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# Adult brain tumour research in 2024: Status, challenges and recommendations

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# 1 Adult Brain Tumour Research in 2024: Status, Challenges and Recommendations

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27 **Conflicts of interest:** GT has provided consultation for QMENTA and Optum Health. PH is a part-time  
28 employee at AstraZeneca. SJJ has a private practice and has investments in Genesis Cancer Centre,  
29 Newmarket. JSL has received research funding from Roche-Genentech, Astex, and Basilea, and is a  
30 member of the Scientific Advisory Boards for Roche-Genentech, Basilea, Eisai, GSK, and Pierre-Faber.  
31 MDJ has received Honoraria from BrainLab, Integra, Servier and GSK. COH received research funding  
32 from BergenBio. LFS is a member of the Scientific Advisory Board for CoSyne Therapeutics Ltd.  
33

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38

## 39 Abstract

40  
41 In 2015, a groundswell of brain tumour patient, carer and charity activism compelled the UK Minister  
42 for Life Sciences to form a brain tumour research task and finish group. This resulted, in 2018, with  
43 the UK government pledging £20m of funding, to be paralleled with £25m from Cancer Research UK,  
44 specifically for neuro-oncology research over the subsequent 5 years. Herein, we review if and how  
45 the adult brain tumour research landscape in the UK has changed over that time, and what challenges  
46 and bottlenecks remain. We have identified seven universal brain tumour research priorities, and  
47 three cross-cutting themes, which span the research spectrum from bench to bedside and back again.  
48 We discuss the status, challenges, and recommendations for each one, specific to the UK.  
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52 **Key Points**

- 53 • Brain cancer leads to more years of life-loss, per patient than any other cancer, but brain  
54 tumour research has, historically, been underfunded in the UK;
- 55 • An increase in UK public awareness of brain cancer prompted the government, and leading  
56 UK cancer charity, to pledge a cumulative £45m of funding for neuro-oncology research in  
57 2018;
- 58 • Herein, a group of multi-disciplinary brain cancer experts assimilate information from cross-  
59 sector focus groups and commissioned reports to provide current perspectives on the adult  
60 neuro-oncology research landscape in the UK;
- 61 • This position paper includes UK-specific recommendations for addressing the significant  
62 challenges and bottlenecks that remain for adult brain tumour research.

63

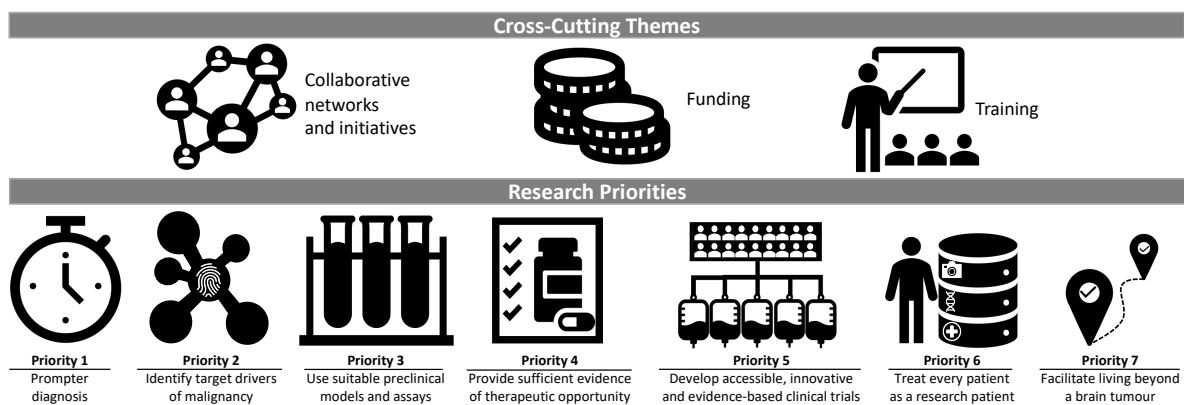
64 Brain cancer is considered to be a rare disease, but it leads to more years of life loss per patient than  
65 any other cancer, and UK incidence rates are on the rise<sup>1</sup>. The trauma and tragedy that so often  
66 surrounds a brain cancer diagnosis led to an increase in UK public awareness, as distressing stories in  
67 which young families, or high-profile personalities, were devastatingly affected became more  
68 widespread. UK parliament was petitioned to fund more research into brain tumours in 2015,  
69 triggering a debate in the House of Commons in 2016. A task and finish group was established, which  
70 highlighted several scientific, clinical, economic and societal challenges that are specific to brain  
71 cancer and have contributed to the fact that cure rates have remained low for decades. For example,  
72 the median survival of the most common aggressive primary brain tumour, glioblastoma, is 12-18  
73 months, with 25% surviving >1 year and 5% surviving>5 years<sup>1</sup> and this has not improved in over 20  
74 years<sup>2</sup>. In 2018, based on the suggestions of the task and finish group, the UK government made a  
75 pledge to commit £20m to fund brain tumour research, paralleled with a Cancer Research UK (CRUK)  
76 commitment of £25m, ring-fenced for neuro-oncology research over the subsequent 5 years.

77 In 2021, the UK National Cancer Research Institute (NCRI) Brain Group (a multi-disciplinary  
78 community of researchers and consumers focused on clinical and translational aspects specific to  
79 brain tumours) held four focus-group-like sessions, attracting >60 participants representing all neuro-  
80 oncology disciplines and sectors, to discuss how the brain tumour research landscape had changed in  
81 the UK since that pledge. The aim was to garner current perspectives on UK neuro-oncology research  
82 and to highlight persistent or new bottlenecks and opportunities. Whilst the NCRI ceased to exist at  
83 the end of 2023, the established working group persevered, assimilating the information received  
84 from the NCRI sessions with that from additional panels convened, or reports published, by Cancer  
85 Research UK (CRUK) in 2019<sup>3</sup>, the National Institute of Health Care and Research (NIHR)-funded James  
86 Lind Alliance in 2015<sup>4</sup>, and the UK All-Party Parliamentary Group on Brain Tumours (APPGBT) in early  
87 2023<sup>5</sup>. This assimilation of fact, experience and opinion from across the whole community resulted in  
88 the identification of **seven research priorities (Fig.1)** that are common to brain cancer research  
89 globally and that span the full research pipeline and patient journey:

- 90 1. Prompter diagnosis;
- 91 2. Identify target drivers of malignancy;
- 92 3. Using suitable preclinical models and assays;
- 93 4. Provide sufficient evidence for therapeutic opportunity;
- 94 5. Develop accessible, innovative, and evidence-based clinical trials;
- 95 6. Treat every patient as a research patient;
- 96 7. Facilitate living beyond a brain tumour.

97 Herein we discuss these priorities specifically in terms of the status, challenges, and recommendations  
98 for the UK. Pertinent to all are **three cross-cutting themes**: collaborative networks and initiatives,  
99 funding, and training (**Fig. 1**). Again, these are discussed with regard to the UK landscape. Biological  
100 and clinical pathways are distinct for paediatric and adult brain tumours, making their investigation  
101 and clinical management quite disparate. For that reason, this position paper focuses on adult disease.

102 Several initiatives and epidemiological studies have attempted to compare adult (neuro)oncology  
 103 metrics worldwide<sup>6-9</sup>. To illustrate how the UK fares against other brain cancer research active  
 104 countries, we have extracted some key statistics, where they were available from published research  
 105 or databases (**Fig. 2**). This indicates that the UK has low relative survival across numerous brain  
 106 cancers<sup>6,8</sup> (**Fig. 2A**). Estimates of incidence and mortality rates for brain tumours are similar for the UK  
 107 (**Fig.2B**), though comparing these metrics are difficult owing to the different ways in which it is  
 108 recorded and collected worldwide<sup>9</sup>. However, the data does highlight that the UK has relatively fewer  
 109 clinical trials compared with these other countries<sup>7</sup> (**Fig.2C**). The aim of this position paper is to  
 110 encourage UK funders, academia, industry and the National Health Service (NHS) to rally behind the  
 111 identified priorities and focus their efforts on releasing some of the recognised bottlenecks to expedite  
 112 more effective brain tumour research to maximise patient benefit. To facilitate this, we have  
 113 employed a scoring system for our recommendations to say whether we believe each one is short-  
 114 term and easily achievable (SE), intermediate-term and moderately difficult to achieve (IM) or long-  
 115 term, ambitious and difficult to achieve (LD).



116  
 117 **Fig. 1.** A schematic outlining the cross-cutting themes and research priorities for brain tumour  
 118 research in the UK

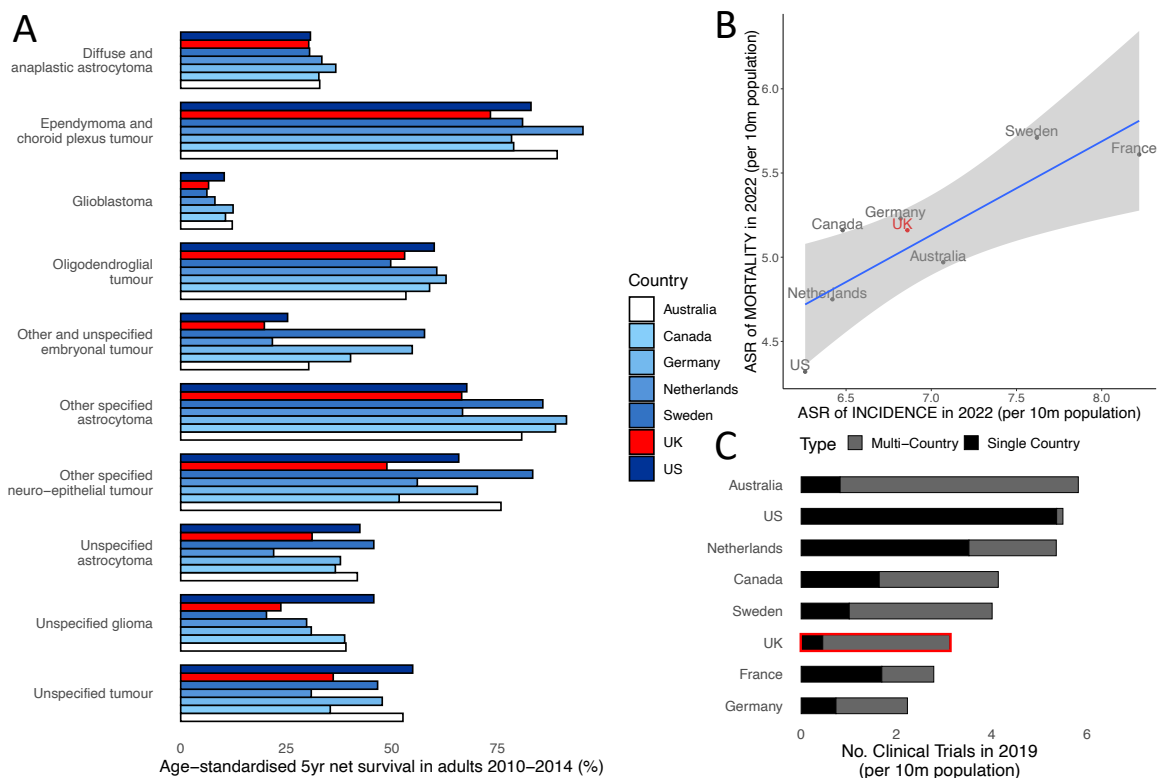
119  
 120 **Cross-cutting themes**

121  
 122 Collaborative Networks and Initiatives

123 The UK is well-placed to lead translational research and innovative trials with global impacts on patient  
 124 outcomes. The NHS offers a unified healthcare service covering a population of over 60 million, with  
 125 existing links between cancer centres, neuroscience centres, and academic units. Almost all patients  
 126 are diagnosed within the NHS allowing for excellent capture and integration of imaging, pathology,  
 127 and clinical data. Clinical trials are embedded within care pathways and access to trials is increasing  
 128 via initiatives like NIHR's 'be part of research'<sup>10</sup>. UK trials provide true standard of care (SOC)  
 129 comparator arms in almost all patients owing to the harmonised nature of UK training and clinical  
 130 practice, including minimal off-label patient-funded drugs, and testing and treatment without  
 131 requiring health insurance coverage. Primary and post-primary care integration with limited points of  
 132 entry allows complex queries to be addressed, including patient-oriented research questions and pre-  
 133 diagnosis journeys.

134 Since 2018, the UK has developed several clinical/research collaborations. The Tessa Jowell  
 135 Brain Cancer Mission (TJBCM) is a national initiative supporting clinical studies to provide platforms  
 136 for facilitating patient enrolment in biomarker-driven trials. Two examples are BRAIN-MATRIX<sup>11</sup> and  
 137 the Minderoo Precision Brain Tumour Programme<sup>12</sup>. BRAIN-MATRIX is a 10-centre trial platform (with  
 138 4 more centres planned) including advanced molecular profiling, which has recruited 395 patients and  
 139 provided the basis for several clinical trials (ARISTOCAT, DETERMINE and 5G). The Minderoo Precision  
 140 Brain Tumour Programme<sup>12</sup> enrolled 230 patients in the first 2 years, exceeding the target of 125  
 141 patients, with whole genome and transcriptome sequencing data provided with a 3-week turnaround  
 142 and a second arm now opening. Other TJBCM programmes include: the Brain Tumour Research Novel

143 Therapeutics Accelerator (BTR-NTA) which launched in 2023 and aims to de-risk drug or device  
 144 development by offering up to 240 hours of free (to academics), systematic multidisciplinary  
 145 evaluation and feedback<sup>13</sup>; NHS clinical neuro-oncology service Centres of Excellence, a designation  
 146 awarded to 17 UK centres between 2020-2022 (next application round in 2024) to acknowledge  
 147 standards of excellence in clinical practice, patient care, staff training opportunities, access to clinical  
 148 trials and research opportunities, which go beyond today's existing guidelines<sup>14</sup>; and a dedicated NHS  
 149 clinical fellowship training programme, which awarded two fellowships in the first round in 2023.  
 150 Neuro-oncology Research Centres of Excellence have also been funded by CRUK (n=2) and BTR (n=4,  
 151 with plans for 3 more)<sup>15-17</sup>. International networks for pre-clinical and clinical studies include UK  
 152 members. The global Glioma Longitudinal AnalySiS (GLASS) consortium<sup>18</sup> analyses longitudinal  
 153 datasets to refine molecular profiling and tumour evolution and includes 3 UK centres, and the Brain  
 154 Liquid Biopsy Consortium<sup>19</sup> was co-founded in the UK and aims to accelerate research and translation  
 155 of neuro-oncology biofluid biomarkers. The EORTC Brain Tumour Group is a European-led clinical trial  
 156 collaborative with UK representation on 6 of its 11 dedicated committees, from which The  
 157 ROAM/EORTC1308 trial for atypical meningioma was facilitated: a UK-led inter-group trial across 59  
 158 sites in the UK, EORTC, and Australia/New Zealand (Trans-Tasmin Radiation Oncology Group  
 159 (TROG))<sup>20</sup>.  
 160 National neuro-oncology conferences are well attended although ideologically segregated –  
 161 principally oriented toward clinicians (e.g. British Neuro-Oncology Society (BNOS) Annual Conference)  
 162 or scientists (e.g. CRUK Brain Tumour Conference). Patient and public involvement and engagement  
 163 (PPIE) in the community is essential. Initiatives such as *brainstrust's* Patient Research Involvement  
 164 Movement (PRIME) bring people closer to research and research closer to funding<sup>21</sup>.  
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**Fig. 2. A)** Survival data for brain cancers in different countries<sup>6</sup> **B)** Age standardised rates (ASR) for brain cancers according to the GLOBOCAN 2022 database version 1.1<sup>9</sup>. The linear regression (blue line) and 95% confidence interval (grey shading) are annotated. **C)** The number of clinical trials that were ongoing in 2019 in different countries<sup>7</sup>.

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*Recommendations:*

- Conferences and events that bring together basic and clinical neuro-oncology, trial methodology expertise, and comprehensive funded PPIE collaboration (SE)
- Clinical trial development in collaboration with international groups (IM)
- Greater collaboration between basic and clinical research, within and between UK centres (IM)
- Integration of accessible and comprehensive biobanking with clinical trial networks (LD)

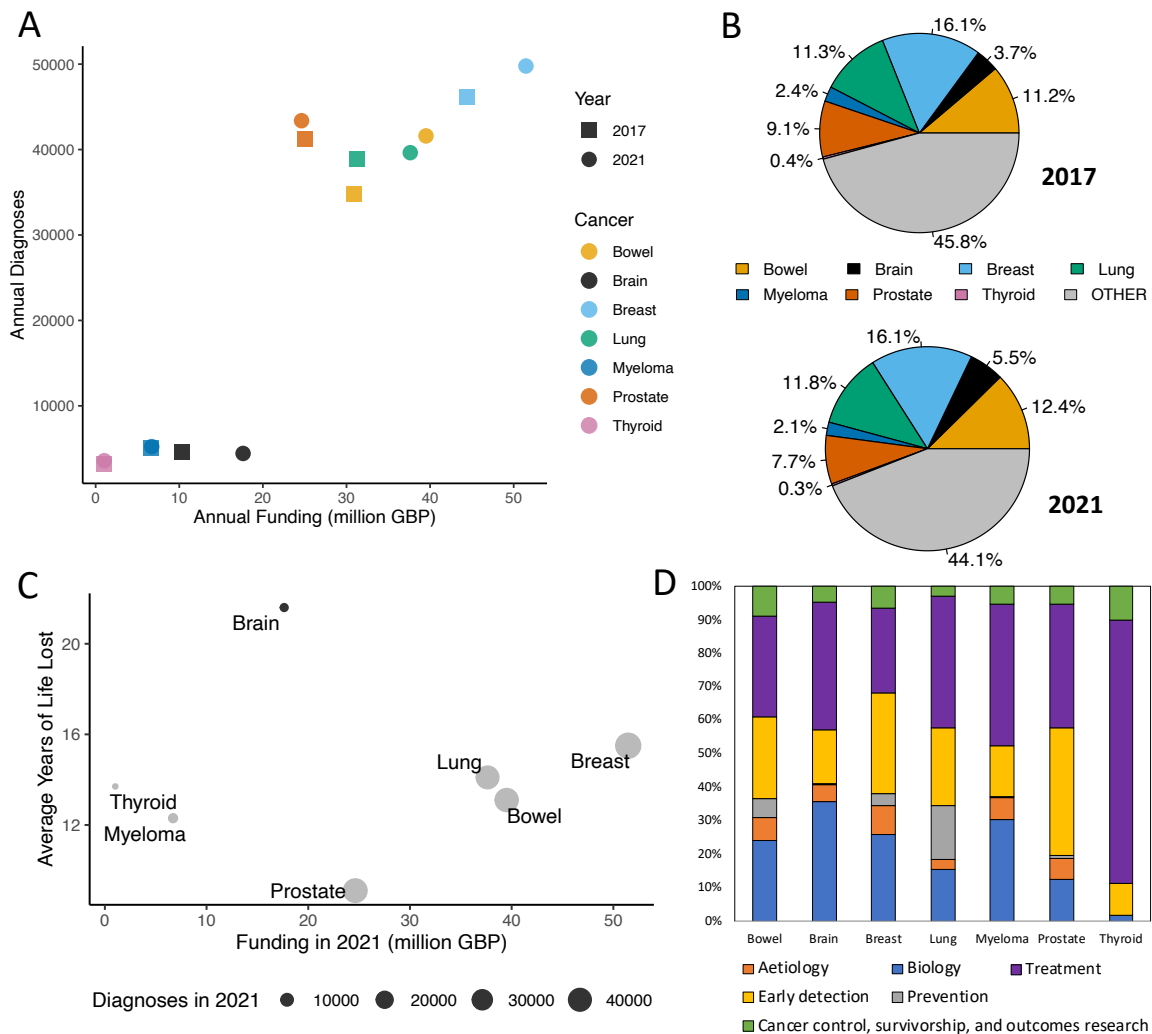
Brain Tumour Research Funding

Despite recently increasing funding levels for brain cancer research, this disease site remains relatively underfunded. Annual NCRI partner<sup>22</sup> funding for brain tumour research increased by £7.4m between 2017 (£10.2m) and 2021 (£17.6m) on par with the increase in funding for breast (£7.0m), bowel (£8.7m) and lung (£6.4m) cancer in the same period (**Fig. 3A**)<sup>23,24</sup>. However, the funding allocated to brain cancer in 2021 still only constituted 5.5% of the total NCRI partner annual spend on cancer research, having risen from 3.7% in 2017 (**Fig. 3B**)<sup>23</sup>. Compare this to breast, bowel and lung cancer for which the allocation has remained consistently high at circa 16%, 12% and 11% of the total budget respectively (**Fig. 3B**)<sup>23</sup>. Whilst **Fig. 3A** indicates that funding allocation is proportional to prevalence, this does not take into account the malignancy of each cancer subtype. Indeed, when funding allocation is plotted according to the average years of life lost, brain cancer is a clear outlier<sup>23,25</sup> (**Fig. 3C**). Inspecting how funding is allocated within cancer subtype, according to the Common Scientific Outline (a 6-tier classification of types of cancer research), we see that a relatively large portion of neuro-oncology research is still focused on understanding the basic biology of the disease, where the more well-funded cancers have more money allocated to earlier detection and prevention research (**Fig. 3D**)<sup>23</sup>. This reflects the complexity of tumours of the brain, but also of the organ itself. Numerous factors, including cell type diversity and idiosyncratic aspects of systems biology, has meant that an in-depth knowledge of the human brain still alludes us. Focused, specific research is still very much needed to understand the human brain and its pathologies, including cancer

More, and more targeted, investment is essential with a change in funding mechanisms and opportunities. For example, integrated research funding that spans the pipeline from discovery science, through translation, to clinical research with a focus on improved patient outcomes. The growth of Collaborative Networks and Initiatives highlights a trend towards funding interdisciplinary groups. Encouraging and rewarding interdisciplinary funding, particularly where accessible and inclusive of early career researchers, is vital for truly translational research to be achieved: this means getting treatments to patients, not simply undertaking a series of disconnected preclinical experiments and clinical studies.

*Recommendations:*

- Brain tumour research should be recognised as a key governmental priority (*cf.* USA Cancer Moonshot) (IM)
- More funders should make brain tumours a strategic focus, prioritising brain tumour-based research that specifically investigates the complexities of this type of cancer in funding calls (IM)
- Ring-fenced funding to support research capacity growth (infrastructure, technology, and people) (IM)
- Increasing the annual investment into brain tumour research to GBP35 million to bring equity with other cancers (LD)
- Facilitate and de-risk collaborative links with private and industry partners to increase funding, drive innovation, and reach the market (LD)



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**Fig. 3.** Data is plotted for some of the most (breast, bowel, lung, prostate) and least (brain, myeloma, thyroid) prevalent cancer subtypes: **A)** The annual research funding allocation by all NCRI partners, plotted according to the number of diagnoses registered, in years ending 2017 and 2021; **B)** The percentage breakdown of the total annual cancer research funding by all NCRI partners for the year ending 2017 (top) or 2021 (bottom); **C)** The annual research funding allocation by all NCRI partners in the year ending 2021 plotted according to the most recently calculated average years of life lost; **D)** The funding allocation by all NCRI partners in the year ending 2021 is broken down according to the percentage spent on each Common Scientific Outline classification of research area.

216 Neuro-oncology Training (Scientific and Clinical)

217 Training in scientific neuro-oncology research faces many challenges: brain cancer biology is uniquely  
 218 complex; the relative disease rarity and accessibility of fresh and fixed tissue limits research samples;  
 219 and there is no suitable single experimental model nor successful bench-to-bedside trajectory. All 47  
 220 UK Masters-level biology programmes with ‘cancer’ or ‘oncology’ in the title<sup>26</sup> cover generalised  
 221 elements of pan-cancer research (genomics, immunology, the tumour microenvironment). More  
 222 specialised cancer-specific research training occurs at the doctoral level, where funding is  
 223 disproportionately allocated to other cancers. This lack of specific training in, and exposure to, basic  
 224 neuro-oncology research, combined with lower funding opportunities, produces fewer desirable  
 225 careers for cancer researchers aiming for independence.

226 Comparable challenges face clinical training. Increasingly complex management of brain  
 227 tumours requires surgery, radiotherapy, and chemotherapy. Advances in these fields necessitate

228 additional ongoing training and development involving multiple specialities. Beyond neurosurgery,  
229 where the pathway is well-defined, there is a paucity of training opportunities for neuro-oncology  
230 clinicians. UK brain tumour management has, historically, been led by clinical oncologists, with limited  
231 time and opportunities to interact with research. Neuro-oncology is not mandatory in the medical  
232 oncology curriculum, leading to a scarcity of early-phase trialists and clinical drug developers with the  
233 expertise to truly accelerate the development of novel therapeutics for brain tumours.

234 A joint UK medical/clinical oncology curriculum has been developed to improve interaction  
235 and alignment between oncology disciplines, however, neuro-oncology remains optional within this  
236 curriculum. Programmes such as the new NIHR/TJBCM Neuro-oncology Fellowship scheme offer  
237 intensive interdisciplinary clinical training. Clinical academic programmes in the UK, from the  
238 specialised foundation programme to clinical fellowships and lectureships, incorporate higher study.  
239 These vary from early, specialty-affiliated (e.g., NIHR Academic Clinical Fellowships) to later,  
240 researcher-initiated (e.g., NIHR and other post-doctoral Clinical Lectureships) programmes. However,  
241 mid-grade and higher speciality training is already lengthy, and academic programmes and/or higher  
242 study extend this. The appropriate balance between clinical and research workloads at the early  
243 career consultant level is also unclear. Ringfencing research time is vital for delivering translational  
244 research, particularly in key supporting specialities such as pathology, genomic medicine and  
245 radiology<sup>12,27</sup>.

246

247 *Recommendations:*

- 248 • High-profile neuro-oncology-focused basic science training initiatives (IM)
- 249 • Greater integration between basic and clinical neuro-oncology training programmes (IM)
- 250 • Greater research training opportunities for all relevant clinical disciplines with programmes that  
251 focus on the skills required to provide high-quality clinical and academic neuro-oncology input  
252 (IM)
- 253 • New higher speciality fellowships that allow trainees to gain translational experiences in neuro-  
254 oncology, combining specialised basic research, clinical trial, and chemo-radiotherapy experience  
255 (LD)
- 256 • Training plans that facilitate high-level dual training, balancing the demands of a clinical workload  
257 and including guidance on securing funding to transition successfully to research independence  
258 (LD)
- 259 • Support across the intermediate transition to research and clinical independence, with greater  
260 flexibility between clinical and research careers and a national commitment to funding early  
261 career consultant-level positions to improve recruitment and retention (LD)
- 262 • Safeguarding research time for senior clinical researchers, with greater stakeholder interactions  
263 between the NHS, Royal Colleges, and academic institutions (LD)

264

## 265 **Research Priorities**

266

### 267 Priority 1: Prompter diagnosis

268 In many cancers, the notion of an ‘early diagnosis’ pertains to identifying the disease in a less mature  
269 state (at a lower ‘stage’ or ‘grade’), which can lead to less intrusive/toxic and/or more effective  
270 treatment. In brain cancer, it is debatable whether diagnosing at *earlier* disease stages impacts  
271 treatment decisions and prognosis. However, it is widely accepted that a *prompter* diagnosis i.e.  
272 shorter time between the development of symptoms of a tumour, irrespective of its stage or grade,  
273 and clinical confirmation of the presence and type of tumour, is beneficial for many reasons<sup>28-30</sup>. Brain  
274 tumours are challenging to diagnose, with idiosyncrasies and barriers at each level from initially  
275 detecting a brain tumour through to the diagnosis of subtype<sup>31</sup>. Presenting symptoms are driven both  
276 by tumour anatomical location and more global effects of tumour growth. The former may produce  
277 stereotypical motor, visual, or speech deficits but the latter are non-specific and secondary to raised  
278 intracranial pressure or regional changes caused by the tumour e.g. headaches, nausea/vomiting,



279 lethargy, behavioural changes, or seizures. The commonality of some non-specific symptoms often  
280 delays patients visiting a doctor until symptoms escalate. Once consulted, medical practitioners often  
281 pursue other more common diagnoses, delaying definitive investigations. Rationing of investigations  
282 such as brain imaging also delays diagnosis. Approximately 2/3 of brain tumours are diagnosed after  
283 an emergency admission to hospital often preceded by several primary care consultations.<sup>32</sup> Only 1%  
284 of patients are diagnosed through the designated NHS England two-week wait suspected cancer  
285 pathway<sup>33</sup>. Campaigns such as ‘HeadSmart’ (The Brain Tumour Charity), ‘Brain Tumour Awareness  
286 Month’, and ‘Wear a Hat Day’ (Brain Tumour Research) are increasing awareness of brain tumour  
287 symptoms with the aspiration of leading to prompter diagnosis.

288 Once the presence of a brain tumour is established, there are subsequent challenges to timely  
289 categorisation. Complementing histopathological assessment, molecular characterisation is central to  
290 brain tumour diagnostic classification<sup>34</sup>. Genomics England and NHS England are working to address  
291 issues with the speed of, and access to, genomic testing. Despite establishing Genomic Laboratory  
292 Hubs in England, there is social and regional inequality in access to molecular profiling across the UK  
293 with inconsistencies in infrastructure, resourcing, funding, and training. More research is needed to  
294 enable prompter diagnosis, such as liquid biopsy, which could be used as part of a primary care work-  
295 up<sup>35</sup>, perhaps even at the point of care.

296

#### 297 *Recommendations:*

- 298 • Work with the Tessa Jowell Equity in Genomics Working group to improve UK-wide access to  
299 genomic testing (SE)
- 300 • Training in the requirements and provision of sufficient biological material for diagnosis  
301 including molecular profiling with standardisation of sample submission processes (SE)
- 302 • Increase public and healthcare provider awareness of brain tumour symptoms (IM)
- 303 • Coordinate with genomic hubs to ensure timely, standardised, easily clinically interpretable  
304 reports (IM)
- 305 • Improve direct access to brain imaging from primary care (IM)
- 306 • Develop novel, non-invasive tools for prompter diagnosis (LD)

307

#### 308 Priority 2: Identify actionable target drivers of malignancy

309 Whilst molecular testing is being adopted for the diagnostic classification of brain tumours (Priority  
310 1), the results do not routinely inform treatment decisions because of limited therapeutically  
311 actionable molecular biomarkers. This results from a limited understanding of genomics of brain  
312 tumours, and the (historical) exclusion of patients with brain tumours from precision medicine  
313 targeted trials.

314 Access to high-quality, well-annotated patient biosamples is essential for identifying target  
315 drivers of malignancy, particularly when co-occurring driver genes typically activate different  
316 collaborating oncogenic pathways. Integrating genomic, epigenomic, transcriptomic, proteomic and  
317 neuroimaging data will be critical to reveal vulnerabilities most amenable to therapeutic targeting.  
318 Disease rarity makes neuro-oncology biobanking relatively costly because the infrastructure needed  
319 is disproportionate to the sample volumes. The resulting sample scarcity for research causes issues of  
320 ownership and access to existing collections. Furthermore, brain bio-banking is often under-  
321 resourced, leading to deficits in: processing to maximise sample usage; collection beyond the tumour  
322 (host, blood, CSF); associated clinical metadata with follow-up; and generation of associated patient-  
323 derived models (see Priority 3). This promotes a negative perception of myriad biobanked samples  
324 sitting unavailable for research, when samples are either not known about, are inaccessible, or lack  
325 sufficient clinical annotation for utility. Even where additional research-allocated samples cannot be  
326 collected, making the genetic data resulting from clinical practice accessible to basic science  
327 researchers, alongside linked clinical metadata and imaging data, would be hugely valuable.

328 In the UK, several initiatives aim to tackle this. BRAIN UK (BRain Archive Information Network  
329 UK)<sup>36,37</sup> is a virtual biobank across a network of NHS Neuropathology Centres, exemplifying the unique

330 UK ability to leverage NHS connectivity. BRAIN UK has generic ethics needed to approve projects and  
 331 coordinate and grant access to archival surplus brain material. However, this is mostly limited to fixed  
 332 tissue and retrospectively collated, centre-specific clinical data owing to a dearth of local  
 333 infrastructure for greater provision. BRAIN MATRIX<sup>38</sup> includes resources to perform a more limited  
 334 collection of frozen adult glioma samples, specifically, and molecularly profile them via NHS England  
 335 Genomic Hubs with linked imaging and clinical data. While centralised tissue cannot be repurposed,  
 336 there is no barrier to using fresh tissue at the site for complementary research techniques such as  
 337 single-cell analyses. Again, this is dependent on local infrastructure. Alongside these national efforts,  
 338 multiple autonomous UK research tissue banks include neuro-oncology collections. These  
 339 independent efforts vary with regard to consenting procedures, types of samples and data collected,  
 340 access, processing, governance, and application requirements. Their coordination would better  
 341 facilitate higher-impact, larger-scale research.

342 Identification of target drivers relies on access to raw data linked to the clinically annotated  
 343 samples and their originating experiments. Dataset generation is often research group-specific,  
 344 requiring significant effort and funding. Academic dissemination and recognition routes discourage  
 345 rapid sharing of core datasets or timely raw data release. Dataset release should itself be a suitably  
 346 credited research output, with appropriate embargoed data usage to protect the originating study.  
 347 International efforts such as The Cancer Genome Atlas<sup>39</sup> and GLASS<sup>18</sup> have championed timely data  
 348 sharing.

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351 *Recommendations:*

- 352 • Develop infrastructure where every patient with brain cancer can contribute to a biobank,  
353 with clinically available molecular testing, and integrate this with clinical trials (LD)
- 354 • Harmonise and consolidate brain tumour tissue banking (**Table 1**) via infrastructure funding  
355 to improve accessibility and availability of linked samples, imaging, and clinical data (LD)
- 356 • Where appropriate, support the transfer of routinely collected samples and data to safe  
357 havens and trusted research environments with suitable governance (LD)
- 358 • Expect and encourage return and linkage of suitable datasets produced from downstream  
359 sample and data processing, partly by making the release of such datasets an appropriately  
360 recognised academic output (LD)

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**Table 1 Specific recommendations for UK biobanking**

Biobanking Aspect	Recommendations
Ethical approval	Harmonised across multiple sites
	Self-governing with generic ethical approval (i.e. applicant does not require project-specific ethical approval)
	Include all forms of analysis (genetic, <i>in vivo</i> , model generation)
	Include industry access with associated cost recovery
	Include fair usage clauses
Informing and consenting patients	Informing and consenting patients should be embedded within the clinical pathways following engagement with neurosurgeons, neuropathologists and neuroradiologists
	Standardised, inclusive information giving (videos) and forms in multiple languages
	Centralised, accessible recording of consent across multiple sites
Resourcing	Multidisciplinary RTBs can link with other disease sites, with potential convergence in pathology departments
	Tiered collection sites would enable biobanking with fewer resources where necessary
Sample Processing	Collection of blood, CSF, saliva, FFPE, fresh tissue

	Harmonised processing SOPs
	Enable future proofing (e.g. single-cell storage)
	Centralised recording of samples across multiple sites
Data Collection	Standardised prospective data collection to include imaging data
	Post-surgery data acquisition at regular intervals to capture short-term (e.g. diagnostic test results) and long-term (e.g. survival) follow-up data
	Adherence to FAIR principles - <a href="https://www.go-fair.org/fair-principles/">https://www.go-fair.org/fair-principles/</a>
Access	Live, open-access database of samples available with forthcoming release schedules
	Unrestricted yet audited access to researchers following suitably reviewed, user-friendly application process
	Access to industry via suitable contractual agreement and cost-recovery

363

364 Priority 3: Use suitable preclinical models and assays

365 Experimental models are needed to: 1) validate the direct involvement of aberrant molecules and/or  
366 mechanisms in pathogenesis as causative rather than consequent for rational prioritisation of drug  
367 development; 2) screen novel therapeutic interventions. Both require the experimental system to  
368 mirror patient biology, or the specific aspect being tested, and this poses a major challenge for brain  
369 tumours<sup>40</sup>. The continued failure of neuro-oncology clinical trials is partly attributable to difficulties in  
370 experimentally modelling brain tumour biology i.e. tumour heterogeneity; tumour microenvironment  
371 (TME); the blood-brain barrier (BBB); and response to standard of care (SOC)<sup>3,41</sup>. Advances in brain  
372 cancer cell culture techniques have led to cell lines that more closely mirror the originating tumour<sup>42</sup>.  
373 These can be used in 2D and 3D systems, with scaffolds and co-cultures to incorporate the TME, and  
374 *in vivo*, but each system models different aspects of tumour biology, and increasing complexity  
375 increases time and cost, forcing trade-offs<sup>43-46</sup>. Organoids and microfluidic *ex vivo* and BBB models  
376 offer great promise for modelling complexity at scale<sup>47-49</sup>. Patient-derived xenotransplants (PDX)  
377 models usually do not fully recapitulate the TME.

378 Most UK institutes cannot derive their own brain cancer models, and there are significant  
379 overheads associated with subsequent genomic and phenotypic characterisation. The CRUK-funded  
380 Glioma Cellular Genetics Resource (GCGR)<sup>50</sup> was established to provide state-of-the-art well-  
381 characterised cell lines to researchers and industry, but such resources are hard to sustain. Developing  
382 and optimising new models is difficult and laborious, precluding any one group from incorporating a  
383 full range into their repertoire. In 2021, the British Neuro-Oncology Society completed a UK survey of  
384 preclinical neuro-oncology models to identify commonly adopted approaches and highlight groups  
385 that are willing to collaborate with and train other researchers<sup>51</sup>. However, barriers to cross-  
386 institutional working, difficulty in retaining ownership (intellectual property), and a lack of  
387 infrastructure and resource funding vastly reduces the impetus to share models across research  
388 groups<sup>52</sup>. GlioModel<sup>53</sup> is a UK-based initiative to develop a preclinical modelling resource, specifically  
389 for target validation in glioblastoma and make it accessible through fee-for-service, although self-  
390 sustainability remains uncertain.

391

392 *Recommendations:*

- 393
- 394 • Underpin initiatives like the GCGR and GlioModel with infrastructure funding that widens  
395 accessibly and ensures longevity<sup>52</sup> (SE)
  - 396 • Standardise model characterisation with regards to molecular profiles, phenotypes, and  
397 response to current SOC (IM)
  - 398 • Tiered approaches to target validation and drug screening are needed, with cascades of  
399 models and assays on a range of scales and complexities, based on the strength of evidence  
for, or biology underlying, the specific target or drug (IM)

- Evolve academic recognition. Researchers focused on model development should be credited on outputs where their models are used while retaining the primacy of the molecule, mechanism, or hypothesis being tested (LD)

#### Priority 4: Provide sufficient evidence of therapeutic opportunity

The adoption of temozolomide as the standard of care for glioblastoma occurred almost 20 years ago<sup>2</sup>, demonstrating the translational failure which casts neuro-oncology as a ‘graveyard’ for novel therapeutics. Among legion contributors, inter- and intra-patient heterogeneity of brain cancer and the blood-brain barrier, which modulates drug delivery, represent major obstacles<sup>54</sup>. Academic research is key to identifying new drug targets (Priority 2), including understanding target biology and links between targets and disease states (Priority 3). However, academic credit and pharmaceutical company value structures do not align. Academic progression prioritises publication and grant funding, often predicated on novelty, while industry prioritises understanding the “right target” which requires thorough, standardised validation (or de-validation) of a scientific hypothesis throughout the lifetime of a project. Furthermore, the ability to de-risk a promising drug target is dependent on the clinical annotation, quantity/quality of patient tissue, and accuracy of the model(s) used in its validation/de-validation. There are problems in both aspects of neuro-oncology research.

Several biopharma companies have adopted the 5R framework (“the right target, right tissue, right safety, right patient, and right commercial potential”) to tackle R&D productivity issues<sup>55,56</sup>. To deliver impactful data packages that can serve as a platform of evidence for the next stages of drug development, research must progress from purely academic exploration to the initiation of efforts to interrogate the drug candidate in the context of pharmacokinetic/pharmacodynamic properties, establishing proof of concept as well as safety/tolerability,<sup>55,57,58</sup>.

The BTR-NTA aims to review and guide the translation and development of novel treatments by an international multidisciplinary group of experts. Independent, transparent advice will help researchers translate a candidate compound that can be rapidly taken forward into clinical trials for patients, optimising trial design, and maximising the likelihood of success<sup>13</sup>.

#### *Recommendations:*

- Synergise academic research and pharmaceutical company requirements via the integration of industry experts into research planning, funding applications, and dissemination events (SE)
- Integration of industry expertise and experiences into neuro-oncology training programmes (perhaps industry experience for research fellows) and consortia (IM)
- Communicate with industry experts on how to overcome intellectual property barriers to facilitate closer working relationships between academic and big biopharma (LD)

#### Priority 5: Develop accessible, innovative, and evidence-based clinical trials

Clinical trials realise translation of novel interventions arising from Priorities 2-4. First-in-man phase 1 trials evaluate safety and test pharmacokinetics with escalated dosing to ascertain the appropriate prescription. Phase 2 trials apply this to a larger cohort to assess safety and indicate activity. Large, randomised phase 3 trials test promising interventions, usually against SOC. This pipeline has limitations for rarer cancers, as reflected in the poor conversion of promising early brain cancer trial results to phase 3 outcomes, and the lack of improvement in overall survival since 2005 (**Table 2**). Some contributing factors are relevant to all clinical trials with others brain cancer specific.

Firstly, patients with brain tumours are excluded from the majority of early phase trials, and tumour agnostic basket trials with <1% of UK recruiting trials listed on the EC trial finder website<sup>59</sup> permitting enrolment of patients with brain tumours. This has historically been attributed to a poor understanding of the blood-brain barrier (and its leakiness) and uncertainty about whether novel agents can achieve meaningful concentrations in the brain. Phase 0 window of opportunity trials which can quantify brain exposure to novel agents, as well as provide pharmacodynamic evidence of

450 pathway modulation will help to identify active drugs more efficiently, but they are challenging to  
 451 deliver.

452 Early phase trials, particularly single-arm trials, typically have small sample sizes which risk  
 453 selection and sampling bias and increased risk of false positives. If surrogate endpoints do not  
 454 correlate with clinical outcomes, they can mislead causing premature and inappropriate  
 455 inclusion/exclusion of candidate interventions. Surrogate biomarkers are lacking and there is  
 456 variability of surgery and radiotherapy, varying by tumour location and proximity to eloquent brain  
 457 and organs at risk, which limits comparator arm comparability. Given the heterogeneity of brain  
 458 cancers, even where targeted agents have been trialled in brain cancer patients, and progressed to  
 459 later-stage registration trials, these have been in an *unselected* patient population and failed to meet  
 460 their endpoints (Table 2). Even with an adaptive clinical trial strategy such as those used in the  
 461 international Phase 2/3 platform GBM AGILE trial (NCT03970447), evaluating multiple regimes in  
 462 *unselected* patients has been disappointing thus far with the initial regimes tested not meeting interim  
 463 efficacy for transition to Phase 3<sup>60</sup>. This suggests an urgent and ambitious need for bespoke novel  
 464 clinical trial designs to specifically overcome the challenges specific to brain tumour trials  
 465 incorporating a seamless transition from Phase 0 surgical trials to biomarker-defined early-phase  
 466 hypotheses testing to later-stage efficacy testing. The MHRA-approved 5G (An AGile Next Generation  
 467 Genomically Guided Glioblastoma Trial) adaptive platform trial (conceived following the NCRI Brain  
 468 Strategic Workshops in 2021) will utilise genomic and transcriptomic data to stratify patients into  
 469 molecular hypotheses testing subprotocols, allowing for agile and rapid *in-flight course correction* and  
 470 refinement of molecular hypotheses as investigators learning as much as they can directly from  
 471 patients enrolled on this platform.

472  
 473 Clinical trial patients commonly do not reflect the wider patient population, with older or comorbid  
 474 patients underrepresented<sup>61</sup>. Trial design will need to be pragmatic eschewing small-scale, single-  
 475 centre and/or single-arm interventions in favour of cross-centre collaboration and/or multi-arm  
 476 settings, to ensure the widening of patient access to biologically appropriate clinical trials and the  
 477 swifter generation of real-world meaningful data impacting patient outcomes. Patient-centred  
 478 outcomes will need to be at the core of all trials.

479

480

481 **Table 2: Clinical outcomes of the major phase 3 randomised controlled trials (RCTs) from 2002-2022**  
 482 **for newly diagnosed glioblastoma.**

Authors	Year	Intervention	PFS (months)	OS (months)	Change in clinical practice?
<i>Unselected</i>					
Stupp et al. <sup>2</sup>	2005	Radiotherapy + Temozolomide (n=287) Radiotherapy (n=286)	6.9 5.0	14.6 12.1	Yes
Gilbert et al. <sup>62</sup>	2014	Bevacizumab + STUPP (n=312) STUPP (n=309)	10.7 7.3	15.7 16.1	No
Chinot et al. <sup>63</sup>	2014	Bevacizumab + STUPP (n=458) STUPP (n=463)	10.6 6.2	16.8 16.7	No
Stupp et al. <sup>64</sup>	2014	Cilengitide + STUPP (n=272) STUPP (n=273)	10.6 7.9	26.3 26.3	No
Westphal et al. <sup>65</sup>	2015	Nimotuzumab + STUPP (n=71) STUPP (n=71)	7.7 5.8	22.3 19.6	No
Weller et al. <sup>66</sup>	2017	Rindopepimut + STUPP (n=371) STUPP (n=374)	8.0 7.4	20.1 20.0	No
Stupp et al. <sup>67</sup>	2017	TTF + STUPP (n=466)	6.7	20.9	Yes*

		STUPP (n=229)	4.0	16.0	
<i>Biomarker selected</i>					
Herrlinger et al. <sup>68</sup>	2019	<i>Methylated MGMT</i> Lomustine + STUPP (n=66) STUPP (n=63)	16.7 16.7	48.1 31.4	No
Lim et al	2022	<i>Methylated MGMT</i> Nivolumab + STUPP STUPP	10.6 10.3	28.9 32.1	No
Lassmann et al	2023	<i>EGFR amplified (FISH)<sup>#</sup></i> STUPP + Depatux-M (323) STUPP (n=316)	8.0 6.3	18.9 18.7	No

483 PFS = progression-free survival; OS = overall survival; STUPP = Fractionated radiotherapy with  
484 concomitant and adjuvant Temozolomide; TTF = Tumour Treating Fields; \*in some healthcare settings  
485 (not approved by NICE in UK based on failure to meet QALY threshold); <sup>#</sup>EGFR FISH assay selected for  
486 both EGFR WT and EGFRvIII amplified tumours which were included in the study despite the binding  
487 domain for Depatux-M being lost in EGFRvIII.

488

489 *Recommendations:*

- 490 • Prioritise research and validation of reliable intermediate or surrogate markers, including
- 491 biomarkers, that can be used to guide early interim stop/go decision-making for novel
- 492 interventions, and which may translate as companion diagnostics for rational clinical delivery (IM)
- 493 • Adopt innovative early-phase clinical trial designs (e.g., window, basket, umbrella, platform) that
- 494 have been successful in other tumours (IM)
- 495 • Prioritise precision medicine approaches with brain penetrant agents to develop a stratified
- 496 personalised approach for brain tumours (LD)
- 497 • Champion the inclusion of patients with brain tumours in early-phase clinical trials/basket trials of
- 498 novel agents with biological rationale (LD)
- 499 • Ambitious scaling up of clinical trial availability aiming for every patient with brain cancer to have
- 500 access to clinical trials (LD)

501

502

503 Priority 6: Treat every patient as a research patient

504 Only 5% of brain tumour patients are entering the limited number of trials available, partly from a lack  
505 of up-to-date clinical trial databases but also the variability in access. The latter results from cross-  
506 centre variation in infrastructure, resources, and capacity, including time allocation for the trial leads  
507 and research nurse support. Improving outcomes needs the right people to drive change, requiring  
508 sufficient time allocation and remuneration. This is unsustainable: recruitment and retention of  
509 (clinical) academics requires suitable rewards. In addition, whilst some may not be eligible for trials,  
510 every patient should be offered to opportunity to donate samples, imaging and clinical metadata to  
511 research.

512 The analysis and interpretation of outcome measures, low adherence, and missing data are  
513 methodological challenges. The current focus on system-wide delivery and outcome measurement  
514 loses sight of the person living with the brain tumour and devalues what matters to them. Patients  
515 are more than their clinical data: e.g. their perception of their health, what motivates or negates  
516 behaviour changes, or how other life events and stressors confound the maintenance of health and  
517 well-being. Yet patient involvement in research remains fragmented and lacks strategic overview. The  
518 multiplication of therapies means more trials, necessitating a paradigm shift in the measurement of  
519 health-related quality of life (HRQoL). The disproportionate focus on outcomes limits understanding  
520 of what individual patients want to achieve. COBRA and COSMIC are patient-centred clinical trials co-  
521 developed with patient and carer stakeholders that are starting to move these goalposts, ensuring

522 that outcome sets are truly meaningful to patients in the real world<sup>69,70</sup>. With personalised medicine,  
523 patients experience different clinical journeys: one size no longer fits all.

524 High rates of physical and cognitive morbidity require alternative supportive interventions to  
525 address the impact of the tumour and its treatment<sup>71,72</sup>. Challenges with discerning tumour-driven  
526 and treatment-driven symptoms are compounded by uncertain disease trajectories. Symptoms cover  
527 a broad spectrum: people can exhibit apathy and indifference through to egocentrism, disinhibition,  
528 and aggression. Decline can be insidious or take only weeks, and tools to measure it, while validated,  
529 are not universal necessitating multiple assessments in a variety of forms.

530

531 *Recommendations:*

- 532 • To ensure meaningful involvement, it is important to consider “how much” patient involvement  
533 is included but also “how, why, and when” (IM)
- 534 • Encourage availability and comparability of routine healthcare data to facilitate “care-based  
535 evidence” to complement evidence-based care (IM)
- 536 • Increase trial delivery capacity across the UK by improving infrastructure (LD)
- 537 • Every patient is a research patient, for their whole trajectory, for all brain tumours (LD)

538

539 Priority 7: Facilitate living beyond a brain tumour

540 The UK is strategically well-placed to contribute to and lead research into survivorship, quality of life,  
541 and patient-reported outcomes<sup>73</sup>. Several centres have produced world-leading outputs in the last  
542 decade with international collaborators. The James Lind Alliance produced a consensus priority list  
543 highlighting ‘quality of life’ questions about lifestyle factors, interval scanning, early referral to  
544 palliative care, the study of late effects, interventions for carers, and strategies for managing fatigue<sup>4</sup>.  
545 Numerous routes for grant funding exist: The Brain Tumour Charity’s dedicated Quality of Life research  
546 grant call funded BT-LIFE, an innovative UK pilot trial of lifestyle interventions for fatigue that recently  
547 published positive results<sup>74</sup>, and the NIHR funded SPRING, a phase 3 trial of levetiracetam prophylaxis  
548 of epilepsy in seizure-naïve patients with newly-diagnosed glioma<sup>75</sup>.

549 Notwithstanding these UK initiatives, survivorship and outcomes research received just 5% of  
550 total NCRI partner spend on brain tumour research in 2021 (**Fig. 3D**), potentially limiting  
551 improvements. Increasing proportional spending requires a shift away from low-impact observational  
552 studies. Although single-centre observational studies are more accessible to trainees or non-career  
553 academics, their analysis is typically confounded by the high number of variables and small sample  
554 sizes. The clinical impact of observational studies is limited and these proposals struggle to attract  
555 funding. Large-scale, collaborative epidemiology or data-linkage studies and RCTs are robust to these  
556 limitations and should be prioritised. Glioma patients also have cognitive impairment, fatigue, and  
557 complex often toxic treatments that can directly and indirectly affect quality of life. Challenges to  
558 clinical trials in these areas require strong mentorship and guidance to support and improve the  
559 methodological quality of proposals.

560 Horizon scanning predicts an increase in early-phase intervention trials (especially non-  
561 pharmacological) to improve survivorship quality of life. In anticipation, we must investigate how to  
562 encourage behavioural change in brain tumour patients, so that effective interventions can be  
563 implemented.

564

565 *Recommendations:*

- 566 • Remunerate clinicians to lead research by increasing the number of UK grant schemes that  
567 cover a proportion of PI salary (SE)
- 568 • Shift metrics from preserving life to enhancing life (SE)
- 569 • Engage with funders to encourage and develop calls prioritising large-scale epidemiology and  
570 RCTs (IM)
- 571 • Leverage existing infrastructure and networks to increase multicentre collaborations (IM)
- 572 • Quality of life research is key, compelling a shift from decision-sharing to option-sharing (IM)

573

574 **Conclusion**

575 Brain cancer is arguably the worst form of cancer, owing to dismal prognosis and often severe impacts  
576 on quality of life. There are inherent challenges to brain tumour research, owing to the complex nature  
577 of the disease, that are shared worldwide. The UK is densely populated and has a unique healthcare  
578 system, potentially providing the opportunity to address, and even overcome, some of these  
579 challenges. Whilst there will be key similarities and shared challenges for paediatric brain tumour  
580 research in the UK, it is noted that there will also be significant differences and unique bottlenecks  
581 that have not been covered herein. We hope that the recommendations made in this position paper  
582 can inspire UK reform, and provide focal points for future UK funding calls and partnerships, to  
583 accelerate progress towards better and longer life for adult brain cancer patients across the whole  
584 world.

585

586 **References**

587

- 588 1. Cancer Research UK. Brain, other CNS and intracranial tumours statistics. Accessed  
589 22nd March, 2023. [https://www.cancerresearchuk.org/health-professional/cancer-](https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours)  
590 [statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours](https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours)
- 591 2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and  
592 adjuvant temozolomide for glioblastoma. *N Engl J Med.* Mar 10 2005;352(10):987-96.  
593 doi:10.1056/NEJMoa043330
- 594 3. Aldape K, Brindle KM, Chesler L, et al. Challenges to curing primary brain tumours. *Nat*  
595 *Rev Clin Oncol.* Aug 2019;16(8):509-520. doi:10.1038/s41571-019-0177-5
- 596 4. National Institute of Health Research: James Lind Alliance. Neuro-oncology. Accessed  
597 22.12.2022, <https://www.jla.nihr.ac.uk/priority-setting-partnerships/neuro-oncology/>
- 598 5. Brain Tumour Research. All-Party Parliamentary Group on Brain Tumours. Accessed  
599 26th March 2023, 2023. [https://www.braintumourresearch.org/campaigning/appg-on-brain-](https://www.braintumourresearch.org/campaigning/appg-on-brain-tumours)  
600 [tumours](https://www.braintumourresearch.org/campaigning/appg-on-brain-tumours)
- 601 6. Girardi F, Matz M, Stiller C, et al. Global survival trends for brain tumors, by histology:  
602 analysis of individual records for 556,237 adults diagnosed in 59 countries during 2000-2014  
603 (CONCORD-3). *Neuro Oncol.* Mar 14 2023;25(3):580-592. doi:10.1093/neuonc/noac217
- 604 7. Kong BY, Carter C, Nowak AK, et al. Barriers and potential solutions to international  
605 collaboration in neuro-oncology clinical trials: Challenges from the Australian perspective.  
606 *Asia Pac J Clin Oncol.* Jun 2022;18(3):259-266. doi:10.1111/ajco.13606
- 607 8. Brain GBD, Other CNSCC. Global, regional, and national burden of brain and other CNS  
608 cancer, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*  
609 *Neurol.* Apr 2019;18(4):376-393. doi:10.1016/S1474-4422(18)30468-X
- 610 9. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates  
611 of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* May  
612 2021;71(3):209-249. doi:10.3322/caac.21660
- 613 10. National Health Service. Be Part of Research. Accessed 22nd March, 2023.  
614 <https://bepartofresearch.nihr.ac.uk/results/search-results>
- 615 11. Watts C, Savage J, Patel A, et al. Protocol for the Tessa Jowell BRAIN MATRIX Platform  
616 Study. *BMJ Open.* Sep 8 2022;12(9):e067123. doi:10.1136/bmjopen-2022-067123



- 617 12. Cancer Research UK. *Creating Time for Research*. 2021.  
618 [https://www.cancerresearchuk.org/sites/default/files/creating\\_time\\_for\\_research\\_februar](https://www.cancerresearchuk.org/sites/default/files/creating_time_for_research_februar_y_2021_-_full_report-v2.pdf)  
619 [y\\_2021 - full report-v2.pdf](https://www.cancerresearchuk.org/sites/default/files/creating_time_for_research_februar_y_2021_-_full_report-v2.pdf)
- 620 13. Tessa Jowell Brain Cancer Mission. Brain Tumour Research Novel Therapeutics  
621 Accelerator (BTR- NTA). Accessed 24th March, 2023.  
622 <https://www.tessajowellbraincancermission.org/strategic-programmes/btr-nta/>
- 623 14. Tessa Jowell Brain Cancer Mission. Tessa Jowell Centre of Excellence for Adults.  
624 [www.tessajowellbraincancermission.org/strategic-programmes/tessa-jowell-centres-of-](http://www.tessajowellbraincancermission.org/strategic-programmes/tessa-jowell-centres-of-excellence)  
625 [excellence](http://www.tessajowellbraincancermission.org/strategic-programmes/tessa-jowell-centres-of-excellence)
- 626 15. University of Edinburgh. CRUK Brain Tumour Centre of Excellence. Accessed 22nd  
627 March, 2023. <https://www.ed.ac.uk/cancer-centre/cruk-brain-tumour-centre-of-excellence>
- 628 16. University College London. CRUK Brain Tumour Centre of Excellence.  
629 [https://www.ucl.ac.uk/cancer/research/centres-and-networks/cruk-brain-tumour-centre-](https://www.ucl.ac.uk/cancer/research/centres-and-networks/cruk-brain-tumour-centre-excellence/cruk-brain-tumour-centre)  
630 [excellence/cruk-brain-tumour-centre](https://www.ucl.ac.uk/cancer/research/centres-and-networks/cruk-brain-tumour-centre-excellence/cruk-brain-tumour-centre)
- 631 17. Brain Tumour Research. Brain Tumour Research Centres of Excellence.  
632 <https://www.braintumourresearch.org/research/centres-of-excellence>
- 633 18. The GLASS Consortium. Glioma through the looking GLASS: molecular evolution of  
634 diffuse gliomas and the Glioma Longitudinal Analysis Consortium. *Neuro-Oncology*.  
635 2018;20(7):873-884. doi:10.1093/neuonc/noy020
- 636 19. Brain Liquid Biopsy Consortium. Brain Liquid Biopsy Consortium. Accessed 23rd Aug,  
637 2023. <https://brainlbc.org>
- 638 20. Jenkinson MD, Javadpour M, Haylock BJ, et al. The ROAM/EORTC-1308 trial: Radiation  
639 versus Observation following surgical resection of Atypical Meningioma: study protocol for a  
640 randomised controlled trial. *Trials*. Nov 14 2015;16:519. doi:10.1186/s13063-015-1040-3
- 641 21. brainstrust. Patient Research Involvement Movement (PRIME). Accessed 22nd March,  
642 2023. <https://brainstrust.org.uk/about-brainstrust/brain-tumour-research/prime/>
- 643 22. National Cancer Research Institute. Our Partners. Accessed 25th March, 2023.  
644 <https://www.ncri.org.uk/about-us/our-partners/>
- 645 23. NCRI. Cancer Research Database. 4th March 2024, [https://www.ncri.org.uk/how-we-](https://www.ncri.org.uk/how-we-work/cancer-research-database/)  
646 [work/cancer-research-database/](https://www.ncri.org.uk/how-we-work/cancer-research-database/)
- 647 24. Statistics OfN. Cancer registration statistics, England.  
648 [https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsa](https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland)  
649 [nddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland](https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland)
- 650 25. Ahmad AS, Offman J, Delon C, North BV, Shelton J, Sasieni PD. Years of life lost due to  
651 cancer in the United Kingdom from 1988 to 2017. *Br J Cancer*. Nov 2023;129(10):1558-1568.  
652 doi:10.1038/s41416-023-02422-8
- 653 26. FindAUniversity Ltd. FindAMasters. Accessed 22.12.2022.  
654 <https://www.findamasters.com>
- 655 27. Corrected oral evidence: Clinical academics in the NHS (2022).

- 656 28. brainstrust. *Earlier, prompt or faster diagnosis of a brain tumour?* 2023.  
657 [https://c6q4s2z2.rocketcdn.me/wp-content/uploads/2023/03/brainstrust-faster-diagnosis-](https://c6q4s2z2.rocketcdn.me/wp-content/uploads/2023/03/brainstrust-faster-diagnosis-27.03.23-1.pdf)  
658 [27.03.23-1.pdf](https://c6q4s2z2.rocketcdn.me/wp-content/uploads/2023/03/brainstrust-faster-diagnosis-27.03.23-1.pdf)
- 659 29. The Brain Tumour Charity. *Brain Tumours: Fighting for Faster Diagnosis.* 2023.  
660 [https://assets.thebraintumourcharity.org/live/uploads/2023/03/Brain-Tumours-Fighting-](https://assets.thebraintumourcharity.org/live/uploads/2023/03/Brain-Tumours-Fighting-for-Faster-Diagnosis.pdf)  
661 [for-Faster-Diagnosis.pdf](https://assets.thebraintumourcharity.org/live/uploads/2023/03/Brain-Tumours-Fighting-for-Faster-Diagnosis.pdf)
- 662 30. National Cancer Research Institute. *Position Statement on Early Diagnosis of Brain*  
663 *Tumours.* 2023. [https://www.ncri.org.uk/wp-content/uploads/NCRI-Brain-Group-Position-](https://www.ncri.org.uk/wp-content/uploads/NCRI-Brain-Group-Position-Paper-2023.pdf)  
664 [Paper-2023.pdf](https://www.ncri.org.uk/wp-content/uploads/NCRI-Brain-Group-Position-Paper-2023.pdf)
- 665 31. Walker D, Hamilton W, Walter FM, Watts C. Strategies to accelerate diagnosis of  
666 primary brain tumors at the primary-secondary care interface in children and adults. *CNS*  
667 *Oncol.* Sep 2013;2(5):447-62. doi:10.2217/cns.13.36
- 668 32. Penfold C, Joannides AJ, Bell J, Walter FM. Diagnosing adult primary brain tumours:  
669 can we do better? *Br J Gen Pract.* Jun 2017;67(659):278-279. doi:10.3399/bjgp17X691277
- 670 33. Ellis-Brookes L, McPhail S, Ives A, et al. Routes to diagnosis for cancer - determining  
671 the patient journey using multiple routine data sets. *Br J Cancer.* Oct 9 2012;107(8):1220-6.  
672 doi:10.1038/bjc.2012.408
- 673 34. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the  
674 Central Nervous System: a summary. *Neuro-Oncology.* 2021;23(8):1231-1251.  
675 doi:10.1093/neuonc/noab106
- 676 35. Brennan PM, Butler HJ, Christie L, et al. Early diagnosis of brain tumours using a novel  
677 spectroscopic liquid biopsy. *Brain Commun.* 2021;3(2):fcab056.  
678 doi:10.1093/braincomms/fcab056
- 679 36. Nicoll JAR, Bloom T, Clarke A, Boche D, Hilton D. BRAIN UK: Accessing NHS tissue  
680 archives for neuroscience research. *Neuropathol Appl Neurobiol.* Feb 2022;48(2):e12766.  
681 doi:10.1111/nan.12766
- 682 37. University of Southampton. BRAIN UK. Accessed 30.01.2023,  
683 <https://www.southampton.ac.uk/brainuk/about/index.page>
- 684 38. University of Birmingham. Tessa Jowell BRAIN MATRIX. Accessed 30.01.2023,  
685 <https://www.birmingham.ac.uk/research/crcctu/trials/brain-matrix/index.aspx>
- 686 39. Cancer Genome Atlas Research N. Comprehensive genomic characterization defines  
687 human glioblastoma genes and core pathways. *Nature.* Oct 23 2008;455(7216):1061-8.  
688 doi:10.1038/nature07385
- 689 40. Rominiyi O, Al-Tamimi Y, Collis SJ. The 'Ins and Outs' of Early Preclinical Models for  
690 Brain Tumor Research: Are They Valuable and Have We Been Doing It Wrong? *Cancers (Basel).*  
691 Mar 25 2019;11(3)doi:10.3390/cancers11030426
- 692 41. Akter F, Simon B, de Boer NL, Redjal N, Wakimoto H, Shah K. Pre-clinical tumor models  
693 of primary brain tumors: Challenges and opportunities. *Biochim Biophys Acta Rev Cancer.* Jan  
694 2021;1875(1):188458. doi:10.1016/j.bbcan.2020.188458
- 695 42. Lee J, Kotliarova S, Kotliarov Y, et al. Tumor stem cells derived from glioblastomas  
696 cultured in bFGF and EGF more closely mirror the phenotype and genotype of primary tumors

697 than do serum-cultured cell lines. *Cancer Cell*. May 2006;9(5):391-403.  
698 doi:10.1016/j.ccr.2006.03.030

699 43. Gomez-Oliva R, Dominguez-Garcia S, Carrascal L, et al. Evolution of Experimental  
700 Models in the Study of Glioblastoma: Toward Finding Efficient Treatments. *Front Oncol*.  
701 2020;10:614295. doi:10.3389/fonc.2020.614295

702 44. Wanigasekara J, Cullen PJ, Bourke P, Tiwari B, Curtin JF. Advances in 3D culture  
703 systems for therapeutic discovery and development in brain cancer. *Drug Discov Today*. Nov  
704 1 2022;103426. doi:10.1016/j.drudis.2022.103426

705 45. Caragher S, Chalmers AJ, Gomez-Roman N. Glioblastoma's Next Top Model: Novel  
706 Culture Systems for Brain Cancer Radiotherapy Research. *Cancers (Basel)*. Jan 4  
707 2019;11(1)doi:10.3390/cancers11010044

708 46. Gomez-Roman N, Chong MY, Chahal SK, et al. Radiation Responses of 2D and 3D  
709 Glioblastoma Cells: A Novel, 3D-specific Radioprotective Role of VEGF/Akt Signaling through  
710 Functional Activation of NHEJ. *Mol Cancer Ther*. Feb 2020;19(2):575-589. doi:10.1158/1535-  
711 7163.MCT-18-1320

712 47. Olubajo F, Achawal S, Greenman J. Development of a Microfluidic Culture Paradigm  
713 for Ex Vivo Maintenance of Human Glioblastoma Tissue: A New Glioblastoma Model? *Transl*  
714 *Oncol*. Jan 2020;13(1):1-10. doi:10.1016/j.tranon.2019.09.002

715 48. Vinel C, Rosser G, Guglielmi L, et al. Comparative epigenetic analysis of tumour  
716 initiating cells and syngeneic EPSC-derived neural stem cells in glioblastoma. *Nat Commun*.  
717 Oct 21 2021;12(1):6130. doi:10.1038/s41467-021-26297-6

718 49. Zwain T, Alder JE, Sabagh B, Shaw A, Burrow AJ, Singh KK. Tailoring functional  
719 nanostructured lipid carriers for glioblastoma treatment with enhanced permeability through  
720 in-vitro 3D BBB/BBTB models. *Mater Sci Eng C Mater Biol Appl*. Feb 2021;121:111774.  
721 doi:10.1016/j.msec.2020.111774

722 50. University of Edinburgh. Glioma Cellular Genetics Resource. Accessed 22.12.2022,  
723 2012. [https://www.ed.ac.uk/cancer-centre/cruk-brain-tumour-centre-of-excellence/glioma-  
724 cellular-genetics-resource](https://www.ed.ac.uk/cancer-centre/cruk-brain-tumour-centre-of-excellence/glioma-cellular-genetics-resource)

725 51. British Neuro-Oncological Society. Preclinical Models.  
726 <https://www.bnos.org.uk/preclinical-models/>

727 52. Fougner V, Hasselbalch B, Lassen U, Weischenfeldt J, Poulsen HS, Urup T.  
728 Implementing targeted therapies in the treatment of glioblastoma: Previous shortcomings,  
729 future promises, and a multimodal strategy recommendation. *Neurooncol Adv*. Jan-Dec  
730 2022;4(1):vdac157. doi:10.1093/noajnl/vdac157

731 53. GlioModel. GlioModel: A Preclinical Modelling Resource for High Grade Glioma.  
732 Accessed 22.12.2022, 2022. <https://gliomodel.org.uk>

733 54. Sokolov AV, Dostdar SA, Attwood MM, et al. Brain Cancer Drug Discovery: Clinical  
734 Trials, Drug Classes, Targets, and Combinatorial Therapies. *Pharmacol Rev*. Oct 2021;73(4):1-  
735 32. doi:10.1124/pharmrev.121.000317

736 55. Morgan P, Brown DG, Lennard S, et al. Impact of a five-dimensional framework on  
737 R&D productivity at AstraZeneca. *Nat Rev Drug Discov*. Mar 2018;17(3):167-181.  
738 doi:10.1038/nrd.2017.244

- 739 56. Fernando K, Menon S, Jansen K, et al. Achieving end-to-end success in the clinic:  
740 Pfizer's learnings on R&D productivity. *Drug Discov Today*. Mar 2022;27(3):697-704.  
741 doi:10.1016/j.drudis.2021.12.010
- 742 57. Shimura H, Masuda S, Kimura H. Research and development productivity map:  
743 visualization of industry status. *J Clin Pharm Ther*. Apr 2014;39(2):175-80.  
744 doi:10.1111/jcpt.12126
- 745 58. Muller S, Weigelt J. Open-access public-private partnerships to enable drug discovery-  
746 -new approaches. *IDrugs*. Mar 2010;13(3):175-80.
- 747 59. Experimental Cancer Medicine Centre Network. Experimental Cancer Trial Finder  
748 Accessed 23rd Aug, 2023. <https://www.ecmcnetwork.org.uk/ec-trial-finder>
- 749 60. Alexander BM, Ba S, Berger MS, et al. Adaptive Global Innovative Learning  
750 Environment for Glioblastoma: GBM AGILE. *Clin Cancer Res*. Feb 15 2018;24(4):737-743.  
751 doi:10.1158/1078-0432.CCR-17-0764
- 752 61. Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment  
753 Practices, and Trial Designs Guidance for Industry (2020).
- 754 62. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for  
755 newly diagnosed glioblastoma. *N Engl J Med*. Feb 20 2014;370(8):699-708.  
756 doi:10.1056/NEJMoa1308573
- 757 63. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for  
758 newly diagnosed glioblastoma. *N Engl J Med*. Feb 20 2014;370(8):709-22.  
759 doi:10.1056/NEJMoa1308345
- 760 64. Stupp R, Hegi ME, Gorlia T, et al. Cilengitide combined with standard treatment for  
761 patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC  
762 EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet*  
763 *Oncol*. Sep 2014;15(10):1100-8. doi:10.1016/S1470-2045(14)70379-1
- 764 65. Westphal M, Heese O, Steinbach JP, et al. A randomised, open label phase III trial with  
765 nimotuzumab, an anti-epidermal growth factor receptor monoclonal antibody in the  
766 treatment of newly diagnosed adult glioblastoma. *Eur J Cancer*. Mar 2015;51(4):522-532.  
767 doi:10.1016/j.ejca.2014.12.019
- 768 66. Weller M, Butowski N, Tran DD, et al. Rindopepimut with temozolomide for patients  
769 with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-  
770 blind, international phase 3 trial. *Lancet Oncol*. Oct 2017;18(10):1373-1385.  
771 doi:10.1016/S1470-2045(17)30517-X
- 772 67. Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance  
773 Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With  
774 Glioblastoma: A Randomized Clinical Trial. *JAMA*. Dec 19 2017;318(23):2306-2316.  
775 doi:10.1001/jama.2017.18718
- 776 68. Herrlinger U, Tzaridis T, Mack F, et al. Lomustine-temozolomide combination therapy  
777 versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with  
778 methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial.  
779 *Lancet*. Feb 16 2019;393(10172):678-688. doi:10.1016/S0140-6736(18)31791-4

- 780 69. Millward CP, Armstrong TS, Barrington H, et al. Development of 'Core Outcome Sets'  
781 for Meningioma in Clinical Studies (The COSMIC Project): protocol for two systematic  
782 literature reviews, eDelphi surveys and online consensus meetings. *BMJ Open*. May 9  
783 2022;12(5):e057384. doi:10.1136/bmjopen-2021-057384
- 784 70. Retzer A, Sivell S, Scott H, et al. Development of a core outcome set and identification  
785 of patient-reportable outcomes for primary brain tumour trials: protocol for the COBra study.  
786 *BMJ Open*. Sep 30 2022;12(9):e057712. doi:10.1136/bmjopen-2021-057712
- 787 71. Collins A, Lethborg C, Brand C, et al. The challenges and suffering of caring for people  
788 with primary malignant glioma: qualitative perspectives on improving current supportive and  
789 palliative care practices. *BMJ Support Palliat Care*. Mar 2014;4(1):68-76.  
790 doi:10.1136/bmjspcare-2012-000419
- 791 72. Piil K, Juhler M, Jakobsen J, Jarden M. Controlled rehabilitative and supportive care  
792 intervention trials in patients with high-grade gliomas and their caregivers: a systematic  
793 review. *BMJ Support Palliat Care*. Mar 2016;6(1):27-34. doi:10.1136/bmjspcare-2013-000593
- 794 73. Kurian KM, Jenkinson MD, Brennan PM, et al. Brain tumor research in the United  
795 Kingdom: current perspective and future challenges. A strategy document from the NCRI  
796 Brain Tumor CSG. *Neurooncol Pract*. Mar 2018;5(1):10-17. doi:10.1093/nop/npx022
- 797 74. Rooney AG, Hewins W, Walker A, et al. Lifestyle coaching is feasible in fatigued brain  
798 tumor patients: A phase I/feasibility, multi-center, mixed-methods randomized controlled  
799 trial. *Neuro-Oncology Practice*. 2022:npac086. doi:10.1093/nop/npac086
- 800 75. Jenkinson MD, Watts C, Marson AG, et al. TM1-1 Seizure prophylaxis in gliomas  
801 (SPRING): a phase III randomised controlled trial comparing prophylactic levetiracetam versus  
802 no prophylactic anti-epileptic drug in glioma surgery. *Journal of Neurology, Neurosurgery*  
803 *& Psychiatry*. 2019;90(3):e8. doi:10.1136/jnnp-2019-ABN.25
- 804
- 805
- 806