Senate Standing Committee on Community Affairs - Inquiry into the availability of new, innovative and specialist cancer drugs in Australia – Submission on behalf of Brain Tumour Alliance Australia Inc (BTAA).

This document addresses the Inquiry, from the perspective of patients, carers and families living with brain tumours, which are a less common cancer:

1. the timing and affordability of access to new innovative specialist cancer drugs for patients in Australia;
2. the operation of the Pharmaceutical Benefits Advisory Committee including the impact of delays in the approvals process for Australian patients;
3. the impact on the quality of care available to cancer patients;
4. other matters (related to the patient and carer voice in PBAC processes).

EXECUTIVE SUMMARY

About us

a. Brain Tumour Alliance Australia (https://www.btaa.org.au/) is primarily a support, educational and advocacy organisation funded through donations.

About brain tumours

a. Brain tumours are the only cancer to directly affect both the mental and physical capability of a patient.
b. The overall incidence of brain tumours is low but the tumours are often lethal – the equivalent of a car crash each day somewhere in Australia that involves almost four fatalities.
c. Statistical information on brain tumours in Australia is deficient – non-malignant brain tumours, the incidence of brain metastases, and the location and histology of brain tumours are not officially published.

Quality of care

a. Gliomas, which represent 32% of all brain tumours, are the most challenging to treat, and produce a variety of debilitating functional and cognitive symptoms, seizures and personality changes. Quality of care is therefore of upmost importance.
b. When the prognosis for a patient with a primary malignant brain tumour is relatively poor then it is even more important that they be provided with first-rate professional care, in addition to the so-called informal care given by a family member or friend. There is a need for more brain tumour-specific care co-ordinators.
c. In comparison with other cancers Federal Government spending on prevention and early detection of brain tumours has been non-existent because it is not relevant.

Availability of treatments for brain tumours

a. There are few new therapies for brain tumour patients on the horizon.
b. In the past 40 years (1975 to 2015) there has only been one major therapy (temozolomide) endorsed by the PBAC that is of direct benefit to adult brain tumour patients. Bevacizumab (Avastin) has been the only new brain tumour therapy for adults submitted to, and rejected by, the PBAC since 2005.
c. In the past 20 years brain tumour patients in Australia, particularly those with a malignant primary tumour, have really only had access to three new therapies – dissolving wafers containing carmustine (an alkylating chemotherapy agent) (Gliadel) that are inserted during neurosurgery, temozolomide (Temodal) and concomitant and adjuvant radiotherapy.
d. The wider use of the neurosurgical navigational aids of Gliadel and intra-operative MRIs could be more cost-effective than proposed new drug therapies for brain tumour patients.
e. The Optune device (applying electric fields to kill rapidly dividing cells, delivered by removable transducer arrays that are placed on the head) is a new therapy that has been approved in the US. Despite attempts to discover new therapies many have failed at the investigative stage.
f. The PBAC and TGA should be flexible and open-minded when evaluating a new multi-drug protocol for brain tumours such as CUSP9* (http://www.bioportfolio.com/resources/pmarticle/1067207/CUSP9-treatment-protocol-for-recurrent-glioblastoma-aprepitant-artesunate-auranofin-captopril-celecoxib-disulfiram.html).

Timing and affordability of access to new drugs

a. For rare cancers such as brain tumours, international evaluations and being part of managed entry schemes to determine the effectiveness of new treatments, and drug utilisation, within the real world of our health system, could have merit. This approach would overcome the long delays in approval in Australia and provide timely information on effectiveness and access to the new treatments. Consumers and support groups would have to be well informed.
b. Access and financial subsidisation decided by genetic characteristics should be treated with caution as this is a rapidly developing field. It should not be used alone to decide patient subpopulations without further information, including the range of diseases that it is applicable to, and therefore the full extent of the treatment population.
c. Any proposed cancer drugs fund should be well funded from its commencement.

The Pharmaceutical Benefits Advisory Committee and its processes

a. The PBAC should offer health consumers an adequate option of a written submission when commenting on its agenda items. The HTAi Patient Group Submission template could be used.
b. The endpoints for randomised controlled trials involving brain tumour therapies need further investigation. The concept of Clinical Outcome

Assessments should be widened to include a measure of any reduction in the caregiver burden.

About BTAA: This submission is made on behalf of Brain Tumour Alliance Australia (BTAA), which is the national peer-led organisation for people diagnosed with central nervous system tumours, and their family and caregivers. BTAA is primarily a support, educational and advocacy organisation and seeks to represent the brain tumour community from the viewpoint of the patient, family and caregiver. It operates a national Freecall telephone counselling service and provides free handbooks and information resources to patients in both the adult and paediatric areas.

Author: The author is a member of the Committee of BTAA and is also a member of the HTAi (Health Technology Assessment International) Interest Sub-Group on Patient and Citizen Involvement in HTA (PCISG). He is a former secretary of BTAA and was Chair and Co-Founder of the International Brain Tumour Alliance (IBTA) between 2005-2014 and received the 2014 Public Service Award of the US-based Society For Neuro-Oncology which is the international organisation for brain tumour specialists. The author is not a medical professional but is a patient advocate. He was involved as Chair of the IBTA during the consideration by the UK National Institute for Clinical Excellence (NICE) of the drug temozolomide during 2005-2006 and helped draft patient advocacy submissions to the PBAC concerning the reimbursement of temozolomide and bevacizumab (Avastin). He has served as a member of a Medical Services Advisory Committee (MSAC) sub-committee examining PET for glioma and was a member of the Committee that drafted the Australian Clinical Practice Guidelines for Glioma. His late wife, who died from a *glioblastoma* brain tumour, is understood to have been the first Canberra patient to receive temozolomide as part of the emerging standard of care for *glioblastoma* patients.

Please note: The Chair of BTAA has absented himself from this submission's development due to a potential perceived conflict of interest.

About brain tumours in Australia: Note – BTAA uses the accepted scientific and clinical term "brain tumour", not "brain cancer", and prefers the description "non-malignant", rather than "benign", which implies insignificance. [1] A non-malignant brain tumour e.g. a meningioma, can kill a person because of its capacity to damage good brain cells through uncontrolled expansion in the confines of the skull.

Statistical information about brain tumours in Australia is deficient, in so far as (1) Most cancer registries in Australia do not include statistics for non-malignant brain tumours, (2) Nor do they publish statistics for brain metastases, which are tumours in the brain caused by a cancer elsewhere in the body, and (3) Nor do they include the specific location in the brain of tumours and their histology.

Brain metastases have been calculated to have three times the incidence of primary malignant brain tumours which, in Australia, would represent about 5,400 cases, the most common originating cancer sites being lung, breast and colorectal.[2]

Despite these limitations in statistical coverage, it can be stated that:

1. The estimated incidence of primary malignant brain tumours in 2014 in Australia was 1060 (males) and 740 (females). Total = 1,800. They are the 15th most common cancer diagnosed in males, and 16th in females. [3]
2. The change in survival rates for those with a brain tumour during the 25 year period from 1982-86 to 2007-2011 was so minor that it was not even statistically significant. [4]
3. 1330 brain tumour patients were estimated to die in 2014 (790 males, 540 females) [5] – the equivalent of a car crash each day somewhere in Australia involving almost four fatalities.
4. Primary brain tumours were the second highest cause of death for children aged 1 – 14 years from all causes – after drowning/immersion; and the highest cause of cancer death for this age group (an average of 31 deaths per year over the period 2008 to 2010). [6]
5. Primary brain tumours were the highest cause of cancer death in persons aged less than 40 years (an average of 111 deaths per year over the period 2006 to 2010). [7]
6. The leading cause of cancer death in males aged less than 45 years (an average of 93 deaths per year over the period 2006 to 2010). [8]
7. The leading cause of cancer death in females aged less than 35 years (an average of 32 deaths per year over the period 2006 to 2010). [9]
8. The largest lifetime financial costs faced by households of any cancer type, at $149,000 per person, and the highest lifetime economic cost of any cancer type, at 1.89 million dollars per person. [10]
9. The median age for diagnosis for both males and females in 2011 was 58 years and 7 months. [11]
10. Prevalence is relatively low – in 2007 there were an estimated 5,600 living Australians who had been diagnosed with primary brain tumours sometime in the previous 26 years (when national records began). This includes 2,444 people diagnosed in the past 5 years. [12]

Living with brain tumours

The largest group of brain tumours are meningiomas, which are regarded as “non-malignant” but, as stated earlier, a meningioma can kill a patient.

Gliomas account for 32% of all tumours and 80% of malignant tumours.[13] They are responsible for the most challenging work undertaken by health professionals and for BTAA as a patient and carer support organisation. In addition to a poor prognosis of from 12 to 14 months[14], they are “associated with debilitating symptoms, including functional and cognitive decline, seizures, and personality changes.” [15]

In one study of the overall effects of all brain tumours it was stated that:

> “Symptoms frequent in patients with brain tumors include seizures, fatigue, pain, cognitive decline, weakness, loss of muscle and sphincter control, and immunodeficiencies. Psychological symptoms may include anxiety, depression, and fear of dying. Patients may be unable to return to work after

> completion of treatments. For some patients, 24-hour supervision may become necessary." [16]

BTAA can confirm the high incidence of anxiety and depression among patients and has combined with Beyond Blue to produce and distribute a Fact Sheet on *Brain Tumours, Anxiety and Depression*. [17]

In a Queensland-based study about caring it was stated:

> "…the level of distress noted provides evidence that supportive care services, perhaps in contrast to other cancer populations, are needed for a large proportion of patients with a brain tumour and their carers". [18]

With an overall incidence of less than 6 cases per 100,000 of population (the European cut off point for a "rare cancer") brain tumours are among the largest grouping of "rare cancers" [19], although it has been suggested with some truth that with the development of personalised therapies each person's cancer will become a "rare cancer".

Treatment – During 2000-2002 a pivotal Phase III clinical trial involving 573 patients from 85 institutions in 15 countries, including one patient from Australia, showed a small median advantage of 2.5 months in extended survival for the use of radiation therapy and temozolomide (Temodal) for patients with a glioma. This became known as the "Stupp protocol" and was published in 2005. Although the increase in survival might appear to be small it was significant within the context of nil progress in the previous 30 years. [20]

At its November 2004 and March 2005 meetings the PBAC approved temozolomide for use in the "Stupp protocol" for newly-diagnosed glioblastoma:

> In the report of its March 2005 meeting the PBAC stated: "The PBAC recommended listing on the basis of acceptable cost effectiveness. The PBAC noted that, based on the more scientifically rigorous evidence submitted for this setting, temozolomide is probably more cost-effective than in the setting following recurrence despite incurring more costs per patient on average.
>
> "The revised listing will allow use in glioblastoma multiforme at an earlier stage than allowed by the existing listing for recurrence of the condition. This was supported by an amendment to the TGA-approved indications for the product and is consistent with current trends in clinical practice." [21]

At its November 2005 meeting the PBAC approved the subsidisation of carmustine implants (Gliadel) for newly diagnosed glioblastoma:

> "The PBAC recommended listing on a cost-minimisation basis with one pack of eight carmustine 7.7 mg implants being equivalent to a course of temozolomide capsules. Based on the indirect comparison across the two trials provided in the submission, the PBAC concluded that, overall, carmustine is no worse than temozolomide for glioblastoma multiforme, the main indication within the requested restriction." [22]

The same meeting also imposed a restriction disallowing the concomitant use of temozolomide and Gliadel wafers. [23]

In November 2010 the PBAC rejected an application for subsidisation of bevacizumab (Avastin) for recurrent glioblastoma.

> "The PBAC rejected the submission on the basis of uncertain clinical benefit and an unacceptably high and uncertain incremental cost-effectiveness ratio." [24]

Avastin had been the only new brain tumour therapy for adults submitted to the PBAC since 2005. It would be true to say that in the past 40 years at least (1975 – 2015) there has been only one *major* therapy (temozolomide) endorsed by the PBAC of direct benefit to adult brain tumour patients. [25]

This situation is more a reflection of the absence of beneficial new discoveries in the past than any difficulties in the PBAC process but it shows a high unmet need.

Brain tumour patients internationally and in Australia have not benefited greatly from new discoveries in cancer treatments and in relation to the relative expenditure by the PBS on therapies for all cancers. Brain tumour patients have therefore probably received a disproportionately small amount of Federal Government funding. [26] This point is worth remembering when looking to the future operation of the PBS and the possible emergence of relatively expensive new therapies targeting small populations within the brain tumour community. Opportunities might present themselves in the future to redress this historical "neglect" of brain tumours. One would hope that these points might be recalled when the PBAC is considering "Any other relevant factor" in section F.3 of the PBAC Guidelines. [27]

Another example of imbalance and neglect of brain tumour patients within Government spending on cancer has been in the emphasis on preventative and screening programs. Those approaches might be highly relevant to some cancers such as breast, prostate and bowel, but are totally irrelevant to brain tumours because these tumours are incapable of prevention (their causes are generally unknown and they are not caused by associated risk factors for other cancers such as poor diet, alcohol consumption, tobacco consumption or lack of physical activity). Early detection by screening is impracticable because it would require population-wide MRIs of the brain at least every six months. [28]

a. the timing and affordability of access for patients;

In the past 20 years brain tumour patients in Australia, particularly those with a malignant primary tumour, have really only had access to three new therapies – Gliadel wafers containing carmustine inserted during neurosurgery, temozolomide (Temodal) and concomitant and adjuvant radiotherapy, and bevicuzamab (Avastin).

Temodal was expensive for the patient until it became subsidised via the PBS and later when generic versions emerged. Avastin continues to be expensive, despite a patient subsidy scheme operated by Roche in the absence of PBS subsidisation. [29] The specific use of Avastin for brain tumours has yet to be confirmed but it may have a role to play in reduced brain swelling in the recurrent setting.

Possible future therapies: At the most recent annual meeting (2014) of the international scientific group associated with brain tumours (Society for Neuro Oncology) a report was presented showing promising results for NovoCure's Optune device based on Tumor Treating Fields (TTFs), used in conjunction with temozolomide. This therapy is not currently available in Australia [30] but if it did become available it would present an interesting challenge for HTA evaluation because it incorporates chemotherapy (temozolomide) *together with* electrodes attached to a cover worn on the skull (a medical device). It is approved by the FDA in the USA.

Promising results were also reported for the rindopepimut therapy from Celldex which has been trialled in Australia as part of a large international trial. [31]

Trials are also taking place in Australia, as part of international studies for immunotherapy agents against glioblastoma, which have been sponsored by Bristol Myers Squibb (BMS). [32] Immuno-Oncology is becoming increasingly relevant to brain tumour therapy development.

(Note: The European Expert Group on Immuno-Oncology, which has patient advocate involvement, has called for the introduction of "adaptive pathways" in the regulatory decision-making process. They claim that the EMA has been piloting such an approach:

> "… In adaptive pathways, approval decisions are not a one-off, but instead decisions to make therapies available to patients are based on an evolving set of evidence, and data gathering and regulatory evaluation are both done in an iterative way. By allowing for continuing evidence generation, adaptive pathways aim to provide patients and professionals with up-to-date information to enable them to make the best-informed individual treatment decisions in light of evolving evidence. Early collaboration between drug developers, regulatory agencies (EMA), HTA agencies and payers is key, as they need to agree to a comprehensive development and licensing plan early on (adaptive licensing), matched with adaptive frameworks for reimbursement and HTA decisions as well." [33])

AbbVie, which included patients from The Austin Hospital in Melbourne in its small Phase I trial of ABT-414, has announced that it will initiate a randomised Phase II trial of ABT-414 in patients with *glioblastoma* and one assumes that The Austin will again be involved. [34]

There are also several vaccine therapies, such as DCVax and ICT107 that have shown promise internationally but have not been trialled on Australian patients. DCVax is being trialled in the USA, Canada, Germany and the UK. [35] ICT107 is scheduled to be tested in a Phase III trial in the USA and European Union countries in the second half of 2015. [36]

There is also a small study, based in Melbourne, of AMG 595 for use in recurrent *glioblastoma.* [37]

(Note: BTAA seeks to establish contact with companies involved with the development of new therapies for brain tumour patients so as to be aware of upcoming trials which we can advise to interested patients. Because we receive no funding from any government or cancer council we have accepted limited funding from some pharmaceutical companies in support of our projects but our overwhelming source of funding is from individuals and foundations.)

The operation of the Pharmaceutical Benefits Advisory Committee and the Pharmaceutical Benefits Scheme in relation to such drugs, including the impact of delays in the approvals process for Australian patients;

Future breakthrough therapies are likely to be put forward to the PBAC by a Pharmaceutical company, even if the discovery might have originated in an independent laboratory. No hospital or research facility on its own is likely to have the funds to take a new drug to the market.

Approval and evaluation are likely to lag behind the USA and Europe if sponsoring companies first seek approval from the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) and, depending on the outcome, then seek approval via the Australian Pharmaceutical Benefits Advisory Committee (PBAC).

Delays can occur between approval by the TGA and finalisation of evaluation by the PBAC. We note that the eventual funding recommendation concerning the immuno therapy drug ipilimumab (Yervoy) and malignant melanoma took 2.5 years. [38] This same drug might become relevant for *glioblastoma* and we would not want to see a similar delay in its consideration for brain tumours, granted everything we have said in this submission about the extreme lethality of many brain tumours and the short time frame for prognosis.

A commercial research company has identified 50 potential new therapies being developed for *glioblastoma*, the commencement of 76 GBM clinical trials in 2013, and the sponsorship of trials since 2010 by 58 pharmaceutical and biotechnology companies. [39] It is also possible that breakthroughs will emerge from a new application for *glioblastoma* arising from the development of a new therapy for another cancer, as has happened with Avastin.

Promising as these statistics might sound, the authors of a survey of studies in 2012 and 2013 reported: “None of the 22 studies of new cytotoxic drugs, or cytotoxic drug combinations for recurrent *glioblastoma* reporting in 2012 gave meaningful clinical benefit. We now report similarly sad results for the 27 studies reporting in 2013.” They claimed that 15 of the 27 studies in 2013 “… were stopped early for futility, disastrous QOL deterioration, or studies where design vagaries didn’t permit OS (overall survival) determination”. [40]

In recent years we have seen the 2013 failure of Cilengitide and standard therapy for newly-diagnosed *glioblastoma* in a Phase III trial involving more than 500 patients in 23 countries [41], the failure in 2010 of cediranib for recurrent *glioblastoma* in a Phase III trial of 325 people [42], and the failure of enzastaurin in a Phase III trial for recurrent *glioblastoma* in 2006. [43]

Each major pharmaceutical company (Merck in Germany, Astra-Zeneca, and Lilly in the USA respectively) would have spent hundreds of millions of dollars in the development of these unsuccessful drugs for brain tumours. BTAA is aware of the heavy investment involved in the development of new therapies and the risky nature of this investment.

The author knows of only one Australian-based company that is developing a new therapy for brain tumours which has reached the pre-clinical stage. The Sydney-based Novogen company is developing TRXE-009 (Trilexium) for use against paediatric and adult malignant brain tumours but if it reaches clinical use any submission to the PBAC is likely to involve a major partner with the necessary funding for taking the therapy to a marketing stage. [44]

International evaluations: There could be merit in an arrangement for the Australian evaluation process to automatically accept a favourable decision by the FDA or EMA without the need for a full assessment but Australia should not surrender its right to make independent evaluations if it so wishes. We are aware of the pilot program – Medical Device Single Audit Program (MDSAP) – for the evaluation of medical devices and Australia's participation in it, together with Brazil, Canada, Japan, and the USA. [45]

Targeted therapies: The experience of the brain tumour community with attempts to limit a therapy to those believed to be more likely to benefit from it provides a salutary lesson for future planning. Concurrently with the development of the "Stupp protocol" (see above) other studies indicated that those patients whose tumour was methylated (MGMT) were more likely to benefit from the chemotherapy. [46] It later emerged that identification of this characteristic depended on (1) the method of analysis, and (2) the area of tumour examined under the microscope and its representative nature for purposes of the test. There would have been some patients who might have benefited from this therapy even though they might have been denied access based on this test. [47] Ten years later the subject is still controversial and will be contested by leading neuro-oncologists in a "mock debate" within the Central Nervous System stream at the European Cancer Congress to be held in September 2015. [48]

In the 2005-2006 NICE consideration of temozolomide there were suggestions of limiting subsidisation based on this criteria.

The editor of the European *Cancer World* magazine sounded a warning about an exaggeration of the benefits of so-called personalised medicine in 2012 when she wrote:

> "Arguing in favour of putting all our eggs in the 'personalised medicine' basket is therefore a flawed strategy that risks creating unrealistic public expectations.
>
> It also takes the focus away from addressing obstacles to delivering personalised care that we do know how to overcome. Much more public funding is needed to conduct the optimisation studies that can show how best to use the therapies we already have. Then there is the question of delivering

> personalised cancer care in everyday practice. Urgent action is required to improve cancer services, so every patient receives the attention of the right mix of specialists, to plan and deliver care tailored to their needs.
>
> And finally, while we certainly need to vigorously pursue the potential for developing therapies designed using our knowledge of cancer genetics, the current heavy focus on drugs is too narrow. What about the potential for more precise tailoring of surgical and radiotherapy strategies, which currently account for only a tiny fraction of research into personalised therapies?" [49]

The suggestion about the potential of surgical and radiotherapy strategies in the last paragraph has particular relevance for brain tumour patients in Australia. A fluorescent-guided neurosurgical aid (Gliolan) is available under the Special Access Scheme (SAS) in 13 hospitals in Australia at a cost of $3,990 per vial (most patients require only one vial). [50] The microscope attachment for using this aid is said to cost $70,000. It and the more expensive Intra-Operative MRI system could both lead to better resections of brain tumours and hence extended survival and improved quality of life for patients.

Following the initial investment in the microscope attachment in individual hospitals and the once-off cost of $3,990 per patient, if the procedure was more widely available in Australia, it could be more cost-effective than the likely cost of emerging drug therapies for brain tumour patients.

The issue of personalised drug therapies also raises the question of who pays for the molecular analysis should a therapy be restricted by the HTA assessment to those patients whose tumour possess certain genetic characteristics?

A Cancer Drugs Fund: We have noted the emergence of the Cancer Drugs Fund (CDF) in the UK and proposals for its introduction in Australia. If something similar is implemented in Australia it will need to be adequately funded from the start so as to guard against the embarrassment and distress experienced in the UK of the withdrawal of approved therapies because of budget constraints. Since its inception in 2010 more than 60,000 patients have benefited from the CDF. [51] Colleagues associated with rare cancer advocacy in the UK have advised that the ability of patients to access drugs before NICE makes a decision has been particularly beneficial.

Fortuitously, we do not have the potential for contradictory HTA evaluations for particular therapies that resulted from independent groupings within the UK National Health Service (NHS). We have learned from our brain tumour advocacy colleagues in the UK that in the early stages of the CDF contradictory decisions for the subsidisation of Avastin, for example, could be received from different geographical areas of the NHS.

It has been argued that cancer diseases should not be favoured, by way of a special CDF, over other equally-deserving serious illnesses such as coronary ailments and dementia. [52] The essential difference is that these illnesses do not have the immediate lethality that many neglected cancers do, particularly brain tumours (see above), which are one of the most lethal of all cancers.

PBAC and consumer input: The PBAC does provide an on-line consumer input form for matters on its upcoming meeting agenda. [53] We are pleased to note that it does include this question "3: How will your life and that of your family and carers be improved by this new medicine?" This question affords an opportunity to comment on a therapy's relevance to caregivers. However, one's response overall to the on-line form is steered by the wording of the five questions, the imposed word limitations, and while there is an opportunity to request a hardcopy of the on-line document, there is no invitation to make a comprehensive written submission. That option could be offered by the PBAC. There needs to be clarity around what information can be provided, how it is collated and presented to the PBAC, and feedback given on the use of the input.

In fact, we believe that the more detailed "Patient Group Submission Template" developed by the Patient and Citizen Interest Sub-Group of Health Technology Assessment International (HTAi) after extensive international discussion during 2013-2014, might be of greater assistance to Australian health consumers who seek to make a submission to the PBAC about a particular therapy. [54]

CUSP9*: In 2013 a new proposal for the treatment of recurrent *glioblastoma* was published. [55] It is called CUSP9* and stands for "Coordinated undermining of survival paths with nine repurposed drugs" and was co-authored by 28 brain tumour researchers from around the world, including Dr Kerrie McDonald from the University of NSW. The proposal involves adding nine nominated non-cytotoxic drugs, which are already available for other non-cancer indications, to continuous low-dose temozolomide for those with recurrent *glioblastoma*. In August 2014 the nine-drug selection was slightly altered. [56]

One of the principal promoters of this protocol has advised the author of this submission that a Phase II trial of this protocol has already commenced in the USA but warned that involvement in it will require a two-year commitment by participants, regular blood work and monthly MRIs. [57]

The purpose of mentioning this new protocol is to illustrate the possible need for the PBAC and the TGA to be flexible in how they evaluate a complex proposal of this nature. Devising a study protocol for such a proposal, with the intent of submitting the results for approval and possible subsidisation, will require major ingenuity by the investigators and open-mindedness by the PBAC and TGA.

A precedent of sorts exists in the work of the Federal Government's former Palliative Care Medicines Working Group, on which the author served as a consumer representative during 2006-2010. The purpose of the group was to identify medicines that had been approved by the PBAC and TGA for certain non-palliative indications and which could be submitted for subsidisation as palliative care medicines following clinical trials proving their efficacy in this additional setting. [58]

(Note: The CUSP9* protocol has been mentioned in a new film "*Surviving Terminal Cancer*" which has had a premiere in the UK and also premiered in New York on 18 February [59]. The complete film is available on-line here: http://www.survivingterminalcancer.com/)

Rule of Rescue and the PBAC Guidelines: The "Rule of Rescue" has been described as: "an ethical imperative to save individual lives even when money might be more efficiently spent to prevent deaths in the larger population" [60] The PBAC Guidelines provide for the application of the "rule of rescue" when four criteria have all been met. As noted in the commentary on the PBAC website one particular criterion could prove problematic and an obstacle:

> "No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no nonpharmacological or pharmacological interventions for these patients." [61]

It has been alarming to note that NICE referred the "Rule of Rescue" to its Citizens Council for study [62] and later pre-emptorily ignored its report and rejected the concept. [63]

b. **the impact on the quality of care available to cancer patients**

Approvals for subsidisation of new therapies are dependent on the results of Randomised Controlled Trials (RCTs). Since 2005 a larger number of Australian oncologists have been invited to participate in international brain tumour clinical trials which are intended to prove the efficacy and effectiveness of new therapies. Australian patients have benefited from participation in these trials because of the focus they bring to patient welfare, including the quality of care. However, we do not necessarily endorse the current design of RCTs and believe that there should be more discussion about relevant end points in these trials, including ways of measuring quality of life for the participants (see later).

A Victorian patient described to the audience at a Patient Forum organised by BTAA and has written about her participation in a brain tumour drug trial at the Austin Hospital, the additional supportive care which accompanied her participation in the clinical trial:

> "Another advantage of participating in a drug trial is the close monitoring we get. If a medical problem arises it is picked up quickly and doctors have access to an international network of specialists. For example, my trial buddy who I mentioned above required two operations earlier this year and through the doctors at the Austin he was able to access the best surgeons in the fields in a very timely manner. Another woman who is also on the trial had to have an additional brain surgery a few weeks ago. From the new tumour being spotted on the MRI scan to surgery it too ten days and it is estimated that the new tumour had only been there about three weeks." [64]

End points: Organisations similar to BTAA have initiated discussions in the USA about suitable end points for brain tumour clinical trials, focussing on the relevance or irrelevance of Progression Free Survival (PFS) and Overall Survival (OS). These discussions have involved the FDA and the most recent consultation meeting held on 15 October 2014 saw the presence of 19 officials from the FDA and others from the National Cancer Institute. The participants are working on the development of

end points that could be more directly relevant to brain tumour patients in the light of perceived inadequacies in radiographic imaging and of novel ways of expanding Clinical Outcome Assessments (COAs). [65]

BTAA recommends that the concept of "Clinical Outcome Assessments" (COA) within clinical trials be widened to include a measurement of the reduction in caregiver burden as a result of the effectiveness of the therapy on an improved quality of life for the patient. The quality of life of caregivers of adults with primary brain tumours has been found to be similar to that of patients and substantially lower than that of the general population. [66] This has been raised in the past with a member of the PBAC who responded that it is always open to such information, which could be submitted by way of a survey of relevant caregivers. Unfortunately, BTAA does not have the funding resources to undertake such surveys.

(Note: The FDA has defined COAs as: "any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. Unlike biomarkers that rely completely on an automated process or algorithm, COAs depend on the implementation, interpretation, and reporting from a patient, a clinician, or an observer. The four types of COAs are patient-reported outcome (PRO) measures, clinician-reported outcome (ClinRO) measures, observer-reported outcome (ObsRO) measures, and performance outcome (PerfO) measures." [67]

When the prognosis for a patient with a primary malignant brain tumour is relatively poor then it is even more important that they be provided with first-rate professional care, in addition to the so-called informal care given by a family member or friend.

BTAA believes that one of the solutions is to provide a greater number of dedicated brain tumour-specific care coordinators. These coordinators should not be treated as a "poor cousin" in the cancer care coordinator environment whereby they are not backed up when taking maternity or annual leave, or where they are asked to share their workload in looking after one or more other cancers unrelated to brain tumours.

Coordination of the care of a brain tumour patient requires continuous and very specific and demanding attention by someone who specialises in the area and has the time to regularly update their professional knowledge. The job is likely to be more time consuming per patient than for most other cancers and is also essential to supporting caregivers to care for patients at home. [68] It could prove to be a useful cost-effective solution to a major problem.

In a Victorian-based study of carers' experience of caring for a person with a primary malignant glioma, the need for coordination and continuity was clearly identified:

> "…Carers described the absence of a central, clearly identified contact person who was responsive, reliable and available. Necessary coordination tasks identified by carers that were unfulfilled included: providing a point of contact within the treating hospital; assisting in navigation through community and hospital settings; providing information; and being a familiar presence who was aware of the whole person when there was frequently little continuity of

> medical care. Many bereaved carers noted community palliative care provided these tasks later in the illness." [69]

It is not appropriate for patients and carers to have to wait until they access community palliative care – very often at the end stages of the disease - before receiving the necessary coordinated care to help them deal with the challenges they face right from the initial diagnosis.

One study of caring in Western Australia found that:

> "Caregivers in this study reported experiences similar to those described by caregivers of people with other cancers. What differed for this group was the rapidity of change and the need for immediate information and support to assist with caring for a person with a high-grade glioma". [70] (Our emphasis.)

Denis Strangman (Committee member)

On behalf of Brain Tumour Alliance Australia

25 February 2015

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[1] *Non-Malignant Brain Tumour Handbook.* 1st Edition. Brain Tumour Foundation of Canada. 2011.
[2] *Toward determining the lifetime occurrence of metastatic brain tumors estimated from 2007 United States cancer incidence data.* Faith G. Davis, Therese A. Dolecek, Bridget J. McCarthy, and John L. Villano. Neuro-Oncology 14(9):1171–1177, 2012. doi:10.1093/neuonc/nos152
[3] Page xii. Australian Institute of Health and Welfare 2014. *Cancer in Australia: an overview 2014.* Cancer series No 90. Cat. no. CAN 88. Canberra: AIHW.
[4] Page 39, AIHW *Overview* op.cit.
[5] Page 94, AIHW *Overview* op.cit.
[6] Australian Bureau of Statistics (ABS). *Underlying cause of death. Selected causes by age at death, numbers and rates, Australia 2008-2010.* Table 1.3
[7] AIHW. Unpublished data. National Mortality Database. Compiled from S&T Registrars of Births, Deaths and Marriages, the National Coronial Information System, and the ABS.
[8] Ibid.
[9] Ibid
[10] *Cost of Cancer in NSW*. 2005. Cancer Council NSW, prepared by Access Economics, 2006.
[11] Page 94, AIHW *Overview.* Op.cit
[12] Australian Institute of Health and Welfare (AIHW) 2012. *Cancer Survival and prevelance in Australia: period estimates from 1982 to 2010.* Cancer Series No 69. Cat No CAN 65. Canberra AIHW, pps 43-44.
[13] *CBTRUS Statistical Report. Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004-2006.* February 2010 pps 18-19.
[14] See: http://en.wikipedia.org/wiki/Glioma#High_grade Accessed 16 February 2015.

[15] *Family Caregivers of Patients With a High-Grade Glioma,* Annemarie Coolbrandt et al. Cancer Nursing, 2014. DOI: 10.1097/NCC.0000000000000216

[16] *The burden of brain tumor: a single institution study on psychological patterns in caregivers,* Claudia Yvonne Finocciaro et al. J Neurooncol (2012) 107: 175-181. DOI 10.1007/s11060-011-0726-y

[17] See: https://www.bspg.com.au/dam/bsg/product?client=BEYONDBLUE&prodid=BL/0803&type=file Accessed 16 February 2015.

[18] *Unmet supportive care needs and interest in services among patients with a brain tumour and their carers.* Monika Janda et al. Patient Education and Counseling 71 (2008) 251–258

[19] See: http://www.rarecancerseurope.org/About-Rare-Cancers Accessed 16 February 2015.

[20] *Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. Roger Stupp et al.* N Engl J Med 2005; 352:987-996. March 10, 2005 DOI: 10.1056/NEJMoa043330 Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa043330 Accessed 19 February 2015.

[21] See: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2005-03/positive-recommendations Accessed 15 February 2015.

[22] See: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2005-11/positive-recommendations Accessed 15 February 2015.

[23] See http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2005-11/carmustine Accessed 16 February 2015.

[24] See: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2010-11/Bevacizumab_AVASTIN_Roche_PSD_2010-11_6-2_FINAL.pdf;jsessionid=kon95ccgxtmk11uqjsi8cvyly/ Accessed 15 February 2015.

[25] We understand that the use of the Gliadel wafers, and hence the impact on PBS expenditure, has been quite small.

[26] The Committee may care to request a table from the Department of Health showing expenditure by disease-specific cancers for all PBS subsidisation. We are not aware of any existing publicly available information about this matter.

[27] See http://www.pbac.pbs.gov.au/section-f/f3-other-relevant-factors.html Accessed 19 February 2015.

[28] One study of brain scanning by MRI has shown that there is a 1 in 37 chance of identifying a vascular abnormality in the brain which is currently producing no symptoms. This can lead to over-diagnosis and unnecessary concern by the subject. See: http://www.bmj.com/content/339/bmj.b3016 Accessed 17 February 2015. See also "*Overdiagnosis under the microscope*", Cancer World, January-February 2015, Number 64. Available at: http://www.cancerworld.org/Articles/Issues/64/January-February-2015/Spotlight-on/700/Overdiagnosis-under-the-microscope-.html Accessed 17 February 2015.

[29] Roche provides free access to Avastin for recurrent *glioblastoma* patients via the Avastin Patient Access Program. Patients are required to pay for the first 4 or 6 doses (depending on how frequently they receive treatment). To date, Roche has supported more than 530 patients via this initiative. The current program will be remain open to recruitment until 30 June 2016 when it will be reviewed. Source: Email from Jamie Nicholson, Corporate Affairs Manager, Roche Products, to D Strangman, 25 February 2015.

[30] See http://www.onclive.com/conference-coverage/sno-2014/Survival-Improvement-With-NovoTTF-Leads-to-Early-End-of-Phase-III-Trial (Accessed 16 February 2015) for an interview with Dr Roger Stupp about the TTF device and See *HealthPACT – emerging health technology* Health Policy Advisory Committee on Technology (Queensland), May 2012 for an early description of the device and its status. http://www.health.qld.gov.au/healthpact/docs/briefs/WP068.pdf Accessed 16 February 2015.

[31] See, for example, the trial for rindopepimut (CDX 110): https://www.clinicaltrials.gov/ct2/show/study/NCT01480479?term=rindopepimut&rank=2&show_locs=Y#locn Accessed 16 February 2015

[32] See the CheckMate 143 study involving nivolumab: https://www.clinicaltrials.gov/ct2/show/NCT02017717?term=checkmate143&rank=1 Accessed 16 February 2015

[33] Available at: http://c00811471m.promo.it/mailing-manager/files/IO_Therapy_Report_AW_181114_HR.pdf Accessed 19 February 2015.

[34] See Media Release, Abbvie. Available at: http://abbvie.mediaroom.com/2014-11-14-AbbVie-Presents-Results-from-Study-of-ABT-414-in-Patients-with-Glioblastoma-Multiforme-at-the-19th-Annual-Scientific-Meeting-and-Education-Day-of-the-Society-for-Neuro-Oncology Accessed 19 February 2015.

[35] See: https://www.clinicaltrials.gov/ct2/show/study/NCT00045968?term=dcvax&rank=1&show_locs=Y#locn Accessed 16 February 2015. See also: https://www.clinicaltrials.gov/ct2/show/study/NCT01280552?term=ict107&rank=1&show_locs=Y#locn for ICT107. Accessed 16 February 2015. ICT107 has been trialled only in the USA.

[36] ImmunoCellular Media Release 18 February 2015. Available at http://investors.imuc.com/releasedetail.cfm?ReleaseID=897045 Accessed 19 February 2015.

[37] See: https://www.clinicaltrials.gov/ct2/show/NCT01475006?term=amg+brain+tumours&rank=2 Accessed 20 February 2015.

[38] See: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-11/ipilimumab Accessed 20 February 2015.

[39] See: http://www.isrreports.com/free-resources/brain-cancer-glioblastoma-multiforme-profile-drug-development/ Accessed 16 February 2015.

[40] See: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4226667/ Accessed 16 February 2015.

[41] See: http://www.merckgroup.com/en/media/extNewsDetail.html?newsId=BE2FE07AD630830EC1257B1D001F007B&newsType=1 Accessed 21 February 2015. See also: http://neuro-oncology.oxfordjournals.org/content/early/2015/02/13/neuonc.nov018.extract Accessed 24 February 2015.

[42] See: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4021043/ Accessed 24 February 2015.

[43] See: https://investor.lilly.com/releasedetail.cfm?releaseid=223119 Accessed 21 February 2015.

[44] See: http://www.novogen.com/pdf/trilexiumJanuary2015.pdf Accessed 15 February 2015.
[45] See *FDA Voice* http://blogs.fda.gov/fdavoice/index.php/tag/medical-device-single-audit-program-mdsap/ Accessed 16 February 2015.
[46] Monika E Hegi et al *MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma,* N Engl J Med 2005; 352:997-1003 March 10, 2005 DOI: 10.1056/NEJMoa043331 Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa043331 Accessed 19 February 2015.
[47] It was stated in a review article in 2012 *"High Grade Gliomas: Pathogenesis, Management and Prognosis".* Vairavan Narayanan. ACNR, Vol 12 No 4, Sept-Oct, 2012. "MGMT methylation status assessment is not without its problems – multiple sites for mutation have been identified making this marker difficult to assess. In addition, the results are semi-quantitative with no clear cut off to define positive or negative status, resulting in non-standard interpretation of test results".
[48] See page 32 of the Advance Programme available at: http://www.europeancancercongress.org/ Accessed 19 February 2015.
[49] Kathy Redmond. "*Personalised Medicine: A note of Caution".* Cancer World. Issue 50. September – October 2012. Available at: http://www.cancerworld.com/Articles/Issues/50/September-October-2012/Editorial/547/Personalised-medicine-a-note-of-caution.html Accessed 19 February 2015.
[50] BTAA has uploaded a FAQ onto its website about this surgical aid. See: http://www.btaa.org.au/page/27/gliolan-faq Accessed 19 February 2015.
[51] See pages 06-08 of Pharma Times Magazine, January-February 2015. Available at: http://edition.pagesuite-professional.co.uk/launch.aspx?pbid=93f21048-0999-4504-a77a-0eb1a06cd2cf Accessed 19 February 2015. CDF critic Professor Karol Sakora claims that "Self-pay will return for those who can afford it, and special insurance policies for cancer are already being developed".
[52] *David Cameron's flagship Cancer Drugs Fund 'is a waste of NHS cash'.* The Guardian 11 January 2915. Available at http://www.theguardian.com/politics/2015/jan/10/cancer-drugs-fund-waste-of-nhs-cash-david-cameron Accessed 19 February 2015.
[53] See: http://www.health.gov.au/internet/main/publishing.nsf/Content/PBAC_online_submission_form Accessed 16 February 2015
[54] The template can be downloaded from here: http://www.htai.org/interest-sub-groups/patient-and-citizen-involvement/patient-group-submissions-to-hta.html Accessed 16 February 2015
[55] See: http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path[]=969 Accessed 16 February 2015.
[56] See: http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path%5B%5D=2408&path%5B%5D=4187 Accessed 16 February 2015.
[57] Email from Dr Richard Kast to Denis Strangman 30 January 2015. Dr McDonald also advised BTAA that she did not know of any implementation of the protocol in Australia.

[58] See "*Working towards improved access to and quality use of palliative medicines in the community".* Available at: http://ruralhealth.org.au/9thNRHC/9thnrhc.ruralhealth.org.au/program/docs/papers/heath_D7.pdf Accessed 19 February 2015.
[59] See http://www.survivingterminalcancer.com/ Accessed 16 February 2015.
[60] See: http://en.wikipedia.org/wiki/Rule_of_Rescue Accessed 19 February 2015.
[61] See: http://www.pbac.pbs.gov.au/section-f/f3-other-relevant-factors.html Accessed 19 February 2015.
[62] See: http://www.nice.org.uk/Media/Default/Get-involved/Citizens-Council/Reports/CCReport06RuleOfRescue.pdf Accessed 19 February 2015.
[63] See: http://healthcareorganizationalethics.blogspot.com.au/2008/08/rule-of-rescue-in-british-national.html Accessed 19 February 2015.
[64] "A drug trial from a patient perspective", Christine Buckingham. Brain Tumour magazine World Edition 2012 (IBTA) Accessible in digital format from here: http://issuu.com/ibta-org/docs/ibta-2012 . Pps 44-45.
[65] See http://braintumor.org/wp-content/assets/Endpoints-Workshop-2-Summary-Final.pdf Accessed 16 February 2015.
[66] See Jandra et al, op.cit
[67] See: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm370262.htm Accessed 19 February 2015.
[68] See *A Specialist Nurse as a Resource for Family Members to Patients With Brain Tumors*. Agneta Spetz et al. Cancer Nursing, Vol 31, No 4, 2008
[69] *"The challenges and suffering of caring for people with primary malignant glioma: qualitative perspectives on improving current supportive and palliative care practices",* Anna Collins et al. BMJ Supportive & Palliative Care 2013;00:1–9. doi:10.1136/bmjspcare-2012-000419
[70] See *"Caring for someone with high-grade glioma: a time of rapid change for caregivers".* R. McConigley et al. Palliative Medicine. 2010 July. Vol 24 (5) pp 473-479. Abstract available at: http://pmj.sagepub.com/content/24/5/473.abstract Accessed 19 February 2015.