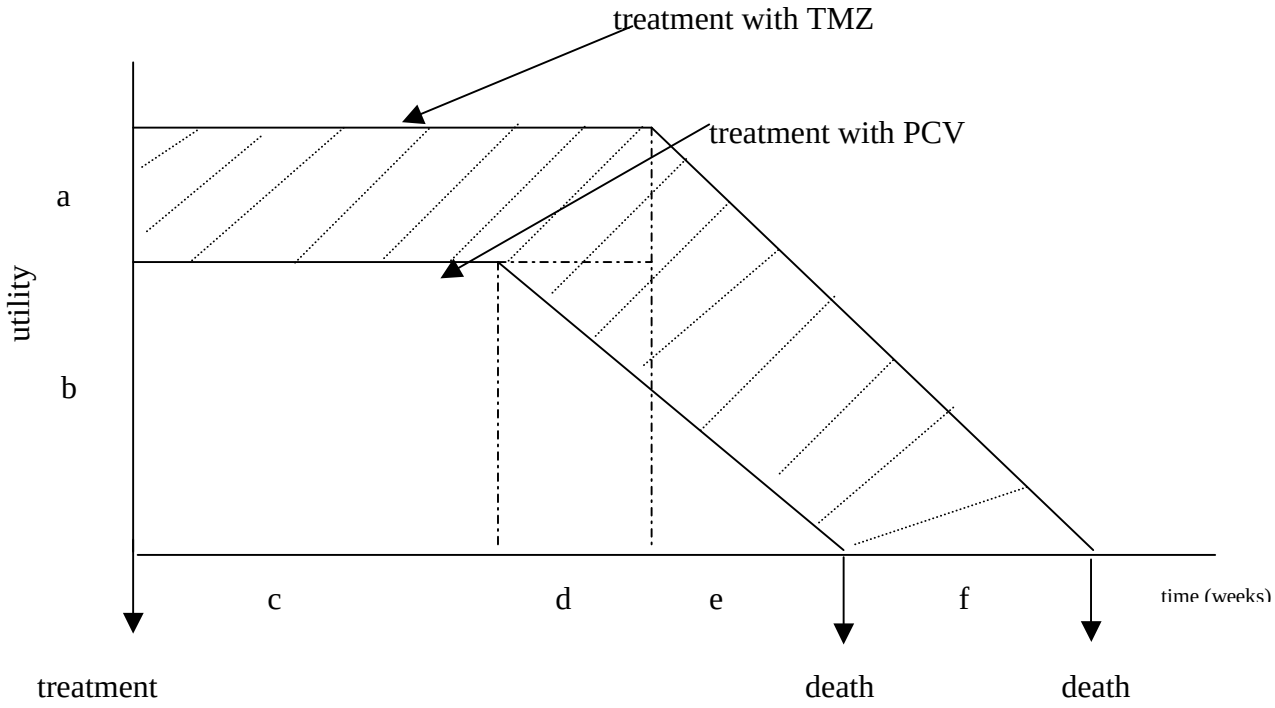
D. MRI SCANS

Following recurrence, glioma patients undergo an MRI scan at baseline, after two cycles of treatment, regardless of cycle length and then at six months follow-up.

The cost of MRI was estimated at £222 (data from Planning Department, Royal Infirmary of Edinburgh).

APPENDIX 10

Utility curves for patients treated with TMZ and PCV



The area under the curve for each treatment was calculated as follows:

For treatment with PCV: $b*c + \frac{1}{2} b(d + e)$ (A)

For treatment with temozolomide: $(a + b)(c + d) + \frac{1}{2} (a + b)(e + f)$ (B)

The number of QALYs gained: $(A - B)/52$

APPENDIX 11

Glioblastoma multiforme cost-effectiveness and cost-utility analyses

A. PARAMETERS TESTED

	PFS	Survival	Utility (while progression-free)
A	+ 4 weeks	+ 6 weeks	1.0
B	+ 0 weeks	+ 0 weeks	0.60
C	+ 8 weeks		0.80

This table describes the effectiveness and cost parameters that were examined in the economic models. As the data for overall survival were felt to be rather weak, only two options were explored: either a six week increase in overall survival, or no increase in overall survival.

The results of each combination of these variables are described in the tables below

B. RESULTS OF THE ECONOMIC ANALYSES

B1. Progression-free weeks gained (PFWG) and cost/progression-free week gained

When there is no increase in overall survival, the incremental cost-effectiveness of TMZ will still be affected by the effect on progression-free survival (longer PFS affects the incremental cost of TMZ). Two options were explored: increase in PFS of 4 weeks or 8 weeks.

Scenario no.	PFS	Survival	PFWG	Cost/PFWG
1	A	B	4	£1011
2	C	B	8	£691

B2. Life years gained and cost/life year gained

When an increase in overall survival is expected, a cost per life year gained can be calculated. As above, the cost-effectiveness ratio is again affected by the impact of TMZ on progression-free survival. Three options for the effect on PFS were explored (increases of 4, 0 and 8 weeks), each combined with an increase in overall survival of 6 weeks.

Scenario no.	PFS	Survival	LYG	Cost/LYG
1	A	A	0.12	£35,051
2	B	A	0.12	£22,159
3	C	A	0.12	£47,943

B3. QALYs gained and cost/QALY gained

When the impact of TMZ on quality of life is included it the analysis, a cost per QALY gained can be estimated. The combination of the eight parameters outlined in table A above produces 18 possible scenarios (described below). The baseline analyses discussed in section 3.2.2 are provided where there is a moderate increase in progression-free survival (4 weeks) and no effect on overall survival (see scenarios 4, 5 and 6).

Scenario no.	PFS	Survival	U	Incr QALY	Cost/QALY
1	A	A	A	0.22	£18,130
2	A	A	B	0.06	£70,102
3	A	A	C	0.14	£28,809
4	A	B	A	0.17	£24,454
5	A	B	B	0.02	£175,256
6	A	B	C	0.09	£42,920
7	B	A	A	0.17	£15,109
8	B	A	B	0.03	£73,865
9	B	A	C	0.10	£25,086
10	B	B	A	0.11	£22,924
11	B	B	B	0.00	[p]
12	B	B	C	0.06	£45,847
13	C	A	A	0.28	£19,976
14	C	A	B	0.08	£68,490
15	C	A	C	0.18	£30,931
16	C	B	A	0.22	£25,233
17	C	B	B	0.05	£119,857
18	C	B	C	0.13	£41,689

Note that where TMZ does not increase quality of life while patients are progression-free, a QALY gain can still be estimated from the increases either in progression-free survival or in overall survival (i.e. scenarios 2, 5, 8, 14and 17). As noted earlier (section 3.1.1.2), no data were available on the utility experienced by patients from progression to death, and a linear deterioration in utility has been assumed.

p No incremental benefit from TMZ, i.e. no increase in progression-free survival, overall survival or utility

APPENDIX 12

Anaplastic astrocytoma cost-effectiveness and cost-utility analyses

A Parameters tested

	PFS	Survival	Utility (while progression-free)
A*	+ 11 weeks	+ 12 weeks	1.0
B	+ 0 weeks	+ 0 weeks	0.60
C	+ 22 weeks		

This table describes the effectiveness and cost parameters that were examined in the economic models. As the data for overall survival were felt to be rather weak, only two options were explored: either a twelve week increase in overall survival, or no increase in overall survival.

The results of each combination of these variables are described in the tables below

B. RESULTS OF THE ECONOMIC ANALYSES

B1. Progression-free weeks gained and cost/progression-free week gained

When there is no increase in overall survival, the incremental cost-effectiveness of TMZ will still be affected by the effect on progression-free survival (longer PFS affects the incremental cost of TMZ). Two options were explored: increase in PFS of 11 weeks or 22 weeks.

Scenario no.	PFS	Survival	LYG	Cost/LYG
1	A	B	11	£737
2	C	B	22	£554

B2. Life years gained and cost/life year gained

When an increase in overall survival is expected, a cost per life year gained can be calculated. As above, the cost-effectiveness ratio is again affected by the impact of TMZ on progression-free survival. Three options for the effect on PFS were explored (increases of 11, 0 and 22 weeks), each combined with an increase in overall survival of 12 weeks.

Scenario no.	PFS	Survival	LYG	Cost/LYG
1	A	A	0.23	£35,129
2	B	A	0.23	£16,441
3	C	A	0.23	£52,856

B3. QALYs gained and cost/QALY gained

When the impact of TMZ on quality of life is included it the analysis, a cost per QALY gained can be estimated. The combination of the eight parameters outlined in table A above produces 18 possible scenarios (described below). The baseline analyses discussed in section

3.3.2 are provided where there is a moderate increase in progression-free survival (11 weeks) and no effect on overall survival (see scenarios 4, 5 and 6).

Scenario no.	PFS	Survival	U	Incr QALY	Cost/QALY
1	A	A	A	0.45	£17,938
2	A	A	B	0.13	£61,095
3	A	A	C	0.29	£27,734
4	A	B	A	0.34	£24,089
5	A	B	B	0.06	£127,743
6	A	B	C	0.20	£40,534
7	B	A	A	0.30	£12,487
8	B	A	B	0.07	£54,804
9	B	A	C	0.19	£20,340
10	B	B	A	0.19	£20,132
11	B	B	B	0.00	[q]
12	B	B	C	0.09	£40,264
13	C	A	A	0.60	£20,329
14	C	A	B	0.20	£62,183
15	C	A	C	0.40	£30,641
16	C	B	A	0.48	£25,169
17	C	B	B	0.13	£96,101
18	C	B	C	0.31	£39,891

Note that where TMZ does not increase quality of life while patients are progression-free, a QALY gain can still be estimated from the increases either in progression-free survival or in overall survival (i.e. scenarios 2, 5, 8, 14and 17). As noted earlier (section 3.1.1.2), no data were available on the utility experienced by patients from progression to death, and a linear deterioration in utility has been assumed.

q No incremental benefit from TMZ, i.e. no increase in progression-free survival, overall survival or utility