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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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37
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.

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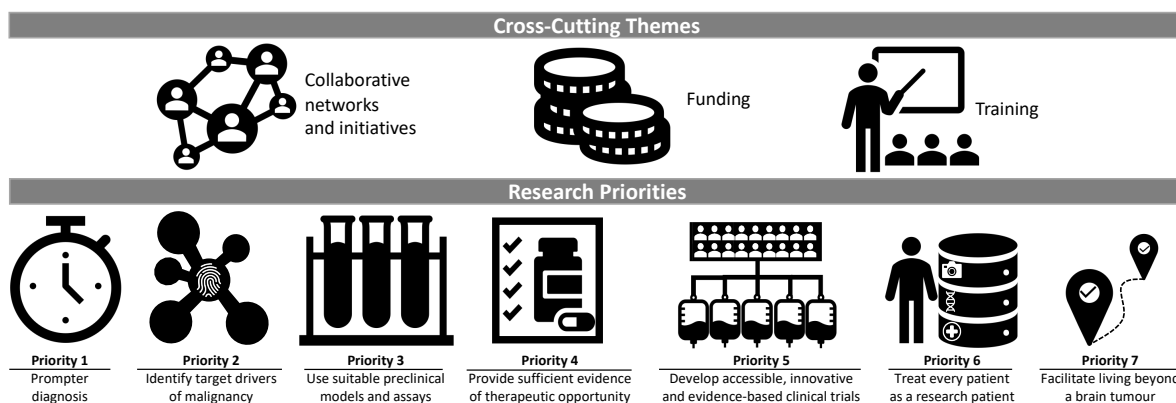
64 Brain cancer is considered to be a rare disease, but it leads to more years of life loss per patient than
65 any other cancer, and UK incidence rates are on the rise¹. The trauma and tragedy that so often
66 surrounds a brain cancer diagnosis led to an increase in UK public awareness, as distressing 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 years¹ and this has not improved in over 20
74 years². 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 2019³, the National Institute of Health Care and Research (NIHR)-funded James
86 Lind Alliance in 2015⁴, and the UK All-Party Parliamentary Group on Brain Tumours (APPGBT) in early
87 2023⁵. 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 worldwide⁶⁻⁹. 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^{6,8} (**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 worldwide⁹. However, the data does highlight that the UK has relatively fewer
 109 clinical trials compared with these other countries⁷ (**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).



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

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 120 **Cross-cutting themes**

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 122 Collaborative Networks and Initiatives

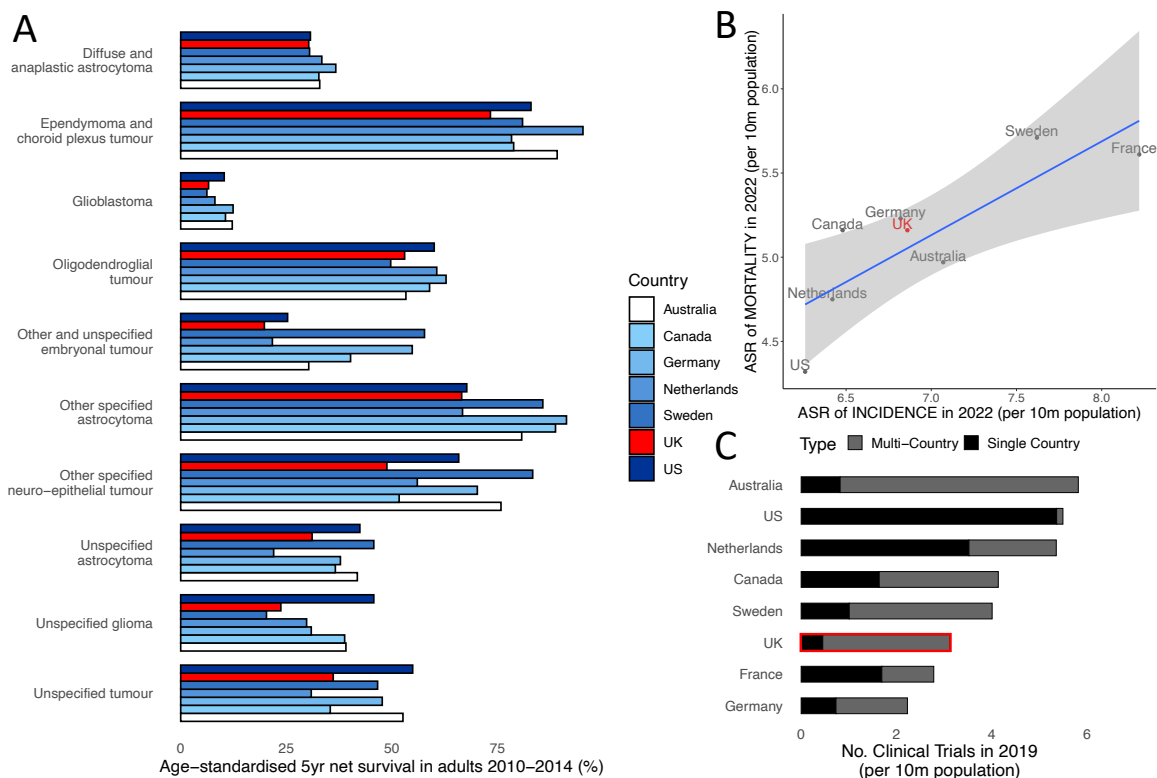
123 The UK is well-placed to lead translational research and innovative trials with global impacts on patient
 124 outcomes. The NHS offers a unified healthcare service covering a population of over 60 million, with
 125 existing links between cancer centres, neuroscience centres, and academic units. 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'¹⁰. 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-MATRIX¹¹ and
 137 the Minderoo Precision Brain Tumour Programme¹². 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 Programme¹² 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 feedback¹³; 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 guidelines¹⁴; 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)¹⁵⁻¹⁷. International networks for pre-clinical and clinical studies include UK
 152 members. The global Glioma Longitudinal AnalySiS (GLASS) consortium¹⁸ analyses longitudinal
 153 datasets to refine molecular profiling and tumour evolution and includes 3 UK centres, and the Brain
 154 Liquid Biopsy Consortium¹⁹ 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))²⁰.

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 funding²¹.

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Fig. 2. A) Survival data for brain cancers in different countries⁶ **B)** Age standardised rates (ASR) for brain cancers according to the GLOBOCAN 2022 database version 1.1⁹. 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 countries⁷.

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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)

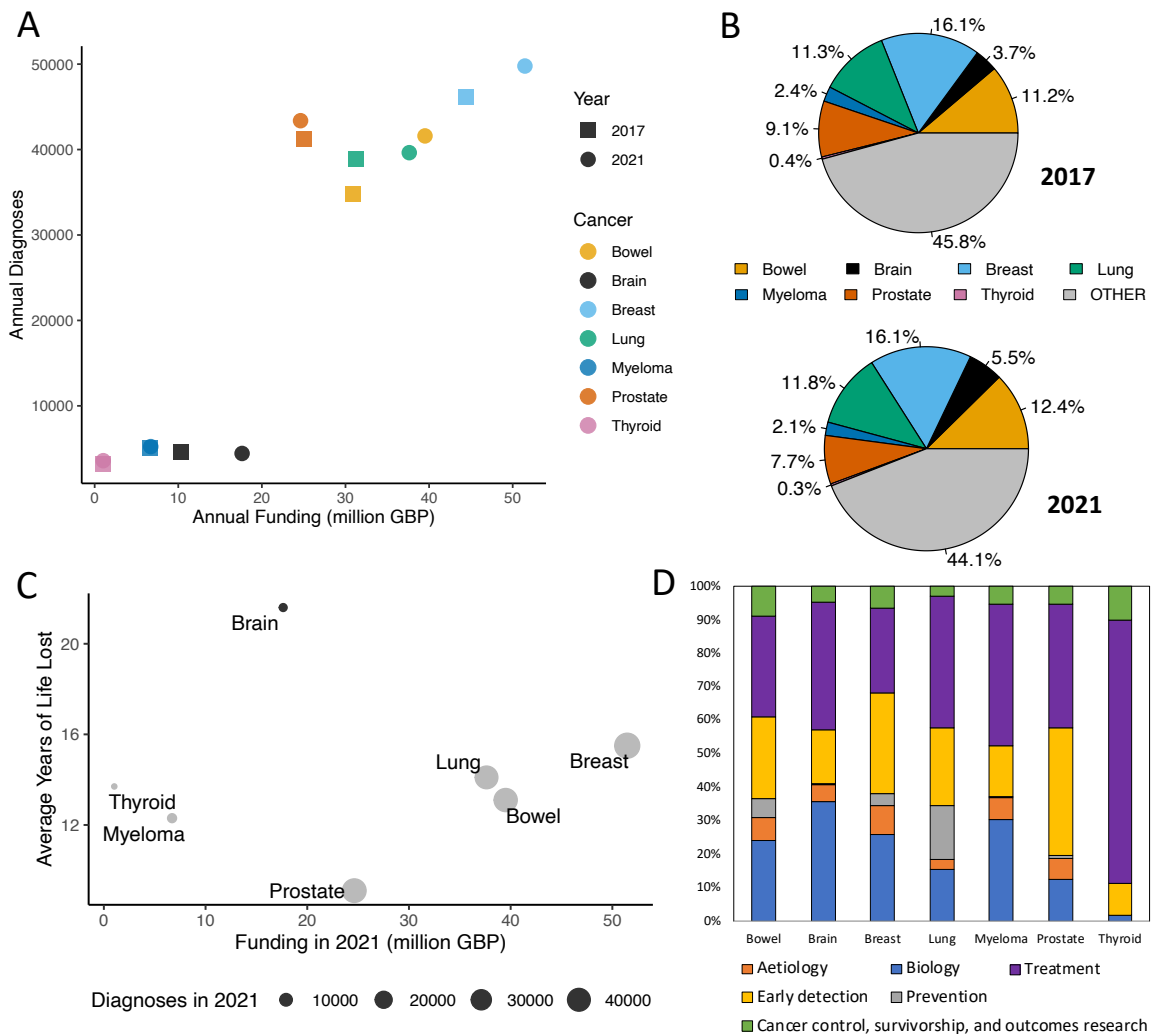
Brain Tumour Research Funding

Despite recently increasing funding levels for brain cancer research, this disease site remains relatively underfunded. Annual NCRI partner²² 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**)^{23,24}. 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**)²³. 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**)²³. 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^{23,25} (**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**)²³. 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 title²⁶ 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^{12,27}.

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 reasons²⁸⁻³⁰. 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 subtype³¹. 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.³² Only 1%
284 of patients are diagnosed through the designated NHS England two-week wait suspected cancer
285 pathway³³. 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 classification³⁴. 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 up³⁵, 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)^{36,37} 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 MATRIX³⁸ 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 Atlas³⁹ and GLASS¹⁸ 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 - https://www.go-fair.org/fair-principles/
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 tumours⁴⁰. 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)^{3,41}. Advances in brain
372 cancer cell culture techniques have led to cell lines that more closely mirror the originating tumour⁴².
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-offs⁴³⁻⁴⁶. Organoids and microfluidic *ex vivo* and BBB models
376 offer great promise for modelling complexity at scale⁴⁷⁻⁴⁹. 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)⁵⁰ 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 researchers⁵¹. 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 groups⁵². GlioModel⁵³ 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 longevity⁵² (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 ago², 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 obstacles⁵⁴. 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^{55,56}. 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,^{55,57,58}.

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 success¹³.

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 website⁵⁹ 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 3⁶⁰. 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 underrepresented⁶¹. 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. ²	2005	Radiotherapy + Temozolomide (n=287) Radiotherapy (n=286)	6.9 5.0	14.6 12.1	Yes
Gilbert et al. ⁶²	2014	Bevacizumab + STUPP (n=312) STUPP (n=309)	10.7 7.3	15.7 16.1	No
Chinot et al. ⁶³	2014	Bevacizumab + STUPP (n=458) STUPP (n=463)	10.6 6.2	16.8 16.7	No
Stupp et al. ⁶⁴	2014	Cilengitide + STUPP (n=272) STUPP (n=273)	10.6 7.9	26.3 26.3	No
Westphal et al. ⁶⁵	2015	Nimotuzumab + STUPP (n=71) STUPP (n=71)	7.7 5.8	22.3 19.6	No
Weller et al. ⁶⁶	2017	Rindopepimut + STUPP (n=371) STUPP (n=374)	8.0 7.4	20.1 20.0	No
Stupp et al. ⁶⁷	2017	TTF + STUPP (n=466)	6.7	20.9	Yes*

		STUPP (n=229)	4.0	16.0	
<i>Biomarker selected</i>					
Herrlinger et al. ⁶⁸	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)[#]</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); [#]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^{69,70}. 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^{71,72}. 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 outcomes⁷³. 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 fatigue⁴.
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 results⁷⁴, and the NIHR funded SPRING, a phase 3 trial of levetiracetam prophylaxis
548 of epilepsy in seizure-naïve patients with newly-diagnosed glioma⁷⁵.

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

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