NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA23 The use of temozolomide for the treatment of recurrent malignant glioma (brain cancer)

This guidance was issued in April 2001

The review date for this guidance is February 2011

Original remit(s)

Clinical and cost effectiveness of temozolomide for brain cancer.

Current guidance

1.1 Patients with recurrent malignant glioma (brain cancer) who have failed first-line chemotherapy treatment with other agents (either because of lack of efficacy or because of side effects) may be considered for treatment with temozolomide. Such patients must have a histologically proven malignant glioma (WHO grades III and IV, or transformed grade II) at first relapse, recurrence or progression (as assessed by imaging), Karnofsky performance status greater than or equal to 70 and a projected life expectancy of 12 weeks or more, at initiation of temozolomide treatment. (See Appendix D for definition of Karnofsky status and Appendix E for definition of WHO tumour grading).

1.2 Temozolomide is not recommended for first-line chemotherapy treatment for patients with malignant glioma who have failed primary therapy (surgery and/or radiotherapy), except in the context of a randomised controlled trial against a standard-treatment comparator.

1.3 As temozolomide is not currently licensed for adjuvant chemotherapy treatment of malignant glioma, its use in this indication has not been considered in this appraisal.

Recommendation

It is proposed that the decision to review TA23 is taken alongside the decision to review TA121 so that the option to combine the review of the two appraisals can be considered. The decision to review TA121 is expected to take place in 2015.

That we consult on this proposal.

We note that the recommendation 1.2 in TA23 has been superseded by TA121. A note should be added to the relevant page on the NICE web site to clarify this.

Rationale[1]

There is no new evidence to change recommendation 1.1 in TA23. It appears that recommendation 1.2 overlaps with and is superseded by the guidance in TA121 'Carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma'. TA121 recommends temozolomide as an option for the treatment of newly diagnosed glioblastoma multiforme (GBM) in patients with a World Health Organization (WHO) performance status of 0 or 1 (that is, first-line chemotherapy).

Combining the review of TA23 with the review of TA121 will allow the position of temozolomide in the treatment pathway to be considered more fully in the light of further evidence. The decision to review TA121 is expected to take place in 2015 following completion of further studies on the use of temozolomide as first-line chemotherapy.

New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from March, 2004 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

Summary of evidence and implications for review

At the time of the original appraisal, temozolomide was indicated for the treatment of patients showing recurrence or progression with standard therapy. At that time, there had been only one randomised controlled trial involving temozolomide versus procarbazine alone in patients with recurrent glioblastoma multiforme (GBM; one of three forms of malignant gliomas). There had been no trials of temozolomide in anaplastic astrocytoma (AA; another of the three forms of malignant gliomas). Based on the evidence available at the time, the current guidance recommends temozolomide as an option for second-line treatment of patients with recurrent malignant glioma (and further disease-specific criteria; see recommendation 1.1). It does not recommend temozolomide as an option for first-line use, except in the context of a clinical trial (see recommendation 1.2). As temozolomide was not licensed for adjuvant chemotherapy treatment of malignant glioma, its use in this indication was not considered in the original appraisal (see recommendation 1.3).

The research recommendations included in the original guidance call for research into the effect of the drug on children and refer to usefulness of a planned trial of temozolomide in comparison with procarbazine, lomustine and vincristine in patients with GBM, AA and other malignant gliomas. The guidance was considered for review in 2004 when it was decided to defer the decision to review until the completion of the clinical trial comparing temozolomide against the combination of procarbazine, lomustine and vincristine in patients with GBM and AA. The results of

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

this trial were published in October 2010 and indicate that the use of temozolomide did not show a clear benefit compared with procarbazine, lomustine and vincristine (1).

Since the publication of the original guidance, the indication has expanded to include: (1) children from the age of three years and adolescents to indication for second-line use (i.e., for the treatment of malignant glioma showing recurrence or progression with standard therapy); and (2) first-line use in adults with GBM (i.e., adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy treatment). The latter addition to the indication (that is, the first-line use in adults with newly diagnosed glioblastoma multiforme) is covered (alongside the similar indication for carmustine implants) in NICE technology appraisal 121 (Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma, June 2007). A decision to review TA 121 has been deferred until 2015 until the results from a number of relevant trials are reported. These new trials (described below) identified during the review proposal for TA121 compare the addition of temozolomide to radiotherapy compared the addition of alternative chemotherapy agents to radiotherapy (using various combinations of procarbazine, lomustine, and vincristine). Other new trials compare the use of radiotherapy or temozolomide alone with the combination of radiotherapy and temozolomide.

Four trials examining the use of temozolomide as first-line treatment (in combination with radiotherapy) for malignant gliomas are currently ongoing. Three of the trials (NCT01236560, a phase III study in children with newly diagnosed high-grade gliomas; and NCT00626990 & NCT00887146, phase III trials on concurrent and adjuvant temozolomide use in subgroups of patients [defined by defined by chromosome abnormalities] with anaplastic gliomas) have estimated completion dates in either 2014 or 2015. The decision to review TA 121 has been deferred until the results of these trials have been reported. Additionally, one trial (NCT00482677, a randomized phase III study of temozolomide and short-course radiation versus short-course radiation alone in the treatment of newly diagnosed glioblastoma multiforme in elderly patients) has an estimated completion date in December 2012.

In summary, since the publication of the original appraisal, the marketing authorisation has expanded to include the use of first-line use of temozolomide. NICE has issued separate guidance on this indication (TA121) and the decision to review has been deferred until 2015. As TAs 121 and 23 represent guidance on the use of various chemotherapy agents at different stages in the treatment pathway, and guidance on the first-line use of temozolomide (TA121) may influence its use second-line (TA23), it is most appropriate defer the decision to review TA23 until 2015 and consider the reviews of TA23 and TA121 together.

Implementation

A submission from Implementation is included in Appendix 3.

The healthcare activity data suggest that there has been both there an increase in the use of temozolomide following its receipt of a NICE recommendation, and a reduction in the variation in its use across UK cancer networks. However, the healthcare activity data are not linked to diagnosis or stage of disease, and so it is

not possible to ascertain what proportion of temolozomide prescribing relates to its first-line use recurrent malignant glioma.

Equality issues

No equalities issues were raised in the original guidance. Recommendation 1.1 of TA23 refers to Karnofsky performance status. Karnofsky performance status relates to the person's level of functional impairment and their need for care and assistance. People with disabilities could have lower scores for reasons that are unrelated to their prognosis with respect to malignant glioma. For this reason more recent guidance that has referred to performance status has normally included a statement to the effect that clinicians should make appropriate judgements taking into account the person's usual functional capacity and requirement for assistance with activities of daily living.

GE paper sign off: Janet Robertson, 4th March 2011

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A partial review of the guidance should be planned into the appraisal work programme.	A partial review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to 2015.	NICE will reconsider whether a review is necessary at the specified date, alongside the decision to review TA121	Yes
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	No

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. The technology falls within the scope of a clinical guideline (or public health guidance)

iii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iv. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

v. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

vi. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Cancer service guidance CSGBraincns Service guidance for improving outcomes for people with brain and other central nervous system tumours Issued: June 2006. Review date: unknown.

Technology appraisals TA121 Carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma. Issued: June 2007. Review decision: December 2010 - To defer the review of the original guidance until 2015 when the results of ongoing trials are available

Suspended/terminated

Technology appraisals TA149 Carmustine implants for the treatment of recurrent glioblastoma multiforme Issued: June 2008. NICE was unable to recommend the use in the NHS of carmustine implantsas an adjunct to surgery in patients with recurrent glioblastoma multiforme for whom surgical resection is indicated because no evidence submission was received from the manufacturer or sponsor of the technology.

Details of changes to the indications of the technology

Indication considered in original appraisal	Current indication (for this appraisal)
Temozolomide (Temodal) is an alkylating agent derived from dacarbazine and first synthesised in 1984. It is indicated for the treatment of patients with malignant glioma showing recurrence or progression after standard therapy.	Temodal hard capsules are indicated for the treatment of: - adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment - children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

Registered and unpublished trials

Trial name and registration number	Details
Vorinostat, Temozolomide, or Bevacizumab in Combination With Radiation Therapy Followed by Bevacizumab and Temozolomide in Young Patients With Newly Diagnosed High-Grade Glioma (NCT01236560)	This randomized phase II/III trial is studying vorinostat, temozolomide, or bevacizumab to see how well they work compared with each other when given together with radiation therapy followed by bevacizumab and temozolomide in treating young patients with newly diagnosed high-grade glioma. Number of participants: 248. Estimated Primary Completion Date: July 2014
Radiation Therapy With or Without Temozolomide in Treating Patients With Anaplastic Glioma (NCT00626990)	This randomized phase III trial is studying giving temozolomide during and/or after radiation therapy to see how well it works compared to radiation therapy alone in treating patients with anaplastic glioma. Number of participants: 748. Estimated Primary Completion Date: June 2015
Radiation Therapy or Radiation Therapy and Temozolomide or Temozolomide Alone in Treating Patients With Newly Diagnosed Anaplastic Glioma (NCT00887146)	This randomized phase III trial is comparing giving temozolomide alone, radiation therapy alone, or Temozolomide together to see which works best in treating patients with newly diagnosed anaplastic glioma. Number of participants: 488. Estimated Primary Completion Date: February 2014
Radiation Therapy With or Without Temozolomide in Treating Older Patients With Newly Diagnosed Glioblastoma Multiforme (NCT00482677)	This randomized phase III trial is studying radiation therapy and temozolomide to see how well they work compared with radiation therapy alone in treating patients with newly diagnosed glioblastoma multiforme. Number of participants: 560. Estimated Primary Completion Date: December 2012

References

1. Brada, M et al (2010) Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma Journal of clinical oncology. 28 (30): 46014608

Appendix 3 – Implementation submission

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

IMPLEMENTATION PROGRAMME

Guidance Executive Review

Technology appraisal TA23: Temozolomide for the treatment of recurrent malignant glioma (brain cancer)

1. Routine healthcare activity data -

This section provides information on prescribing cost and volume for drugs issued in hospitals in England. The data are obtained from the IMS HEALTH Hospital Pharmacy Audit Index. All costs stated in this report are based on estimated cost.

1.1 IMS HEALTH Hospital Pharmacy Audit Index (HPAI) – Temozolomide

Figure 1 Trend in the cost of prescribing temozolomide in hospitals in England

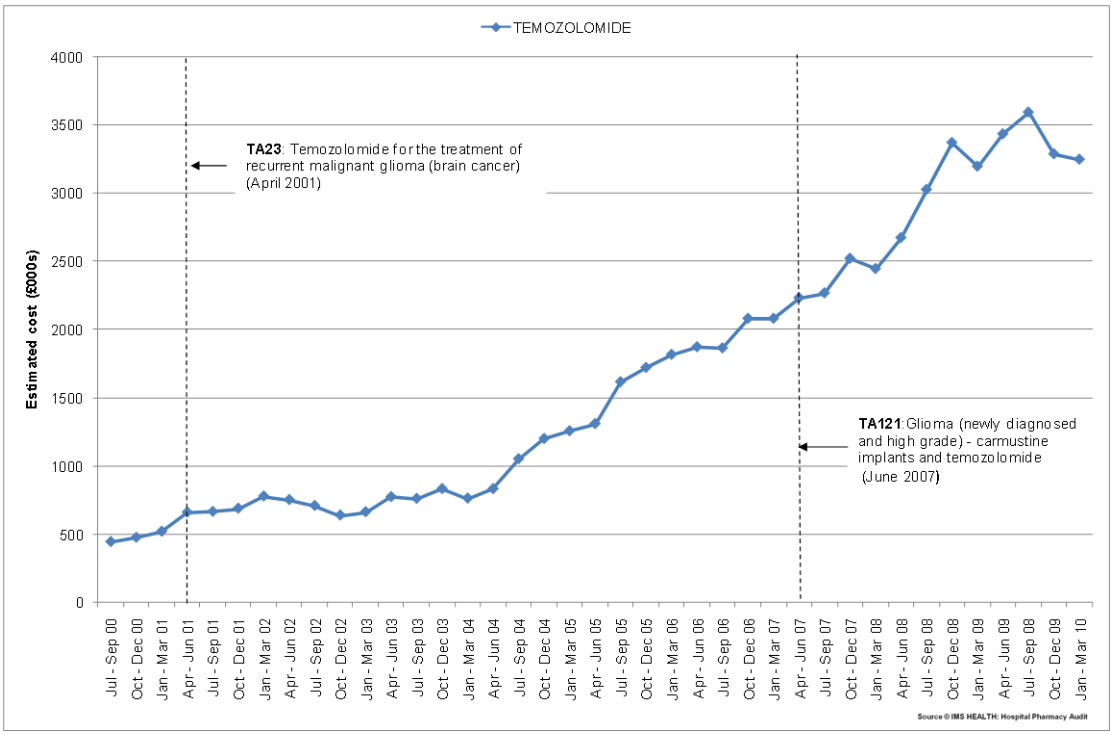
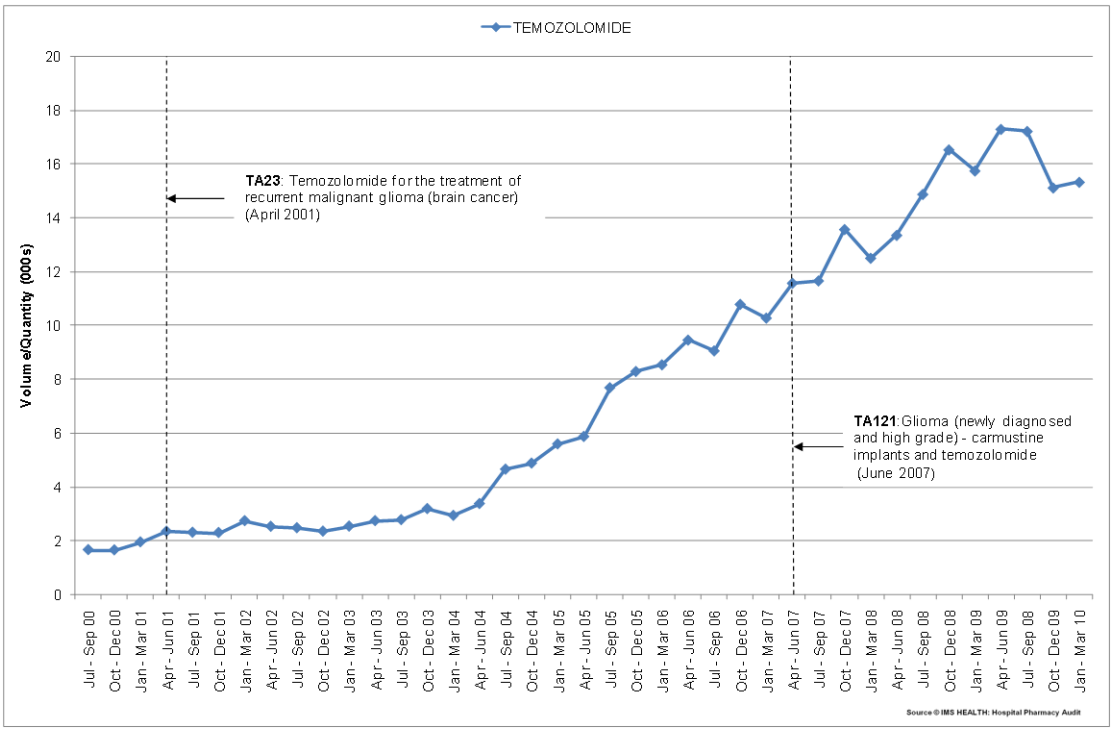


Figure 2 Trend in the volume of prescribing temozolomide in hospitals in England



The above charts show that following the publication of NICE technology appraisal 23 and up until 2004, the prescribing costs and volume for temozolomide fluctuated between £650,000 and £800,000 (2,000 and 3,000 items). In the second quarter of 2004 the prescribing cost and volume for temozolomide began to increase. This trend has continued and by January to March 2010, the estimated costs was £3,246,779. There has been a variation in prescribing cost and volume since the third quarter of 2008, It is unclear yet whether this is a temporary or ongoing trend.

This data must be interpreted with caution as data are not linked to diagnosis / stage of disease. It is therefore not possible to ascertain what proportion of prescribing relates to patients with recurrent malignant glioma.

Notes:

- The IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI) collects information from pharmacies in hospital trusts in the UK. The IMS HPAI database is based on 'issues' of medicines recorded on hospital pharmacy systems. 'Issues' refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

- Volume/Quantity: This is the number of packs of a medicine that are issued. They should not be added together due to differences in dosages/pack sizes.

- Cost (in £s): Estimated costs are calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost. Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

- Ideally data would show the total number of patients prescribed a medicine and the volume and duration of treatment. However, the current datasets do not facilitate this type of analysis. Cost and volume therefore need to be considered together to provide the closest approximation. Cost provides a more accurate view of the total amount of a medicine dispensed. However, it does not provide an indication of the number of patients prescribed a medicine. Volume therefore provides an indication of the number of packs used, although it does not account for patients receiving different dosages or durations.

- Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance.

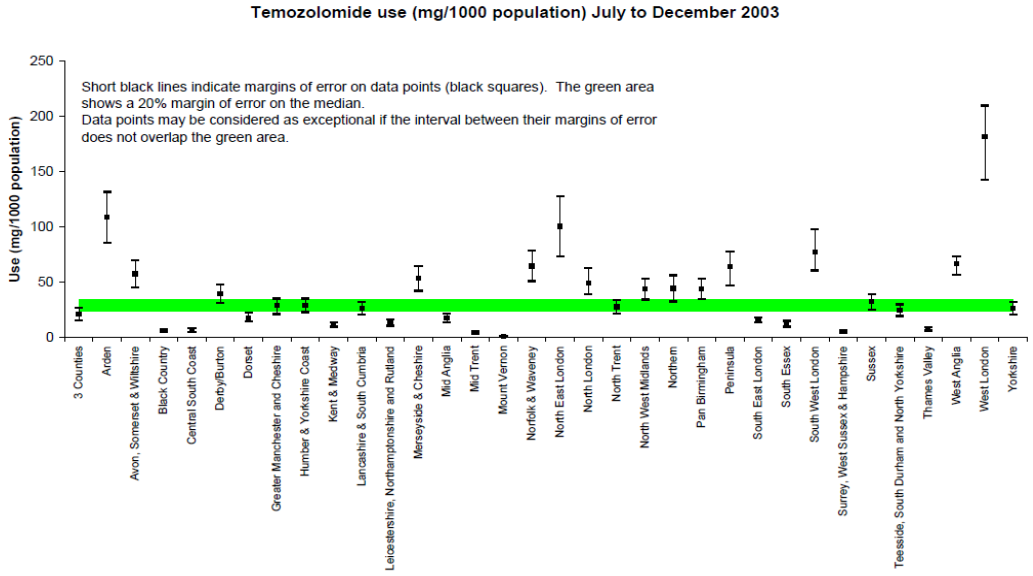
2. Implementation studies from published literature

Information taken from the ERNIE website

2.1 Richards M (2004) "Variations in usage of cancer drugs approved by NICE: Report of the Review undertaken by the National Cancer Director." Department of Health: London.

This review conducted by the National Cancer Director in 2004 reported that (i) overall usage of cancer drugs had generally increased following a positive NICE appraisal, (ii) there was considerable variation in usage among cancer networks that could not be accounted for by differences in case-mix alone. the widest variation was for Temozolamide (Temodal) used for brain cancer [11.6 fold variation]. A further

review was conducted in 2005 and published in September 2006 showing significant reductions in the levels of variation across cancer networks.



2.2 Richard M (2006) Usage of cancer drugs approved by NICE: Report of Review undertaken by the National Cancer Director London: Department of Health

The 2006 report shows: (i) a continued increase in uptake of cancer drugs following a positive NICE appraisal, (ii) a reduction in the variation in usage of all 15 NICE-approved drugs since a 2003 analysis. Variations in usage between cancer networks were wider for some NICE-approved drugs than others. The X-fold variation in usage for Temozolamide (Temodal) over the first half of 2005 was 9.5, a reduction in variation of 18% since the second half of 2003.

2.3 Department of Health (2009) Uptake of NICE approved cancer drugs 2007/2008 London: Department of Health

An analysis of prescribing data across cancer networks. Data show a 107% increase in prescribing of temozolomide from 2005 to 2007/08 and a 68% reduction in variation across networks (NB data is not linked to diagnosis).

Note: The use of NICE appraised medicines in England: report is due to be updated and published on the 26th January 2011.