NCRI
National
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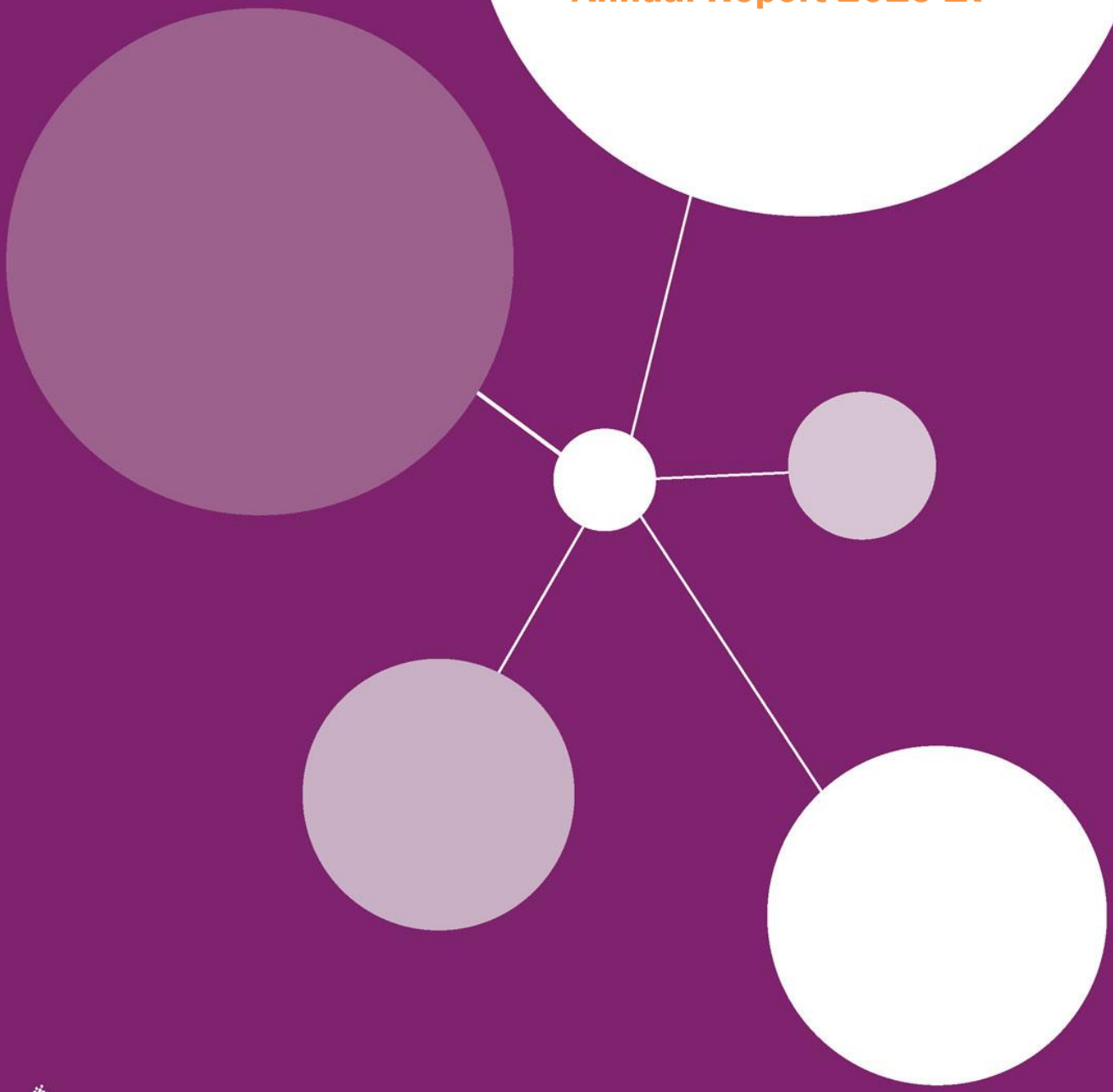
Institute

NCRI Brain Tumour Clinical Studies Group

Annual Report 2016-17



Partners in cancer research

NCRI Brain Tumour CSG Annual Report 2016-17

1. Executive Summary (including top 3 achievements in the year)

Several trials have opened and are recruiting well:

1. A single-centre trial exploring the role of ketogenic diet has been funded by Vitaflow International Ltd (NCT03075514) and is now on the national portfolio (CI: Dr Jenkinson). This will address one of the areas highlighted by patients for more evidence-based data on the role of diet in brain cancer.
2. BRACED: The BRAin Cancer Early Detection Study (CI: Dr F Walters), an early detection study funded by The Brain Tumour Charity, is a qualitative study of patient perspectives on factors affecting timely diagnosis of brain cancer has recruited ahead of schedule. This explores symptomatology and help-seeking behaviour in patients with a brain tumour.
3. CamBMT1: Cambridge Brain Mets Trial 1 (CI: Dr R Baird) is a randomised phase II study of afatinib penetration into cerebral metastases for patients undergoing neurosurgical resection, both with and without prior low-dose, targeted radiotherapy. This was jointly funded by CRUK and The Brain Tumour Charity.

A significant challenge going forward will be to ensure that clinical trial development is done in tandem with basic research initiatives developed by the CRUK Brain Tumour Group. Strategic collaboration will be essential if we are to develop robust pre-clinical disease models that can be used to develop mechanism-based studies leading to clinical trials. With this in mind, two of the Group's Subgroups, Novel Agents and Technology, have been reconfigured along disease-specific lines to form the Glioma and a Meningioma & Metastases Subgroups.

In parallel, we have appointed a basic scientist to the Group to exploit opportunities that may arise from clinical studies as they come on line. We have also appointed an oncologist with radiation oncology/SRS expertise to strengthen links with CTRad and develop trials in this neglected area.

These initiatives reflect some of the feedback from last year's report and the current active and dynamic nature of the Brain CSG. It is now ripe for a new Chair to build on this progress.

2. Structure of the Group

We have appointed a neurooncologist, Dr Paul Sanghera, who has a specialist interest in radiation oncology and SRS with the aim of further developing links with CTRad and promoting

radiotherapy trials in the UK. Professor Oliver Hanemann, a neurologist, has returned with the aim of developing further trials in NF1/NF2 related disease. Mr Stuart Smith, a neurosurgeon, has been appointed to replace Mr Stephen Price who has rotated off the CSG. Finally, we have appointed a scientist Dr Igor Vivanco with the aim of strengthening links with the basic science community and maximise added scientific value from clinical studies.

3. CSG & Subgroup strategies

Main CSG

The CSG has restructured to establish two disease-orientated Subgroups and a Supportive & Palliative Care Subgroup (see below). The aim is to focus trial applications along disease specific lines and bring together cross-cutting expertise (e.g. imaging) as required.

In-house development of investigator-led studies has resulted in PARADIGM opening to recruitment and REOGLIO (CI: Professor Short) and PARADIGM-2 (CI: Professor Chalmers) being funded by CRUK NAC. These are now in set up and will start recruiting in the coming year. A significant challenge going forward will be to encourage other oncologists to engage with clinical trial development. Within the NAT investigator-led portfolio, two oncologists (Professors Chalmers and Short) have established the OPARATIC, PARADIGM, PARADIGM-2, and REOGLIO trials. More recently, Professor Hanemann (neurologist) is working to improve recruitment into his trial exploring Sorafenib in NF2. He is also seeking funding for a biomarker study in NF2 and meningioma.

Currently all three Subgroups are supporting the development of new trials and are also actively engaged in out-reach activities such as the CNS Bootcamp. This initiative, led by Dr Jefferies, hosted clinical and radiation oncologists to inform them about clinical trials and to provide a forum to discuss new ideas.

A surgical trial network has been established with the formation of the tumour section of the SBNS, which has been formally endorsed by the SBNS council. A second successful meningioma study day took place in London with case presentations and clinical trial ideas discussed. Several surgical clinical trials are under consideration including risk stratification of incidental meningiomas and surgical management of residual disease in glioma. A proposal to evaluate intra-operative imaging technologies to better define tumour margin and improve tumour removal is currently being prepared by CSG surgeons for submission to an NIHR commissioned call.

The Supportive & Palliative Care Subgroup continues to focus around issues raised by the James Lind Alliance in their neuro-oncology priority setting (http://www.jla.nihr.ac.uk/top-tens/neuro-oncology-top-ten). The Subgroup is also developing work around epilepsy. Currently the group is undertaking consultation exercises with incubator days in epilepsy, coping with fatigue and lifestyle changes. This has led to a trial proposal to examine the impact of seizure prophylaxis on patients with a brain tumour. Following supportive feedback from the NIHR, who invited a revised submission, a grant application is being developed.

Glioma Subgroup (Chair, Dr Sarah Jefferies)

The formation of the Glioma Subgroup is to aim to improve the access and entry of patients with a diagnosis of a glioma into clinical trials.

Aims and objectives

- Provide direct or targeted support for the development of UK-led clinical trials.
- Provide direct or targeted support for one-two grant applications per year for studies in glioma.
- To optimise access across the UK to international and commercial studies.
- To develop a network for UK clinical oncologists who treat glioma.

The first meeting will take place in June at the British Neurosurgical Oncology Society. The second is scheduled for October, prior to the main CSG meeting.

Meningioma & Metastases Subgroup (Chair, Mr Michael Jenkinson)

The strategic aims of the Subgroup are to support and develop new clinical trials for patients with meningioma and metastases. This will build on existing portfolio trials including ROAM, MOT, HIPPO and CamBMT1.

Two Subgroup members (Michael Jenkinson and Thomas Santarius) are part of the founding committee of the British-Irish Meningioma Society (https://britishirishmeningiomasociety.wordpress.com) and have good links to the EORTC meningioma research committee and the Society for Neuro-Oncology International Meningioma Consortium which also has Subgroup representation. These networks will be essential for developing UK trials and intergroup trials with EORTC.

The Subgroup also draws on expertise in metastasis trials (Gillian Whitfield and Richard Baird). Establishing links with other CSGs, e.g. Lung, Breast, Skin and Renal, will be essential to develop new trials in this challenging patient group.

Aims and objectives

- Advise on early study applications by providing brief expert peer review at outline proposal stage. PPI advice will be through our consumer representative.
- Establish links with other CSGs to offer expert advice in study design/methodology/tissue sampling for brain metastases trials.
- Define SOPs that will harmonise data collection for meningioma studies covering tumour tissue, blood samples and imaging (MRI).
- Establish a network a research active clinicians (surgeons, oncologists, pathologist, radiologist) working on meningioma (via the British-Irish Meningioma Society).
- Explore funding options for several study proposals:
    - Long term management of incidental meningioma.
    - Prophylactic antiepileptic drugs in meningioma surgery.
    - Supramarginal resection of brain metastases.
    - Imaging biomarkers of Primary CNS lymphoma.

Supportive & Palliative Care (S&PC) Subgroup (Chair, Dr Robin Grant)

The strategic aims of the S&PC Subgroup are to encourage development of high quality clinical studies and trials in the top 10 priority areas, identified through the Neuro-Oncology JLA process and other key areas. This will be done by increasing reach and involvement with UK researchers through support available from the Subgroup, specialty engagement, engagement with the British Neuro-Oncology Group and other clinical meetings and development of the NOCTURN Website (http://www.neuro-oncology.org.uk/). The production of a twice yearly newsletter promoted

through UK clinical meetings and online will provide an overview of the direction of travel and progress made.

Aims and objectives

- Advise on early study applications by providing brief expert peer review at outline proposal stage. External review by the Subgroup twice a year will follow the CTRad model and PPI advice will be through our consumer representatives.
- Give priority to applications involving >=3 centres.
- Encourage and support involvement of the Research Design Service, key CTUs and, where helpful, health economic advice.
- Work collaboratively with other relevant NCRI groups, e.g. the Supportive & Palliative Care and Psychosocial Oncology & Survivorship CSGs and the NCRI Living with and Beyond Cancer (LWBC) initiative. We will engage with Partners that can support development of studies in the priority areas, e.g. Cochrane Neuro-Oncology Group.

4. Task groups/Working parties

Not applicable.

5. Patient recruitment summary for last 5 years

In the Brain Tumour CSG portfolio, 7 trials closed to recruitment and 10 opened.

Table 1 Summary of patient recruitment by Interventional/Non-interventional

Year	All participants		Cancer patients only		% of cancer patients relative to incidence	
	Non-interventional	Interventional	Non-interventional	Interventional	Non-interventional	Interventional
2012/2013	1594	168	927	168	19.5	3.5
2013/2014	829	136	783	136	16.5	2.9
2014/2015	716	171	716	170	15.1	3.6
2015/2016	147	112	145	106	3.05	2.23
2016/2017	189	116	188	108	3.96	2.27

6. Links to other CSGs, international groups and network subspecialty leads

The Supportive & Palliative Care Subgroup has made links with other CSGs (Supportive & Palliative Care and Psychosocial Oncology & Survivorship) and with the Association of Palliative Medicine.

The Group is continuing to develop a strengthening relationship with other CSGs, in particular the Breast and Lung CSGs. For example, the early phase trial CamBMT1 (NCT02768337) is an open label, three arm, randomised phase II trial investigating whether administration of a low dose of targeted radiotherapy during afatinib treatment could increase the concentration of drug penetration into brain metastases.

The CSG is actively pursuing closer links with the EORTC, which has resulted in agreement to develop a national network of trial competent centres in the UK based on the existing EORTC centres. We are now seeking an appropriate trial to formalise this process.

7. Funding applications in last year

Investigator-led funding applications have been more limited this year. It is hoped that refreshing and reorganising the Subgroups, alongside a more clearly defined and published strategy, will encourage new submissions.

Table 2 Funding submissions in the reporting year

Cancer Research UK Clinical Research Committee (CRUK CRC)			
Study	**Application type**	**CI**	**Outcome**
May 2016			
None			
November 2016			
SYSTEMS-2 sample collection for translational research	Sample Collection	Professor Anthony Chalmers	Not Supported
Other committees			
Study	**Committee & application type**	**CI**	**Outcome**
Ketogenic Diets as an Adjuvant Therapy in Glioblastoma (KEATING) NCT03075514 - August 2016	A randomised feasibility trial Vitaflow International Ltd	Michael Jenkinson	Successful

8. Collaborative partnership studies with industry

The CSG has several industry studies on its portfolio. The CSG is usually notified about these studies when the protocol and participating centres have already been determined and usually has limited input into study design. To date, no industry study has competed with other portfolio studies for patients.

The following industry studies currently sit on the Brain CSG portfolio:

- NCRN 396: Open-label, phase II study of vemurafenib in patients with BRAF V600 mutation-positive cancers.
- NCRN 592: Phase III clinical trial evaluating DCVax®-L, autologous dendritic cells (DC) pulsed with tumor lysate antigen for the treatment of glioblastoma multiforme (GBM) - currently suspended.
- NCRN 631: ACT IV Rindopepimut/GM-CSF + Adjuvant Temozolomide in EGFRvIII-positive Glioblastoma - closed March 2016 for lack of efficacy.
- NCRN 605: TAMIGA Phase IIIb:SOC +/- bevacizumab in GBM after radiotherapy + temozolomide + bevacizumab - did not meet the primary endpoint.
- NCRN 2698: Pilot study to develop methodology for 2-HG MRS.
- PARADIGM - an AZ Alliance study on the horizon is now on the portfolio.
- INTELLANCE-2 (NCT02343406) to evaluate the efficacy and safety of ABT-414 alone or with temozolomide versus temozolomide or lomustine alone in participants with recurrent glioblastoma multiforme.
- Checkmate 143 (the checkpoint inhibitor nivolumab vs bevacizumab in 1st relapse of GBM) – the results were presented at the WFNO in Geneva which were entirely negative.
- Checkmate 498 (first line for unmethylated GBM - RT + TMZ vs RT + nivolumab) has closed, having reached accrual.

- Checkmate 548 (first line for methylated GBM, RT + TMZ + nivolumab / placebo) reached accrual but is re-opening as it is being extended.

9. Impact of CSG activities

Clinical trials within the Brain CSG have impacted on routine UK clinical practice:

- BR12: this trial has helped rationalise the management of patients with recurrent GBM in the UK. The use of PCV versus TMZ in the context of early versus late relapse respectively has been incorporated into clinical practice.
- EORTC 22952: randomised trial examining the role of whole brain radiotherapy after resection or radiosurgery for patients with one-three brain metastases. This has influenced the management of patients with cerebral metastases.
- EORTC 26052: the role of dose dense TMZ v standard protocols. The data confirms that dose dense regimens do not convey advantage.

More recently, large multicentre trials have not shown impact on clinical outcome for GBM. In contrast, long-term follow up of 1p19q co-deleted anaplastic oligodendrogliomas has confirmed that radiation therapy (RT) combined with PCV chemotherapy improves survival compared to RT alone.

10. Consumer involvement

The consumers continue to be a very active and influential presence, both on the main Group and on the Subgroups. Ongoing engagement with trials has led to stronger proposals, with input into lay summaries, representation on trial management groups and named co-applicants on trials. The CSG understands the difference that consumer input makes to the research agenda and consumer engagement is in the DNA of the CSG and its subgroups.

Key drivers have been:

- The top ten uncertainties identified by the James Lind Alliance Priority Setting Partnership:
    - Developing clinical studies for supportive care/quality of life.
    - Increasing accrual rates to studies in supportive care/quality of life.
    - Developing questions related to quality of life
- Building links with other groups and CSGs, e.g. CTRad, Proton Beam Consortium, CRUK, NCIN and Use My Data.
- Increasing engagement across the four nations, with links to Brain Tumour Research Focus Group at the Belfast Centre for Cancer Research and Scottish CTUs.
- Attending conferences and presenting posters.
- Developing the sustainability of the brain tumour tissue bank: http://www.southampton.ac.uk/brainuk/index.page.

11. Open meetings/annual trials days/strategy days

In June 2014, a Group strategy day discussed potential studies for patients with brain metastases. As a result, plans were implemented to develop new trial opportunities for patients with brain metastases resulting in CamBMT1 (see above) and HIPPO evaluating whether sparing the hippocampi during whole brain radiotherapy following neurosurgery or stereotactic

radiosurgery in patients with brain metastases from a systemic tumour helps preserve brain function (NCT02147028), which has now opened.

Building on this success, a full CSG strategy day was held in October 2016. The Group liaised closely with the Department of Health Task & Finish Working Group on brain tumours to highlight that greater emphasis needs to be placed on co-leadership of research initiatives by scientist and clinicians working together. This would allow scientists to optimise benefit from material and data generated in clinical studies and clinicians to ensure NHS practice is conducted in a research-supportive manner. Early-phase trials in neuro-oncology are especially challenging and greater investment is required to develop a core number of units able to support brain cancer research (in tandem with developing a cadre of medical neuro-oncologists). Wider recognition of the challenges around patient recruitment into clinical studies is needed with greater support devolved through the CRNs. Any single centre will only ever recruit a small number of patients so many centres must be involved through a networked approach. A summary paper has been submitted for publication (see appendix 2).

12. Priorities and challenges for the forthcoming year

Priorities and challenges for the CSG are outlined below:

1. Promoting the collection of linked clinical and biological (especially genomic) data with the objective of establishing the use of prognostic biomarkers in routine clinical practice for patients with glioma. Currently some prognostic biomarkers are not made available to the MDT before treatment planning has started. This can lead to delays in establishing a correct diagnosis or starting a treatment regime that could be altered/refined in the light of a full panel of validated biomarkers. We aim to develop approaches to standardise clinical management and biomarker availability.
2. Promoting surgical trials: We will strengthen links with the SBNS tumour section to promote surgical neuro-oncology trials. Specific areas of interest are to investigate the surgical management of residual enhancing disease in glioma and synergise this initiative with the CRUK PRaM study, develop a feasibility/prospective cohort study to apply validated biomarkers as early as possible in the clinical decision-making process and a prospective risk stratification trial in incidental meningiomas.
3. Engaging with the clinical oncology community in a more robust manner. The Group will work to engage clinical oncologists to develop clinical trials with a particular emphasis on radiation and radiation combination studies.

13. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies
- A – Main CSG Strategy
- B – Glioma Subgroup Strategy
- C – Meningioma & Metastases Subgroup Strategy
- D – Supportive & Palliative Care Subgroup Strategy

Appendix 3 - Brain tumor research in the UK: current perspective and future challenges: A strategy document from the NCRI Brain Tumour CSG

Appendix 4 - Portfolio Maps

Appendix 5 - Publications in previous year

Appendix 6 - Major international presentations in previous year

Dr Colin Watts (Brain Tumour CSG Chair)

Appendix 1

Membership of the Brain Tumour CSG

Name	Specialism	Location
Dr Paul Sanghera	Clinical Oncologist	Birmingham
Dr Sara Erridge	Clinical Oncologist	Edinburgh
Dr Catherine McBain	Clinical Oncologist	Manchester
Mr Babar Vaqas*	Clinical Research Fellow	London
Mr Peter Burchill	Consumer	Sheffield
Ms Debbie Keatley	Consumer	Belfast
Dr Sarah Jefferies	Medical Oncologist	Cambridge
Dr Igor Vivanco	Molecular Oncologist	London
Dr Robin Grant	Neurologist	Edinburgh
Professor Oliver Hanemann	Neurologist	Plymouth
Dr Kathreena Kurian	Neuropathologist	Bristol
Dr Alasdair Rooney*	Neuroscience PhD Student	Edinburgh
Dr Martin McCabe	Paediatric Oncologist	Manchester
Professor Silvia Marino	Pathologist	London
Mrs Erica Moyes	Project Officer, Brain Tumour Charity	Hants
Dr Samantha Mills	Radiologist	Liverpool
Dr Helen Bulbeck	Representative, brainstrust the brain cancer people	Isle of Wight
Dr Lorna Fern (Observer)	Research Development Coordinator	London
Dr Wendi Qian	Statistician	Cambridge
Mr Michael Jenkinson	Surgeon	Liverpool
Mr Stuart Smith	Surgeon	Nottingham
Dr Colin Watts (Chair)	Surgeon	Cambridge

* denotes trainee member

Membership of the Subgroups

Glioma Subgroup		
Name	**Specialism**	**Location**
Dr Sarah Jefferies (Chair)	Clinical Oncologist	Cambridge
Dr Sara Erridge	Clinical Oncologist	Edinburgh
Dr Catherine McBain	Clinical Oncologist	Manchester
Dr Igor Vivanco	Molecular Oncologist	London
Mr Stuart Smith	Surgeon	Nottingham
Dr Natalie Cook	Medical Oncologist	Manchester
Dr James Powell	Clinical Oncologist	Cardiff
Dr Paul Brennan	Neurosurgeon	Edinburgh
Dr Estelle Healey	Pathologist	Belfast
Dr Laura Clifton–Hadley	Trials Group Lead	London
Dr Gerard Thompson	Radiologist	Edinburgh
Dr Helen Bulbeck	Consumer	Isle of Wight

Meningioma & Metastatic Subgroup		
Name	**Specialism**	**Location**
Dr Richard Baird	Medical Oncologist	Cambridge
Professor Oliver Hanemann	Neurologist	Plymouth
Mr Michael Jenkinson (Chair)	Surgeon	Liverpool
Ms Debbie Keatley	Consumer	Belfast
Dr Joanna Lewis	Clinical Oncologist	Newcastle
Dr Samantha Mills	Neuro-radiologist	Liverpool
Mr Jonathan Pollock	Surgeon	Essex
Mr Thomas Santarius	Surgeon	Cambridge
Dr Gillian Whitfield	Clinical Oncologist	Manchester
Mr Rasheed Zakaria	Surgeon	Liverpool

Supportive & Palliative Care Subgroup		
Name	**Specialism**	**Location**
Dr Catherine McBain	Clinical Oncologist	Manchester
Mrs Kathy Oliver	Co-Director, IBTA	Surrey
Dr Diane Playford	Consultant Neurologist	London
Dr Helen Bulbeck	Consumer	Isle of Wight
Dr Anthony Byrne	Director, Marie Curie Palliative Care Research Centre	Cardiff
Professor Willie Hamilton	General Practitioner	Exeter
Dr Robin Grant (Chair)	Neurologist	Edinburgh
Dr Alasdair Rooney*	Neuroscience PhD Student	Edinburgh
Dr Ann Arber	Senior Lecturer, Cancer & Palliative Care	Surrey
Dr Florien Boele	YCR Academic Fellow	Leeds

*denotes trainee member
**denotes non-core member

Appendix 2

A – Main CSG Strategy

Patients with brain tumours continue to suffer from poor clinical outcomes because of under-developed clinical research infrastructure, pre-clinical models that do not accurately represent clinical disease and a limited scientific base in the UK.

Aims

- To promote and support the development of clinical trials for patients with all types of brain tumours through disease-focused subgroups.
- To promote research into survivorship, quality of life and patient reported outcomes through a specific subgroup.
- To work more closely with scientists to generate added value from clinical trials and develop mechanistic and discovery science.
- To support, promote and advocate on behalf of brain tumour patients and their carers.

To achieve these aims, we have:

- Re-organised the subgroup structures to better reflect clinical research priorities.
- Appointed basic scientists to the CSG and Subgroups to encourage synergy between science and clinical trials.
- Appointed clinical trainees to the CSG to encourage the clinical investigators of tomorrow.
- Engaged with patient representative through CSG PPI members and brain tumour charities to support clinical trial development and prioritise what matters to patients.
- Worked with all our stakeholder to improve recruitment and identify barrier to recruitment into clinical trials.

Going forward we have established a clear research strategy, which will be published in Neuro-Oncology Practice. We will use this to inform the future direction of the CSG as a new chair takes over. In this way we will ensure continuity of development against defined metrics.

B – Glioma Subgroup Strategy

The formation of the Glioma Subgroup is to improve the access and entry of patients with a diagnosis of a glioma into clinical trials throughout the United Kingdom.

The Subgroup has been selected to have representation from centres in England, Scotland, Wales and Northern Ireland. It has neurosurgical representation to build on the successful current platform of neurosurgical trials. A medical oncologist with phase I experience has been appointed as it is recognised that this is an area that needs improvement in the current trial portfolio. A scientist with a dedicated interest in translational science has been appointed to help with this aspect within trial design. A radiologist and neuropathologist have been appointed for specialist advice in clinical trial development. It is planned to advertise for two trainees to join the Subgroup from any of the contributing disciplines to foster links with developing expertise for those working in neuro-oncology in the future.

The Subgroup will act as platform to provide support for the development of UK-led clinical trials, including commercial and academic studies. Plans are in place to provide a quick guide to apply for adoption to the portfolio for commercial studies.

We will also provide direct or targeted support for one-two grant applications per year for studies in glioma. Work is already underway for the development of a re-irradiation protocol which will be able to be utilised in multiple studies. The Subgroup also aims to develop a network for UK clinical oncologists who treat glioma.

There is a well-established group for neurosurgeons in the British Society of Neurosurgical Oncology and similarly there is a forum for basic research at the glioma club meeting. The infrastructure for an annual neuro-oncology meeting has been established at the CNS Bootcamp which aims to optimise information about current clinical trials and protocols that are in development to optimise trial entry across the UK. The ultimate aim will be to combine these three meetings to optimise clinical trial design and execution from the UK neuro-oncology community.

Outcome measures

The assessment of the outcomes from the Glioma Sub-group will be measured by:

1. Increased entry of patients into the current glioma portfolio.
2. Involvement in the development of 1-2 UK developed clinical trials.
3. Establishment of a neuro-oncology network that includes clinical oncologists.

C – Meningioma & Metastases Subgroup Strategy

Vision

To create a large portfolio of clinical trials for patients with meningioma and metastases.

Mission statement

It is our goal to build on the existing portfolio and to develop new clinical trials for patients with meningioma and metastases. We will accomplish this by focusing on clinical priorities for patients, identifying research-active clinicians and providing a forum to advise on study applications. Our success will be measured by the number of successful grant applications and new studies adopted onto the portfolio.

Strengths

Two Subgroup members (MDJ and TS) are part of the founding committee of BIMS (https://britishirishmeningiomasociety.wordpress.com) and have good links to the EORTC meningioma research committee (MDJ is a member) and the Society for Neuro-Oncology International Meningioma Consortium (MDJ, TS, OH and SM). These networks will be essential for developing UK trials and intergroup trials with EORTC. The Subgroup also draws on expertise in metastasis trials (GW and RB).

Weaknesses

New Subgroup members (JP and JL) do not have experience of submitting grant applications. Current links with other CSGs is poor and many primary cancer trials specifically exclude patients with brain metastases.

Strategy for success

- Meningioma: Establish a network a research active clinicians (surgeons, oncologists, pathologist, radiologist) working on meningioma (via the British-Irish Meningioma Society) – in progress, expected May 2018. Define SOPs that will harmonise data collection for meningioma studies covering tumour tissue, blood samples and imaging (MRI) - in progress, expected May 2018.

- Metastases: Establish links with other CSGs (e.g. Lung, Breast, Skin and Bladder & Renal) to develop new trials for metastases patient groups, with reference to study design/methodology/tissue sampling for brain metastases trials – MDJ to contact CSG Chairs – in progress, expected September 2017.

Clinical studies under consideration/development by CSG subgroup

- Meningioma: Long term management of incidental meningioma – JP has submitted suggestion to NIHR as potential for commissioned research. Prophylactic antiepileptic drugs in meningioma surgery – MDJ has completed systematic review, clinical practice survey and hospital audit. To develop clinical trial outline in PICO format by October 2017.
- Metastases: Supramarginal resection of brain metastases – preliminary trial idea from RZ who will explore whether trial technically feasible, given challenges of surgical technique trials. In progress, expected October 2017.
- Other tumours: Imaging biomarkers of Primary CNS lymphoma – SM proposed study. Preliminary work required. In progress, expected October 2017.

NCRI National Cancer Research Institute

brainstrust the brain cancer people

NCRI Brain and CNS CSG: supportive and palliative care news

December 2016

'Janus facing' describes the first newsletter from the *"supportive and palliative care" subgroup*; it looks back to what has defined our work in 2016 and is looking forward to new directions and what's making the cut as we move into 2017.

What is the raison d'etre of the group? Quite a wide brief, but the bottom line is that we have two objectives. We need to:

- develop neuro-oncological clinical studies for supportive care and quality of life.
- increase accrual rates to neuro-oncological studies in supportive care and quality of life.

This is not done in isolation. The quality of life agenda is being advanced in cancer advocacy; we are finding a new narrative that is responding to the changing demographic characteristics of the cancer population, as more people are living longer with primary cancer "Living with and Beyond". Clinically, tending to quality of life concerns and patient and caregiver values is now universally recommended by professional oncological organisations and concurrent oncologic and palliative care is supported not only by a majority of patients in public opinion research[1] but also by clinicians via evidence-based recommendations. To maintain physical and emotional function and supporting quality of life at any age and any stage across the care continuum, psychosocial and rehabilitation services must be integrated into palliative care. This message carries more weight in neuro-oncology[2] where there is progressive neurological deficit; exercise, neurocognitive training, neurocognitive behavioural therapy, and medications to treat fatigue, behaviour, memory, mood, and removal of drugs that may be associated with neurocognitive side effects (e.g., anti-epileptic drugs) all show promise in helping patients to manage the effects of their neurocognitive impairments better. Yet the identification and selection of patients for early neurological rehabilitation and routine evaluation of cognition is uncommon, remains adhoc and service delivery remain fragmented[3].

So what has this group been doing to take this agenda forward? Remember the JLA Top Ten Priorities for clinical research in brain and spinal cord tumours?

These have been underpinning our work and are a key driver for change in the supportive and palliative care agenda.

1 Center to Advance Palliative Care. *2011 Public Opinion Research on Palliative Care: A report based on research by public opinion strategies*. New York, NY: Center to Advance Palliative Care; 2011

2 Day, J., Gillespie, D.C., Rooney, A.G. et al. Curr Treat Options Neurol (2016) 18: 22. doi:10.1007/s11940-016-0406-5

3 *brainstrust 'Quality of life: what the brain cancer community needs'* November 2014 https://issuu.com/brainstrust/docs/150309_what_the_community_needs_fin

Incubator days

Our incubator days are critical in taking the clinical research study agenda forward and move forward from descriptive studies to intervention studies in supportive and palliative care. So far we have held six.

What is an incubator day?
It's a think tank, where ideas are incubated and grown. It takes the form of an interactive workshop, structured to drive lateral thinking and radical approaches to address research challenges, with the aim of producing research proposals. These are things an incubator event achieves. Working collectively we:

- find out about the state of current research evidence (Cochrane or other systematic review)
- explore research ideas around the "theme" of the incubator event – a JLA question"
- bring an expert team together to build a study/trial submission – usually three centres or more
- seek advice from the study design experts in Research Design Service – http://www.rds.nihr.ac.uk/
- develop the study proposal with the help of a Clinical Trials Unit (CTU) http://www.ukcrc-ctu.org.uk/
- consider the trial management, protocol, statistics, data management implications
- provide robust peer review of clinical research proposal through the National Cancer Research Institute (NCRI)
- seek the most appropriate funding route for the study with partners – NIHR, cancer charities, brain tumour charities
- work collaboratively to produce the best funding application to appropriate most appropriate funder

Our Incubator Days have focused on the following questions:

Caregivers

(supported by *brainstrust*)

What is the effect of interventions to help caregivers cope with changes that occur in people with a brain or spinal cord tumour, compared with standard care?
JLA uncertainty 8

This is an important area of research because we know the detrimental impact to the health and wellbeing of informal caregiver for a patient who is living with a brain tumour. Providing caregivers with support and guidance empowers them and lowers levels of distress, which in turn influences patients' health for the better. This research will explore what the best interventions are for this vulnerable group of people. In particular, plans regarding the adaptation of a supportive intervention developed in the US were discussed. This programme called SmartCare© is an online intervention programme which is guided by a nurse, and was developed specifically for family caregivers in neuro-oncology. The main outcome of the incubator day was that attendees felt a good first step would be to undertake a pilot/feasibility study, and to make adaptations to the programme as necessary to better fit the needs of caregivers in the UK. Funding opportunities were discussed.

In the meantime, a Cochrane systematic review protocol focused on evaluating the current level of evidence for the effectiveness of neuro-oncology caregiver programmes has been submitted for review. Efforts are being undertaken to apply for a NIHR01 grant with Leeds as a European site (deadline February 2017).

Fatigue

(supported by *brainstrust*)

Is there any evidence that the addition of an exercise programme reduces fatigue in patients with primary brain tumours, compared with standard care?

JLA uncertainty 9

The Brain CSG SPC subgroup hosted an incubator day on 28th June at the University of Leeds. The overall purpose of the day was to focus on the James Lind Alliance Uncertainty 9: "What is the effect of additional strategies for managing fatigue, compared with standard care, in people with a brain or spinal cord tumour?" Fatigue is one of the most frequent and distressing problems described by people living with a brain tumour. It remains troublesome throughout the course of survivorship and is therefore an extremely common and persistent side effect of brain cancer and its treatment. It is important to discover how to manage it effectively. It is associated with other burdensome symptoms, and with reduced quality of life. However high-quality evidence is lacking on how to treat fatigue in PBT patients. In particular, no RCTs have studied the effectiveness of exercise for fatigue in adults. The specific aim of the day was therefore to design a research question an RCT utilising an exercise intervention for fatigue in these patients.

The day was well attended, with international expertise around the table regarding symptoms, quality of life, and exercise. We agreed that a feasibility study would be the most appropriate design at this stage. There was general consensus on recruiting patients with PBT rather than metastasis (owing in part to the practical difficulty of recruiting the latter); age 16 or older including the 'TYA' group, with reasonable functional level with life expectancy >1 year. It became clear during the day that further discussion will be needed on precisely when to intervene. There was also no clear consensus on a single best intervention. Some people favoured and had experience with behavioural approaches, others exercise. This led to the proposition of two kinds of intervention: broadly, cognitive-behavioural versus exercise.

By the end of the day we had developed a nascent research question. In fatigued patients (>16yrs) with primary brain tumour, with good functional status and who are otherwise clinically stable, is there any evidence that it is feasible to study (1) home-based, objectively monitored aerobic exercise and/or (2) a motivational, cognitive-behavioural approach to fatigue management? In 2017 we will seek to shape this encouraging start towards a funding proposal.

Diet

Do lifestyle factors (e.g. sleep, stress, diet) influence tumour growth in people with a brain or spinal cord tumour?

JLA uncertainty 1

The ketogenic diet and brain tumours

An incubator day to explore the idea of a trial of the ketogenic diet in patients with brain tumours was held in November in London. The day was led by Dr. Matt Williams from Imperial (http://www.imperial.ac.uk/people/matthew.williams) and supported by Brain Tumour Research (www.braintumourresearch.org). The Astro Brain Tumour Fund (http://www.astrofund.org.uk/) and Matthew's Friends (http://www.matthewsfriends.org) have also been instrumental in championing the ketogenic diet. The meeting was attended by over 30 stakeholders including clinicians, dieticians, scientists, patient representatives and research funding bodies. With over one-third of the incubator day participants from charity or carer backgrounds, there was strong patient, carer and public involvement.

The KD low carbohydrate/high protein diet serves to alter cellular metabolism and the biochemical pathways involved in energy generation. It has been shown to improve seizure control in children with intractable epilepsy. Preclinical studies have suggested that the diet may also have a benefit for people with brain tumours. The aim of the incubator day was to assess the available evidence upon which any future study would be based in addition to considering the feasibility of carrying out such a study. Another study on the use of the ketogenic diet as adjuvant therapy in glioblastoma is also being planned in Liverpool to determine how well patients would adhere to the diet, considering its strict nature.

It was agreed at the London incubator day, based on the evidence currently available, that an initial randomised Phase 2 trial on the feasibility of the modified ketogenic diet in patients with grade 2, 3 and 4 gliomas should be undertaken. Because of the aforementioned strict nature of the KD, compliance may prove challenging and result in a degree of drop-out therefore this will influence the number of trial participants who would need to be recruited. Further discussions will be required about the sample population, the duration of the trial and the primary outcomes to be assessed. These will form the basis of any future application for trial funding.

Early diagnosis

Does earlier diagnosis improve outcomes, compared to standard diagnosis times, in people with a brain or spinal cord tumour?
JLA uncertainty 3

Building on the momentum of the other days we packed one in in August on early diagnosis, led by Willie Hamilton and supported by The Brain Tumour Charity. The outcome? A well defined PICO'd question emerged: how can we expedite the diagnosis of brain tumors in the UK?

And also two main areas to be addressed.

1 GP dx through cluster of symptoms (work underway on this – Edin/Bristol/Exeter/Camb)

2 GP access to sophisticated imaging, in short time frame (audit/routinely collected data)

- Barriers to imaging – Need to know what is happening now re: fast imaging, where (regionally in UK) and how can barriers be overcome.
- Access to neurologist/ neurological advice

Population:	Headache Plus Suspicious of Cancer
Intervention:	Open access sophisticated imaging CT/MRI
Comparison:	Usual Care (MRI England/CT Scotland) or referral to neurological advice)
Outcome:	Time to imaging, patient satisfaction, cost effectiveness

Fingers crossed for SPRING (Seizure Prophylaxis IN Glioma)-time!

We also ran two other incubator events, supported by *brainstrust*, around tumour associated epilepsy in patients who are living with a brain tumour – SPRING and SANAD 2. We need to provide up to date evidence based guidance to neurosurgeons about prophylactic Anti-Epileptic Drugs (AED) prior to surgery and so SPRING has sprung!

The SPRING study asks an important question; it has a high quality submission team – neurology x2, neurosurgery x2, oncology x1, PPI x1, health economics x1, and an excellent committed trials unit (Scottish Clinical Trials Research Unit that is part of NCRN) with experience in cancer trials, with methodological and statistical support. In line with the Incubator Day model there are multiple collaborative centres involved in the application (Edinburgh, Cambridge, Liverpool, Newcastle), and there has been Research Design Service advice along the way.

Patients with suspected primary brain tumours, who have never had seizures will be randomized to levetiracetam prophylactically prior to surgery or no anti-epileptic drug (AED)/placebo (to be confirmed). Entry criteria are broad, no additional scans or bloods required, infrequent simple follow-up and a simple primary endpoint – "time to first seizure" with many secondary endpoints, some of which are around patient reported outcomes with health economic involvement. The study has passed the first two NIHR committee hurdles and has been shortlisted for final submission will be in late January 2017 and we should know by Spring!

The second event, SANAD 2, focused on late onset epilepsy. It appears that AEDs (+/- resection +/- Chemo/ RT) are effective in controlling seizures in 50% of cases. Patients with tumour associated epilepsy (TAE) are probably more susceptible to side effects of AEDs, possibly related to age of onset and effects of tumour or treatment. There are currently no RCTs to determine which is the best AED to prescribe in patients who present with epilepsy and are subsequently found to have a brain tumour. There is an existing HTA funded study run by Liverpool Clinical Trials Research Centre (CTRC) (Prof Marson) comparing different AEDs in a RCT. Patients found to have brain tumours are currently excluded from SANAD 2. There is a possibility of a trial in BTRE using the SANAD 2 network and infrastructure. We had explored the development of such a study and whether it would help to inform management of patients with epilepsy and glioma. The lead trials unit would be Liverpool CTRC working in collaboration with the Scottish Clinical Trials Research Unit, which is part of the Cancer Clinical Trials Unit Scotland (CaCTUS).

Outcomes of this day were not what we expected, just showing how agile we need to be when working on supportive care agendas. We need to assess the seizure control – survival trade off from the patient perspective. We need to await the results of SANAD II to inform further decisions about a trial in tumour patients. We should consider too whether we can extrapolate from focal epilepsy to tumour related epilepsy. If so a trial may not be needed. And finally we need to consider whether to pursue repurposing of drug in addition to chemoradiotherapy for glioblastoma.

Other incubator events are in the pipeline for 2017, including one for early intervention for palliative care in March.

Conference updates

European Association of Neuro-oncology, Mannheim/Heidelberg October 12–16 2016

Lots of diamonds at EANO for quality of life in neuro-oncology, ranging from epilepsy management, to patient centred outcomes, and caregiver mastery. Top notes were the trial updates, and the focus on managing challenging behaviour and cognitive function.

National Cancer Research Institute annual conference, Liverpool November 6–9 2016

If neuro-oncology was a little thin on the ground at NCRI this year then supportive and palliative care for brain tumor patients was even thinner. But this is being addressed for next year. Networking proved worth while with discussion around pyscho-social interventions for people living with a brain tumour.

We have been told that Neuro-oncology will feature more in Nov 2017 NCRI Meeting and one of the two NCRI Supportive and Palliative Care Sub-group update meetings will be held then.

Society for Neuro-Oncology annual meeting, Scottsdale Arizona, November 17–20 2016

Click here for a full round up of SNO highlights on the IBTA website. Much of this is clinical however. Topics covered that related to supportive and palliative care included:

- Bringing precision to patient management: prediction, prevention, and supportive care in the new era
- Physical health risks in neuro-oncology family caregivers
- Family camp: a multi-disciplinary, holistic QLIF-10 intervention for brain tumour patients and their families
- Comparison of neurocognitive functioning NCOG-11 in paediatric brain tumour survivors and children with neurodevelopmental ADHD
- Sexual function in patients with primary QLIF-06 brain tumours

Looking forward to 2017

Cochrane Neuro-Oncology/NCRI NIHR Systematic Review Programme Grant

SRPG Project: 16/114/18 (http://www.nets.nihr.ac.uk/programmes/sr)

No – not 'guess the acronym'...

An application has been submitted to NIHR for the above Programme Grant in partnership with Cochrane Neuro-Oncology (GNOC – Cochrane Gynaecology, Neuro-Oncology and Orphan CRG). The application is for 3 year grant funding to support complex reviews that cover JLA Neuro-Oncology priority areas that are important as an early step in planning of NCRI brain S&PC subgroup promoted areas. If successful the funding will sit with GNOC but benefit those in brain CSG involved in the areas for systematic review. The funding is for a full time funded systematic reviewer trained in Cochrane SRs to help content editors (NCRI brain CSG). It will engage the support of the NIHR Complex Reviews Support Unit (CRSU) and the Health Economics Unit in Newcastle who will assist with Brief Economic Commentary (BEC) in some areas. Funding for PPI involvement is included. The Diagnostic Test Accuracy (DTA) Systematic Reviews will be led by NCRI brain CSG members and others are in the remit of the S&PC subgroup.

The areas are:

- Second Recurrence GBM. Lead Catherine McBain – CSRU +/- BEC
- Molecular subtyping techniques: Lead NCRI brain CSG (DTA review+BEC)
- Long-term physical & cognitive: Lead Protons – Lead Gillian Whitfield. LGG – TBA (Cochrane Non-Randomised Studies)
- Extent of Resection: Lead Colin Watts/Mike Hart. (CSRU +/- BEC).
- Interval & Special MR Imaging. Lead TBA (DTA review &BEC).
- Early Referral: Lead Robin Grant/ Willie Hamilton Cochrane Effective Practice & Organisation of Care (EPOC) or CSRU)
- Elderly GBM. Lead TBA. Cochrane Prognostic Review.

November 2016 – NIHR Shortlisted the submission.

February 2017 – Full application deadline – 10th February 2017.

If successful August – October 2017 projects to start.

British Neuro-Oncology Society Annual Meeting 21–23rd June 2017 (Edinburgh)

An exciting programme has been put together for this meeting, which includes an update on NCRI and CTRad Trials in addition to talks from Prof Jan Buckner (Mayo Clinic) on trials in low grades following the NEJM 2016 article http://www.nejm.org/doi/full/10.1056/nejmoa1500925#t=article and Dr James Perry (Toronto) on RCTs in GBM in the Elderly following the presentation of the RT +

Temozolomide data presented at EANO and ASCO 2016 http://health.sunnybrook.ca/cancer/brain-tumour-doctor-james-perry/

We plan to have an NCRI stand and perhaps a "pitching" competition where ideas for possible JLA NCRI S&PC can be discussed or submitted.

NCRI: Living with and beyond cancer

The NCRI prides itself on providing strategic oversight of the research landscape to identify areas where collaborative working adds value. Two areas where the NCRI has identified challenges to research progress are in surgery research and in the area of living with and beyond cancer.

As cancer treatments improve and more people are living with and beyond cancer, NCRI, in consultation with partners, researchers, funders and consumers, has recognised the need to identify research priorities in the field of 'living with and beyond cancer'. This year it has established an 18-month initiative that will include a James Lind Alliance, Priority Setting Partnership scheduled to take place early in 2017. Its focus is to develop strategies around the priorities, once identified, to do an evaluation of granstmanship and to plan for the next phase. Our involvement is two-fold, through CTRad and also through the work we are doing within the subgroup, aligning closely with our JLA neuro-oncology priorities.

And there's more...

In addition to business as usual, the S and PC sub group is working on its Strategy, taking a forward view until 2020 and is exploring barriers to trials in supportive and palliative care, training to build resource, developing collaborations and relationships, exploring outcome measures and reaching to anyone and everyone who will help to drive this agenda forward.

Happy New Year!

Robin Grant and the S and PC subgroup

Upcoming dates

19th January	**S&PC subgroup meeting**	London
25th January	**NICE Guidelines Committee Meeting Brain and CNS**	London
23th February	**NCRI Early Diagnosis Conference**	London
16th March	**British Pyscho-Oncology Conference**	Oxford
24th March	**JLA Palliative Care Incubator Day**	Cardiff
19th April	**NCRI Brain and CNS Tumour CSG meeting**	London
20th April	**EORTC Quality of Life Conference**	Brussels
5th May	**World Federation of Neuro-Oncology Societies**	Zurich
21th June	**British Society of Neuro-Oncology**	Edinburgh

Neuro-Oncology Group
a JLA priority setting partnership

James Lind Alliance
Priority Setting Partnerships

Appendix 3

Brain tumour research in the UK: current perspective and future challenges

A strategy document from the NCRI Brain Tumor CSG

Abstract

The National Cancer Research Institute (NCRI) is a partnership of charity and government research funders whose purpose is to improve health and quality of life by accelerating progress in cancer-related research through collaboration. Under this umbrella, the NCRI Brain Tumor Clinical Studies Group is focused on improving clinical outcomes for adult patients with brain and central nervous system tumors, including those with brain metastasis from other primary sites. This document discusses the current state of clinical brain tumor research in the UK and the challenges to increasing study and trial opportunities for patients. The clinical research priorities are defined along with a strategy to strengthen the existing brain tumor research network, improve access to tissue and imaging and to develop the future leadership for brain tumor research in the UK.

Introduction

The National Cancer Research Institute (NCRI) partnership was established in 2001 to ensure collaboration and coordination amongst cancer research funders in order to maximize the value and benefits of cancer research for patients and the public. Within the NCRI, clinical studies groups (CSGs) were established across the major cancer sites to provide a forum for stakeholders to develop trials and build a strategic portfolio within their areas of expertise. The original remit of the CSGs was to promote trials within the clinical community and also to provide constructive support for study proposals prior to submission to funding agencies. More recently the remit has changed and CSGs are now expected to be more active in developing clinical trials in-house, with particular emphasis on interventional rather than observational studies.

Since its formation the brain tumor CSG has been supported by subgroups; namely (i) Translational and Novel Agents, (ii) Imaging and Technology [originally separate groups which merged in 2012] and (iii) Supportive and Palliative Care. These subgroups provided a crosscutting approach to studies across all brain tumor types. Pediatric brain tumors fall under the remit of the Children's Cancer and Leukaemia CSG and due to the age eligibility criteria for most clinical trials, the groups function largely independently. Over the last decade the number of trials on the NCRI portfolio has increased. Neurosurgeons have developed and led both surgical trials such as GALA-5 [1] and GALA-BIDD [2] and radiotherapy trials such as the ROAM trial (an international multi-center phase III trial for atypical meningioma) [3]. Imaging trials such as DIG PRaM-GBM have been developed and led by neuroradiologists and neurosurgeons. Similar success has been achieved by oncologists who have taken laboratory research in DNA damage and repair biology into clinical trials for patients with gliomas, in the form of the PARADIGM [4] and OPARATIC trials [5].

Despite these successes, feedback from the NCRI highlighted that by their nature only a limited number of patients were eligible for these trials. Targeting therapeutics in stratified patient cohorts is likely to exacerbate this trend, and such trends are exacerbated in less common cancers such as those of the brain. There is a need to balance how we can achieve large-scale research involving patients across the whole of the UK and addressing all aspects of the cancer journey.

The NCRI brain tumor CSG held a strategy meeting at Peterhouse College, Cambridge on 10-11th October 2016. Members of the CSG and subgroups, along with representatives from The Brain Tumor Charity, brainstrust – the brain cancer people, Cancer Research UK (CRUK), the Department of Health and the National Institute of Health Research (NIHR) discussed the current state of brain tumor research in the UK and its future challenges. This document summarizes those discussions and outlines a forward strategy for clinical brain tumor research in the UK.

Burden of disease

Approximately 9000 patients are diagnosed with a primary brain tumor each year in the UK, and it has been estimated that 16,000 patients suffer from brain metastasis from other primary sites making a total of approximately 25,000 patients affected per year in the UK [6]. Over 102,000 people are living with a brain tumor in the UK [7] and overall, only 14% of patients with primary brain cancer are alive 10 years after diagnosis [6]. Although there are approximately 120 different types of brain tumor, the most common are gliomas, meningioma and metastases from extra-cranial sites such as breast, lung, kidney and skin. Glioblastoma is the commonest primary malignant brain tumor and the cause of the greatest average loss of life-years among all cancers [8] with a 2 year survival of ~25% and 5 year survival of ~5%.

Meningiomas, meanwhile, are the commonest primary intracranial tumor overall. The majority can be cured by surgical resection but in a subset of patients with clinically aggressive meningioma the tumor may recur. Radiotherapy may also help control these tumors, but there are no effective chemotherapy treatments [9]. Furthermore, cure or disease control does not necessarily equate to maintained quality of life and patients can often suffer a great deal of morbidity due to the location of the meningioma and the post treatment effects.

Brain metastases affect up to 40% [10] of patients with an extracranial primary cancer, with an increasing incidence because of both more effective control of the primary tumor and greater use of brain imaging for detection of metastasis. Surgery, stereotactic radiosurgery and whole brain radiotherapy continue to be the mainstay of treatment but increasingly therapies are targeted according to primary tumor type, including molecular subtype. Although some patients undoubtedly benefit from these targeted therapies, the overall prognosis for brain metastases is generally poor, and there are few effective treatments that can achieve long-term control [10].

Brain tumors of all types have a major impact on patients and carers, since they directly affect personality, mood, speech, physical function, cognitive function, seizure threshold, and levels of fatigue. As well as a primary effect of the tumor, patients often suffer from destructive or toxic side effects of the treatment (surgery, radiotherapy, and chemotherapy). Accordingly quality of life is a major issue for patients living with and beyond brain cancer. Taken together there is an urgent need both to improve brain tumor survival, and to improve the quality of life for those who do live longer and have additional morbidity from treatment.

Stakeholders in brain tumor research

Patients with brain tumors can suffer from a range of neurological and quality of life issues that require coordinated management by a large multi-disciplinary team (MDT). NICE Guidance on "improving outcomes for people with brain and other CNS tumors" (https://www.nice.org.uk/guidance/csg10) identifies key MDT members including neurosurgeons,

neurologists, neuropathologists, neuroradiologists, oncologists, clinical nurse specialists, and Allied Health Professionals. Many different professions and organisations therefore contribute to and are integral to brain tumor research. There is strong backing within this community to fund and support research that will directly benefit patients, families and carers. As well as Cancer Research UK (CRUK), charities specifically dedicated to brain cancer research, including The Brain Tumor Charity (TBTC), Brain Tumor Research (BTR) and brainstrust – the brain cancer people, identify this as a priority area. Nurturing this broad community of stakeholders is central to improving outcomes for patients living with brain tumors.

Funding landscape: lessons from other cancers

Two types of cancer demonstrate clearly the positive long-term correlation between research investment and survival rates; namely breast cancer and leukemia, which account for 8.5% and 6.9% of all NCRI spending, respectively (www.ncri.org.uk). Breast cancer survival after 5 years is now as high as 84.3%, despite more than 50,000 new cases being diagnosed every year. This remarkable success story is the product of sustained funding over decades, helping inform a detailed understanding of underlying tumor biology that in turn translates into new treatments.

Brain tumor research is not at this advanced stage of investment or understanding and the cumulative research-spend on brain tumors in the UK between 2002 and 2011 was less than 1%, and in 2014 only 1.5% of all research-spend by the NCRI (www.ncri.org.uk). Compounding this under-funding, brain tumors benefit very little from advances elsewhere in "general cancer research" since brain tumors are very different from other cancers. In particular the blood-brain barrier makes it more difficult for novel treatments, developed for systemic cancers, to reach the tumor at therapeutic concentrations. Encouragingly, brain tumors have been identified as a cancer of unmet need and prioritized for research funding, such that CRUK would like to see a 2-3 fold increase in spend over the next 5 years [11]. Whilst increased investment in research does not come with guarantees of lowering mortality, the more we understand these complex cancers and invest in research infrastructure, the greater chances we will have to treat them effectively over the ensuing decades, adding both years to life and life to years of the affected patients and their families.

Brain tumor research priorities

A key part of developing a strategy is having a shared perspective on the priorities for research. The James Lind Alliance (JLA) is funded through the NIHR, aims to address uncertainties about the effects of treatment. It achieves this by bringing together patients, carers and clinicians to agree which clinical areas matter most and deserve priority attention. In 2015, the JLA Neuro-Oncology Priority Setting Partnership identified 10 clinical areas in brain and spinal cord tumors on which the research community should focus (table 1) [12]. They cover all aspects of the patient journey from lifestyle factors, early diagnosis, surgery, radiotherapy, disease monitoring, molecular genetics, imaging, quality of life and symptom burden. Many of these map onto NHS service provision and clinical studies, which fall within the remit of the brain CSG. The JLA top 10 priority questions provide a valuable benchmark and the clinical importance of these research priorities are exemplified as follows.

JLA priority 3: *Early diagnosis of brain tumors*

Symptoms of a developing brain tumor can be non-specific, and the average general practitioner (GP)

will see few patients who are diagnosed with a brain tumor during the course of their career. In the UK in 2013, 38 % of brain tumor patients visited their GP more than 5 times before diagnosis [13]. Indeed 62% of all brain cancers are only discovered following presentations via Accident and Emergency departments, even where the same patient often previously presented to their GP. This delay in diagnosis increases patient anxiety, and may impact on treatment options and outcome. Timely diagnosis of brain tumors remains a challenge. The ambition is that earlier diagnosis will identify tumors at a smaller size which might be more amenable to complete surgical resection, in turn leading to a better outcome and prognosis [14].

JLA priority 6: *Molecular subtyping of tumors*

The advent of The Cancer Genome Atlas (TCGA) heralded a revolution in our molecular understanding of brain tumors. In May 2016 the World Health Organization (WHO) published a revision of the 2007 classification of brain tumors [15] advising an integrated diagnosis combining molecular and genetic information of tumors with morphology in the classification process [16]. A precise molecular diagnosis impacts on both research and routine clinical decision making, facilitating clinical and translational research by allowing better stratification of patients based on the underlying biology of an individual's tumor. It is envisaged this will facilitate the recruitment of more homogenous populations into clinical trials and support a pharmacogenomics exploration of datasets to create novel drug repositioning opportunities. Genome-wide screening at tumor progression/recurrence on tissue or liquid biopsies could facilitate patient reallocation in basket trials. However, at the interface of research and clinical service delivery, one of the challenges is getting the appropriate test results within a clinically meaningful timeframe.

Challenges to addressing the research priorities

The brain tumor research community in the UK is small. There are very few research-leading oncologists and neuroradiologists, and only a modest number of brain tumor researchers in neurosurgery and neuropathology. This has an impact on the breadth of leadership within the field, the ability to provide mentorship to aspiring researchers and also the number of clinical studies that can be developed and delivered on to the NCRI portfolio for patients to access. Despite these challenges, in the UK all patients are treated within the NHS with good contribution to national clinical data sets, such as HES (Hospital Episode Statistics) and the Cancer Registries.

The current infrastructure to develop a clinical study relies heavily on individual university academics or research-active NHS clinicians to develop a research question into a short proposal for review by the CSG and relevant subgroups. That individual will make use of their local network of collaborators that may include a clinical trials unit lacking experience of brain tumor trials. This model is fundamentally flawed and relies heavily on a single motivated individual to navigate the complexities and nuances of grant applications, clinical trial development and protocol writing. Failure is more often because of limited experience with the process, time pressures, or limited supportive infrastructure, rather than the lack of a good idea.

In contrast, the pharmaceutical industry and European Organization for Research and Treatment of Cancer (EORTC) have access to infrastructure and expertise, but their trials will often only open in the UK in a few pre-selected centers - typically the same 5 or 6 units for each successive trial. This inevitably leads to geographic variation in access to new trial drugs for patients. In addition, the pharmaceutical industry does not prioritize brain cancer for new drug development, due to the challenges of delivering trials in this small but diverse group of patients and the issue of drug delivery across the blood-brain barrier. The research community persists in this approach in order to access

novel agents and derive marginal but meaningful gains in prognosis and outcome, but it is worthy to note that within the UK, medical oncologists, who tend to have dedicated research time and with whom the pharmaceutical industry often have most links, have not routinely been involved in brain tumor patient management. This stems from the UK's dual training of clinical oncologists in both systemic and radiation therapy and from the historical lack of effective systemic agents. However, with a growing focus on tailored, individualized therapy in all cancer groups, the lack of medical oncology involvement risks missing opportunities and cross-cutting expertise which might present themselves via early phase units and other connections. It is of note that most of the recent phase III trials in gliomas, whilst negative in terms of improving survival, have been from industry or the EORTC and the lead investigator has been a medical oncologist or neurologists [17-19].

A strategy for brain tumor research in the UK

The UK neuro-oncology research community is striving towards the dual goals of prevention or cure of brain tumors, and also that people living with and beyond a brain tumor should have the best quality of life possible. At present neither of these ambitions are remotely met. A strategy is needed that can encompass and harness the potential of the community as it works towards improving the diagnosis, treatment, prognosis, and supportive care of patients with brain tumors.

1. Strengthen the existing brain tumor research network

Following publication of the 'Neuro-Oncology JLA Top Ten' (table 1), the stakeholders and funders involved in that process developed a strategy to improve the success of funding applications for clinical research and clinical trials. This strategy includes collaborative multi-center research, the support of Clinical Trials Units and the NIHR Research Design Service, and early involvement of public and patient involvement through the use of focused 'Incubator Days' (http://www.neuro-oncology.org.uk/). Over the last 1-2 years incubator days have been held to develop clinical trials to address epilepsy in glioma and the use of diet in gliomas. As a result the existing network of clinical researchers has been expanded and an application has been submitted to NIHR for the SPRING trial (Seizure PRophylaxis IN Glioma). Whilst this networked approach is more likely to generate successful clinical trials grant applications, it relies heavily on existing networks and collaborators. The neurosurgical community has established a tumor section of the SBNS to promote research that will enable early career surgeons to develop their ideas. A similar network, the British Neurosurgical Trainee Research Collaborative (BNTRC), exists for trainees to develop their ideas with established links to academic neurosurgeons across the UK and is successfully running a study on long-term survivors with glioblastoma. In a similar fashion the annual Glioma Club meeting provides a forum to foster interactions and networking between scientists and clinicians in the field.

Although the British Neuro-Oncology Society (BNOS) hosts an annual conference to provides a forum for scientists to interact with clinicians treating brain tumor patients, it is poorly attended by clinical oncologists or pediatric oncologists – for whom brain tumors may account for only a proportion of their overall clinical practice. As such, clinical and pediatric oncologists are more likely to attend either more general cancer conferences or conferences targeted towards pediatric malignancies respectively, for research updates. This has inevitably resulted in a poor network. However in September 2016, Addenbrooke's Hospital hosted a 2-day 'bootcamp' that brought together clinical oncologists treating brain tumor patients from across the UK. A follow-up 'CNS bootcamp' is planned for 2017 to develop new clinical trials.

2. Improve access to tissue and imaging

The limited impact of brain cancer research worldwide on clinical outcomes for patients is multifactorial. Central amongst these factors is a fundamental lack of understanding of brain cancer biology. Rectifying this requires more dedicated research focused on brain tumors. A key priority, then, must be to invest more in fundamental research that will generate novel, rational therapies based on a clearer understanding of the biology of these tumors. This idea is gaining momentum in the UK but it will take many years for the clinical benefit to be realized. Parallel investment in translational research and infrastructure is equally important to optimize the use of currently available drugs and technologies and to accelerate innovation into the clinic. Recent research has identified specific molecular biomarkers for brain cancer and research is urgently required to optimize their use to guide clinical management in the NHS. Imaging advances in humans and pre-clinical models can augment early phase drug development through mechanistic studies linked to tissue-derived data and measurement of novel agent distribution and CNS penetration *in vivo*, in addition to providing early markers of therapeutic response in both early and later phase studies. Whilst the 100,000 Genome project will provide further insight into improving diagnosis, prognosis and personalized treatment of glioma [20], the real cornerstone to improving the understanding of brain tumor biology is to enable access to fully annotated tissue samples enriched with clinical, imaging and outcome data.

Brain Tumor Biobank

Although biobanking is routine for most pediatric brain tumors, only around 30% of adult patients are asked about gifting tumor tissue for research and patients are often not aware that tissue surplus to diagnostic requirements could be used for future research. Healthcare professionals meanwhile are uncertain about the best time and method to broach the subject of tissue donation, and often the discussion does not take place [7]. Furthermore, there is wide variation across the UK in the resources allocated for tissue biobanking. BRAIN UK [21] is a network of pathology laboratories and 28 of 29 UK neuroscience centers have made their diagnostic and autopsy archives available to researchers. Nevertheless, more funding is needed to improve adult biobanking infrastructure to include frozen tissue samples, primary patient-derived tumor cells and liquid biopsies to create an essential resource to support leading research into disease biology that will have an impact on treatment and care. Crucially, the biological material and molecular annotation must be supplemented with verified clinical data on symptoms, treatments and outcomes. Investment is needed to develop the data infrastructure and regulatory framework that will allow this to happen on a routine basis. In tandem, a standard minimum imaging protocol should be developed and implemented so that every patient in every unit has the same MRI acquisition.

A national biobank initiative is being developed to provide these valuable resources for laboratory and translational researchers. Support is essential to maximize sample collection by neurosurgeons (e.g. technician support in the operating room) as well as cataloging in the neuropathology department. The full complement of tissue, imaging and clinical data is invaluable to researchers, and access to samples will be based purely on the scientific quality of the application and the proposed exit strategy of the research, as assessed by external peer reviewers - so called scientific meritocracy.

3. Developing capacity

The UK clinical brain tumor research community must develop capacity in order to more effectively deliver clinical studies, through investment in both people and infrastructure. There should be a move away from the traditional split of University ‘academics’ and NHS (non-academic) clinicians, and

instead to focus on clinical research teams that can effectively deliver successful grant applications and clinical trials.

People and infrastructure

The multi-disciplinary nature of the management of brain tumors mandates that wider engagement of the clinical neuro-oncology community is essential in order to identify future sustainable leadership. More needs to be done to develop specialist clinical training in the UK through engagement with the Royal Colleges and specialist organizations. Positive examples are the development of sub-specialist neurosurgical oncology by the SBNS and the Association of British Neurologists Neuro-Oncology Advisory Group. Within neuropathology, training in molecular pathology is to be implemented in the postgraduate curriculum – a positive step towards integrating molecular genetics into routine NHS practice, and a byproduct of which is likely to be research-active individuals. Clinical neuro-oncology imaging forms part of the Royal College of Radiologists core curriculum for higher specialist/ Neuroradiology training, although exposure to advanced quantitative imaging techniques is inconsistent across neuroscience centers. The latter is being addressed through training days recently instituted through the British Society of Neuroradiologists (BSNR), however small numbers of trainees undertaking higher degrees towards clinical academic careers and clinical pressures in NHS posts limits research activity in imaging.

Dedicated fellowships for senior trainees that provide a broad exposure to both oncology and neurology could be considered. Efforts to promote neuro-oncology as a positive career for both clinical and medical oncology need to be developed and greater engagement by neurologists should be promoted. Indeed many of the functional consequences of brain cancer and its treatment highlighted by patients are neurological (e.g. seizures, fatigue, language disturbance and cognitive changes) and more neurologists with an interest in brain cancer are required. Education in clinical trial development and implementation, through fellowships or a higher degree will help ensure that future neuro-oncology leaders will have the skills, contacts and networks to deliver well designed clinical trials.

A further point to consider is that in most other developed countries, once they have completed surgery and radiotherapy, adult brain cancer patients are managed by medical oncologists/neurologists. Brain cancer is a fundamental component of pediatric oncology training, but is not currently part of medical oncology training, but this group of clinicians could deliver future drug trials as part of a wider research community. Indeed early-phase trials in neuro-oncology are especially challenging and greater investment is required to develop a core number of units able to support brain cancer research with expertise on novel trial designs, in tandem with developing a cadre of research leading clinical and medical oncologists.

Recruiting patients with brain cancer into clinical studies can be challenging therefore no single center will be able to deliver a suitably powered clinical trial. Several clinical trials unit have experience of coordinating and delivering large multi-center brain cancer studies (e.g. Liverpool, Glasgow and University College London) and this network should be exploited and extended for future trials from the initial trial concept. The expertise provided in trial methodology and health economics is invaluable for submitting competitive grants and ultimately delivering trials for patients onto the research portfolio.

The Role of the Brain CSG

The NCRI Brain CSG overarching strategic aim is to support adult brain tumor research through outreach and stakeholder engagement, promoting capacity development and training, developing data and tissue collection and prioritizing clinical research throughout the patient journey. To implement the strategy the following are proposed:

- Re-organization of the brain CSG subgroups: (i) the Glioma subgroup, (ii) the Meningioma, Metastases and others tumors subgroup and (iii) the Survivorship subgroup. Changing the subgroup focus will facilitate a more disease-orientated approach and establish a clear framework for clinicians and researchers to discuss and develop their study and trial ideas.
- Complete a scoping exercise of clinical, imaging and laboratory research interests across the UK to identify strengths, weakness and existing collaborations with a view to strengthening the existing networks.
- Build the profile of the group through regular engagement with the neuro-oncology community using existing networks. These networks include the ABN and SBNS academic networks and newly formed tumor section, British Neurosurgical Trainees Research Collaborative (BNTRC), British Neuropathology Society (BNS), British Society of Neuroradiologists (BSNR), CNS Bootcamp, Glioma Club, British Neuro-Oncology Society (BNOS) and BRAIN UK, and at annual conference meetings.
- Through engagement activities provide mentorship to early-career clinicians with study ideas that can be developed via the CSG subgroups and that will encourage individuals to join the subgroups, which will aid with succession planning when members reach their term on the main group.
- Map the CSG strategy to the forthcoming CRUK strategic review for brain tumor research key priorities.
- Ensure that the quality of research applications are internationally competitive prior to submission to funding organizations.

Conclusions

Brain tumor research in the UK has increased over the last 10-15 years, but a formal, cohesive national strategic direction has been lacking. In order to realize improvements in treatment and prognosis for patients with brain tumors we need to work collaboratively. Being a comparatively small academic community can be an advantage, and we should exploit this. Greater emphasis needs to be placed on co-leadership of research initiatives by a scientist and a clinician working together. This would allow scientists to optimize benefit from material and data generated in clinical studies and allow clinicians to ensure NHS practice is conducted in a research-supportive manner. National biobanking initiatives are essential to provide high quality clinically annotated samples, linked to national cancer registries that will drive translational research for new drug discovery. Finally we must identify those future leaders, both clinical and laboratory based who can build on the proposed strategy.

Table 1

James Lind Alliance Neuro-Oncology priority questions for research

	Research Priority
1	Do **lifestyle factors** (e.g. sleep, stress, diet) influence tumour growth in people with a brain or spinal cord tumour?
2	What is the effect on prognosis of **interval scanning** to detect tumour recurrence, compared with scanning on symptomatic recurrence, in people with a brain tumour?
3	Does **earlier diagnosis** improve outcomes, compared to standard diagnosis times, in people with a brain or spinal cord tumour?
4	In second recurrence glioblastoma, what is the effect of **further treatment** on survival and quality of life, compared with best supportive care?
5	Does **earlier referral to specialist palliative care** services at diagnosis improve quality of life and survival in people with a brain or spinal cord tumours?
6	Do **molecular subtyping techniques** improve treatment selection, prediction and prognostication in people with a brain or spinal cord tumour?
7	What are the **long-term physical and cognitive effects** of surgery and/or radiotherapy when treating people with a brain or spinal cord tumour?
8	What is the effect of interventions to help **carers** cope with changes that occur in people with a brain or spinal cord tumour, compared with standard care?
9	What is the effect of additional **strategies for managing fatigue**, compared with standard care, in people with a brain or spinal cord tumour?
10	What is the effect of **extent of resection** on survival in people with a suspected glioma of the brain or spinal cord?

References

1. http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-5ala-and-gliadel-wafers-as-part-of-treatment-for-glioblastoma-gala5. Accessed at April 14, 2017
2. http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-to-see-if-a-drug-called-gliolan-can-help-to-confirm-the-grade-of-a-brain-tumour-during. Accessed at April 14, 2017
3. Jenkinson MD, Javadpour M, Haylock BJ, et al. The ROAM/EORTC-1308 trial: Radiation versus Observation following surgical resection of Atypical Meningioma: study protocol for a randomised controlled trial. *Trials.* 2015; 16:519.
4. http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-olaparib-and-radiotherapy-for-people-with-glioblastoma-paradigm. Accessed at April 14, 2017
5. http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-olaparib-with-temozolomide-glioblastoma-has-come-back. Accessed at April 14, 2017
6. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours/mortality. Accessed at April 14, 2017
7. *Living with a brain tumor: prevalence of intracranial brain tumors. brainstrust and National Cancer Registration Service*2013.
8. Burnet NG, Jefferies SJ, Benson RJ, Hunt DP, Treasure FP. Years of life lost (YLL) from cancer is an important measure of population burden--and should be considered when allocating research funds. *Br J Cancer.* 2005; 92(2):241-245.
9. Moazzam AA, Wagle N, Zada G. Recent developments in chemotherapy for meningiomas: a review. *Neurosurgical focus.* 2013; 35(6):E18.
10. Jenkinson MD, Haylock B, Shenoy A, Husband D, Javadpour M. Management of cerebral metastasis: Evidence-based approach for surgery, stereotactic radiosurgery and radiotherapy. *Eur J Cancer.* 2011; 47(5):649-655.
11. http://www.cancerresearchuk.org/our-research/our-research-by-cancer-type/our-research-on-brain-tumours. Accessed at April 14, 2017
12. http://www.jla.nihr.ac.uk/priority-setting-partnerships/neuro-oncology/. Accessed at April 14, 2017
13. Schmidt-Hansen M, Berendse S, Hamilton W. Symptomatic diagnosis of cancer of the brain and central nervous system in primary care: a systematic review. *Fam Pract.* 2015; 32(6):618-623.
14. Brown TJ, Brennan MC, Li M, et al. Association of the Extent of Resection With Survival in Glioblastoma: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2016; 2(11):1460-1469.
15. Louis DN, Ohgaki, H., Wiestler, O.D., et al. *WHO Classification of Tumours of the Central Nervous System*. Lyon: IARC Press; 2007.

16. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* 2016; 131(6):803-820.

17. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med.* 2014; 370(8):709-722.

18. Stupp R, Hegi ME, Gorlia T, et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014; 15(10):1100-1108.

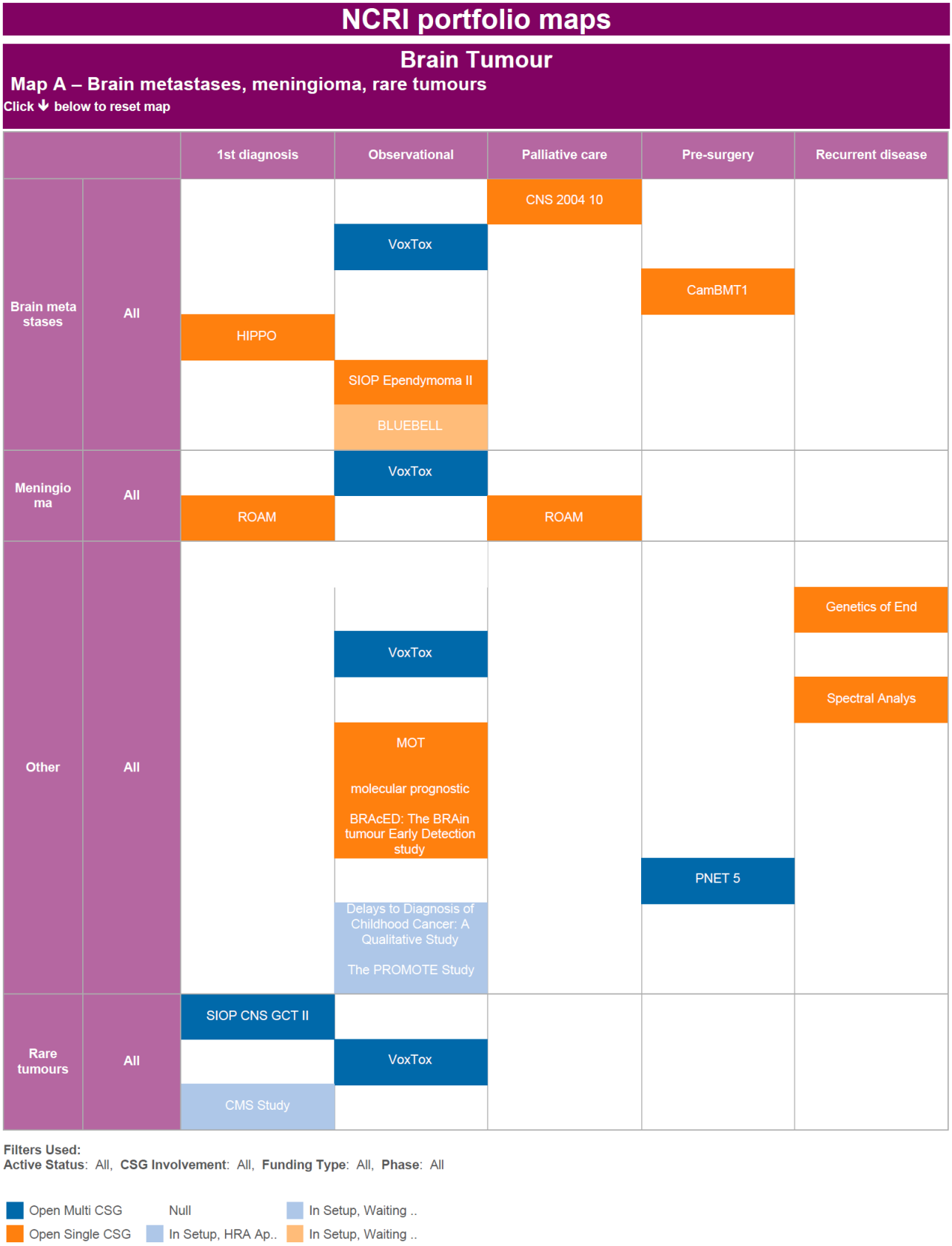
19. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005; 352(10):987-996.

20. https://www.genomicsengland.co.uk/the-100000-genomes-project/. Accessed at April 14, 2017

21. http://www.southampton.ac.uk/brainuk/index.page. Accessed at April 14, 2017

Appendix 4

Portfolio maps



NCRI portfolio maps

Brain Tumour

Map B – Gliomas, astrocytoma, glioblastoma

Click ↓ below to reset map

		1st diagnosis	Observational	Palliative care	Pre-surgery	Recurrent disease
Anaplastic astrocytoma (grad..	All	TSPO PET Imaging in GBM	MR characterisa GBM VoxTox Imaging in Trans Glioma Brain Tissue at	Diffusion imagi		TSPO PET Imaging in GBM
Anaplastic oligodendroglioma..	All		MR characterisa GBM VoxTox Imaging in Trans Glioma	Diffusion imagi		
Glioblastoma	All	DCVax PARADIGM ReoGlio PRaM-GBM The KEATING trial TSPO PET Imaging in GBM PARADIGM 2	MR characterisa GBM molecular markers in VoxTox Imaging in Trans Glioma Cerebral Tumours		GALA/BIDD RTOG 3508/AbbVie M13/813	TSPO PET Imaging in GBM
Low grade glioma	All	Biomede	MR characterisa GBM VoxTox Imaging in Trans Glioma MISSION: GliomaS	Diffusion imagi		VINILO

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All

Open Multi CSG | In Setup, HRA Ap.. | In Setup, NHS Per..
Open Single CSG | In Setup, HRA Ap.. | Suspended Single..

Appendix 5

Publications in the reporting year

Study	Reference
Biomarkers in Brain Tumours	DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Sahm F, Schrimpf D, Stichel D, Jones DT, Hielscher T, Schefzyk S, Okonechnikov K, Koelsche C, Reuss DE, Capper D, Sturm D, Wirsching HG, Berghoff AS, Baumgarten P, Kratz A, Huang K, Wefers AK, Hovestadt V, Sill M, Ellis HP, Kurian KM, Okuducu AF, Jungk C, Drueschler K, Schick M, Bewerunge-Hudler M, Mawrin C, Seiz-Rosenhagen M, Ketter R, Simon M, Westphal M, Lamszus K, Becker A, Koch A, Schittenhelm J, Rushing EJ, Collins VP, Brehmer S, Chavez L, Platten M, Hänggi D, Unterberg A, Paulus W, Wick W, Pfister SM, Mittelbronn M, Preusser M, Herold-Mende C, Weller M, von Deimling A. Lancet Oncol. 2017 Mar 14. pii: S1470-2045(17)30155-9. doi: 10.1016/S1470-2045(17)30155-9
	Decreased expression of the mitochondrial BCAT protein correlates with improved patient survival in IDH-WT gliomas.Conway ME, Hull J, El Hindy M, Taylor SC, El Amraoui F, Paton-Thomas C, White P, Williams M, Ellis HP, Bertoni A, Radlwimmer B, Hutson SM, Kurian KM.Brain Pathol. 2016 Nov;26(6):789-791. doi: 10.1111/bpa.12385.
	Genetic alterations in uncommon low-grade neuroepithelial tumors: BRAF, FGFR1, and MYB mutations occur at high frequency and align with morphology. Qaddoumi I, Orisme W, Wen J, Santiago T, Gupta K, Dalton JD, Tang B, Haupfear K, Punchihewa C, Easton J, Mulder H, Boggs K, Shao Y, Rusch M, Becksfort J, Gupta P, Wang S, Lee RP, Brat D, Peter Collins V, Dahiya S, George D, Konomos W, Kurian KM, McFadden K, Serafini LN, Nickols H, Perry A, Shurtleff S, Gajjar A, Boop FA, Klimo PD Jr, Mardis ER, Wilson RK, Baker SJ, Zhang J, Wu G, Downing JR, Tatevossian RG, Ellison DW. Acta Neuropathol. 2016 Jun;131(6):833-45.
	The transcription factor PPARalpha is overexpressed and is associated with a favourable prognosis in IDH-wildtype primary glioblastoma.Haynes HR, White P, Hares KM, Redondo J, Kemp KC, Singleton WG, Killick-Cole CL, Stevens JR, Garadi K, Guglani S, Wilkins A, Kurian KM. Histopathology. 2016 Dec 7. doi: 10.1111/his.13142
DORIC	P Mulholland, D Krell, I Khan, C McBain, C Patel, K Wanek, K Hopkins, S Jefferies, R Jager, P Smith, Q Liu, R Stupp, I Tomlinson (2016) Multicentre, randomised, double-blind phase II study comparing cediranib (AZD2171) plus gefitinib (Iressa ZD1839) with cediranib plus placebo in subjects with

	recurrent/progressive glioblastoma. PLOS ONE 2016 May: 11(5): e0156369
EORTC 22033-26033	Brigitta G Baumert, Monika E Hegi, Martin J van den Bent, Andreas von Deimling, Thierry Gorlia, Khê Hoang-Xuan, Alba A Brandes, Guy Kantor, Martin J B Taphoorn, Mohamed Ben Hassel, Christian Hartmann, Gail Ryan, David Capper, Johan M Kros, Sebastian Kurscheid, Wolfgang Wick, Roelien Enting, Michele Reni, Brian Thiessen, Frederic Dhermain, Jacoline E Bromberg, Loic Feuvret, Jaap C Reijneveld, Olivier Chinot, Johanna M M Gijtenbeek, John P Rossiter, Nicolas Dif, Carmen Balana, Jose Bravo-Marques, Paul M Clement, Christine Marosi, Tzahala Tzuk-Shina, Robert A Nordal, Jeremy Rees, Denis Lacombe, Warren P Mason, Roger Stupp (2016). Lancet Oncology. 2016; 17:1521-32
Functional Imaging of Tumours	Rebecca Birch, Andrew C. Peet, Hamid Dehghani, and Martin Wilson. Influence of Macromolecule Baseline on 1H MR Spectroscopic Imaging Reproducibility. Magnetic Resonance in Medicine. 2016 Jan 22. doi: 10.1002/mrm.26103.
	Franklyn A Howe & Andrew C Peet, Characterizing Brain Tumors by MRS, eMagRes, 2016 Mar 15; 5(1). doi: 0.1002//9780470034590.emrstem1425.
IMA 950	R Rampling, S Peoples, PJ Mulholland, A James, O Al-Salihi, C Twelves, C McBain, S Jefferies, A Jackson, W Stewart, J Linder, S Kutscher, N Hilf, L McGuigan, J Peters, K Hill, O Schoor, H Singh-Jasuja, SE Halford, JWA Ritchie (2016) A Cancer Research UK first time in human phase I trial of IMA950 (novel multi-peptide therapeutic vaccine) in patients with newly diagnosed glioblastoma. Clinical Cancer Research 2016 Oct: 22(19); 4776-85
Magnetic Resonance Imaging to Characterise Invasive Phenotypes in Cerebral Gliomas	SJ Price, AM Young, WJ Scotton, J Ching, LA Mohsen, NR Boonzaier, VC Lupson, JR Griffiths, MA McLean, TJ Larkin (2016) Multimodal MRI can identify perfusion and metabolic changes in the invasive margin of glioblastomas. Journal of magnetic resonance imaging: Journal of Magnetic Resonance Imaging 43(2): 487–494.
	J-L Yan, A van der Hoorn, TJ Larkin, NR Boonzaier, T Matys, SJ Price (2016) Extent of resection of peritumoural DTI abnormality as a predictor of survival in adult glioblastoma patients. Journal of Neurosurgery 2016 Apr 8:1-8.
	NR Boonzaier, TJ Larkin, T Matys, A van der Hoorn, J-L Yan, and SJ Price (2017) Multiparametric MRI assessment of diffusion and perfusion in contrast-enhancing and non-enhancing components in glioblastoma. Radiology (accepted for publication).
	J-L Yan, A van der Hoorn, TJ Larkin, NR Boonzaier, T Matys, SJ Price (2017) Extent of resection of peritumoural DTI

MR Imaging Invasive Phenotypes	abnormality as a predictor of survival in adult glioblastoma patients. Journal of Neurosurgery 126(1):234-241.
	T Ajithkumar, SJ Price, G Horan, A Burke and SJ Jefferies (2017) Prevention of radiotherapy-induced neurocognitive dysfunction in survivors of paediatric brain tumours - the potential role of modern imaging and radiotherapy techniques. The Lancet Oncology (accepted for publication).
	A van der Hoorn, J-L Yan, TJ Larkin, NR Boonzaier, T Matys, SJ Price (2016) Validation of a semi-automatic co-registration of MRI scans in patients with brain tumors during treatment follow-up. NMR in Biomedicine 29(7):882-889.
	SJ Price, K Allinson, H Liu, NR Boonzaier, J-L Yan, VC Lupson and TJ Larkin (2016) IDH-1 mutated glioblastomas have a less invasive phenotype than IDH-1 wild type glioblastomas: a diffusion tensor imaging study. Radiology Nov 16 [Epub ahead of print].
	MG Hart, R Ypma, R Romero-Garcia, SJ Price and J Suckling (2016) Graph theory analysis of complex brain networks: new concepts in brain mapping applied to neurosurgery. Accepted for publication in Journal of Neurosurgery 124:1665-1678.
	A van der Hoorn, J-L Yan, TJ Larkin, NR Boonzaier, T Matys, SJ Price (2016) Posttreatment ADC changes in the periresectional area in patients with glioblastoma. World Neurosurgery 92:159-65.
PARADIGM	Glioblastoma in the elderly - How do we choose who to treat?Lorimer CF, Saran F, Chalmers AJ, Brock J. J Geriatr Oncol. 2016 Nov;7(6):453-456. doi: 10.1016/j.jgo.2016.07.005. Epub 2016 Jul 29.PMID: 27478132
	Clinical development of new drug-radiotherapy combinations. Sharma RA, Plummer R, Stock JK, Greenhalgh TA, Ataman O, Kelly S, Clay R, Adams RA, Baird RD, Billingham L, Brown SR, Buckland S, Bulbeck H, Chalmers AJ, Clack G, Cranston AN, Damstrup L, Ferraldeschi R, Forster MD, Golec J, Hagan RM, Hall E, Hanauske AR, Harrington KJ, Haswell T, Hawkins MA, Illidge T, Jones H, Kennedy AS, McDonald F, Melcher T, O'Connor JP, Pollard JR, Saunders MP, Sebag-Montefiore D, Smitt M, Staffurth J, Stratford IJ, Wedge SR; NCRI CTRad Academia-Pharma Joint Working Group..Nat Rev Clin Oncol. 2016 Oct;13(10):627-42. doi: 10.1038/nrclinonc.2016.79. Epub 2016 Jun 1. Review PMID: 27245279
	Science in Focus: Combining Radiotherapy with Inhibitors of the DNA Damage Response. Chalmers AJ. Clin Oncol (R Coll Radiol). 2016 May;28(5):279-82. doi: 10.1016/j.clon.2016.01.035. Epub 2016 Feb 23. No abstract available.PMID 26920234
	Clinical development of new drug-radiotherapy combinations.

PARADIGM-2	Sharma RA, Plummer R, Stock JK, Greenhalgh TA, Ataman O, Kelly S, Clay R, Adams RA, Baird RD, Billingham L, Brown SR, Buckland S, Bulbeck H, Chalmers AJ, Clack G, Cranston AN, Damstrup L, Ferraldeschi R, Forster MD, Golec J, Hagan RM, Hall E, Hanauske AR, Harrington KJ, Haswell T, Hawkins MA, Illidge T, Jones H, Kennedy AS, McDonald F, Melcher T, O'Connor JP, Pollard JR, Saunders MP, Sebag-Montefiore D, Smitt M, Staffurth J, Stratford IJ, Wedge SR; NCRI CTRad Academia-Pharma Joint Working Group..Nat Rev Clin Oncol. 2016 Oct;13(10):627-42. doi: 10.1038/nrclinonc.2016.79. Epub 2016 Jun 1. Review.PMID: 27245279
	Science in Focus: Combining Radiotherapy with Inhibitors of the DNA Damage Response. Chalmers AJ. Clin Oncol (R Coll Radiol). 2016 May;28(5):279-82. doi: 10.1016/j.clon.2016.01.035. Epub 2016 Feb 23. No abstract available.PMID 26920234
ROAM	Goldbrunner R, Minniti G, Preusser M, Jenkinson MD, Sallabanda K, Houdart E, von Deimling A, Stavrinou P, Lefranc F, Lund-Johansen M, Moyal EC, Brandsma D, Henriksson R, Soffietti R, Weller M. EANO guidelines for the diagnosis and treatment of meningiomas. Lancet Oncol. 2016 Sep;17(9):e383-91. doi: 10.1016/S1470-2045(16)30321-7. Review.
	Santarius T, Jenkinson MD, Kirollos RW. A quest towards personalised medicine for grade II meningiomas--will need to zoom in. Acta Neurochir (Wien). 2016 May;158(5):931-2. doi: 10.1007/s00701-016-2774-8. No abstract available.

Appendix 6

Major international presentations in the reporting year

Study	Conference details
Functional Imaging of Tumours	Worthington LA, Ramm L, Parulekar M, Peet AC, and Davies NP. A preliminary study using fractional anisotropy difference maps as an aid to detect visual function changes in children with optic pathway glioma. IPEM Fetal, Neonatal and Paediatric MR Imaging - Techniques and Applications, Leeds March 2016.
ROAM	Jenkinson et al. 1308-ROAM: International trial of Radiation versus Observation following surgical resection of atypical meningioma. Invited speaker EORTC EGAM meeting, Brussel, Belgium. 10 March 2017
ROAM	Jenkinson MD et al. The ROAM / EORTC 1308 trial: Radiation versus Observation following surgical resection of atypical meningioma: a randomised controlled trial – study update. Invited speaker. Society for Neuro-Oncology Conference on Meningioma, Toronto, Canada. 17-18 June 2016