NCRI
National
Cancer
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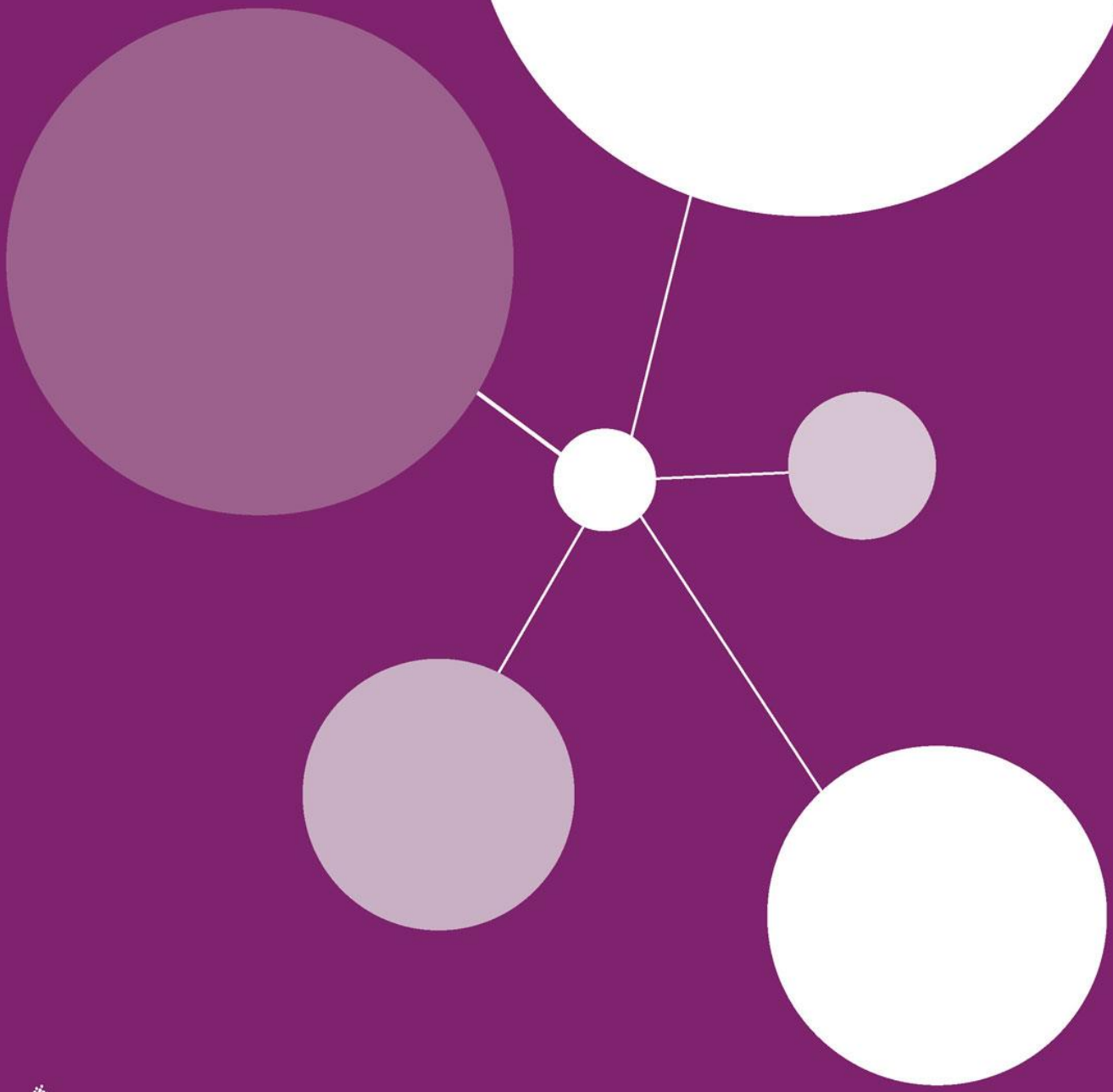
Institute

NCRI Brain Tumour Clinical Studies Group

Annual Report 2015-16



Partners in cancer research

NCRI Brain Tumour CSG Annual Report 2015-16

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

The principle achievements of the main CSG have been the re-invigoration of the quality of life subgroup, securing CRUK funding of the imaging biomarker study PRaM and the growth of surgeon-led clinical trials supported by the CSG.

The quality of life subgroup is concentrating on clinical trials around epilepsy and prioritised topics from the James Lind Alliance. Two successful incubator days to consider clinical trials on epilepsy prevention in brain tumour patients has pulled together a multidisciplinary group that is now developing a trial proposal. Future incubator days will focus on patient priorities including role of a ketogenic diet, managing fatigue and lifestyle factors such as stress.

A biomarker study (PRaM) will investigate imaging markers that may predict where local areas of recurrence could emerge. This study is now is setup. Additional studies are planned that will couple the imaging data with biological sampling to support translational research.

The main 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. Reconfiguration of the Novel Agents Subgroup may be necessary to bring in medical oncology expertise in early-phase drug trials and combination trials. Efforts to develop radiotherapy trials will also be encouraged. A clinical oncology boot camp will be hosted by Dr Jefferies to begin to identify key research questions for clinical oncologists to examine. This will be followed by the Brain CSG strategy day in October to carry forward new initiatives.

2. Structure of the Group

Dr Anthony Chalmers and Dr Gillian Whitfield have left the group. Dr Sarah Jefferies and Dr Sara Erridge have joined the group as new oncologists. We have appointed two new trainee members, Dr Babar Vaqas (neurosurgical trainee) will work with the technology subgroup under Mr Price and Dr Ali Rooney (psychiatry trainee) will work with the quality of life subgroup under Dr Grant.

The Chair of the Novel Agents Subgroup is vacant following the resignation of Dr Chalmers and the role and structure of this Subgroup is currently under review.

3. CSG & Subgroup strategies

Main CSG

The Quality of Life/Palliative Care Subgroup has been re-invigorated following the appointment of Dr Robin Grant. Strategy for this Subgroup is focused 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 Subgroup is undertaking consultation exercises with incubator days in epilepsy, coping with fatigue and lifestyle changes planned. An important priority for the next reporting year will be to ensure that the energy and enthusiasm is translated into successful clinical trial proposals.

Developing a surgical trial network is well underway with the formation of the tumour section of the SBNS and a successful Meningioma study day held at the Sanger Centre. Several surgical clinical trials are under consideration including risk stratification of incidental meningiomas and surgical management of residual disease in glioma.

In-house development of investigator-led studies by the novel agents subgroup has resulted in PARADIGM opening to recruitment and REOGLIO (lead Prof Short) and PARADIGM-2 (lead Prof Chalmers) being funded by CRUK NAC. These latter two are phase I trials now in set up. A significant challenge going forward will be to encourage other oncologists to engage with clinical trial development. Within the NAT investigator-led portfolio OPARATIC, PARADIGM, PARADIGM-2, HCQ and REOGLIO were all developed by just two oncologists (Prof Chalmers & Prof Short). Sorafenib in NF2 was developed by Prof Hanneman (neurologist). A strategy day will be held in October to consider how these activities can best be supported within the Brain CSG.

Imaging & Technology Subgroup (Chair, Dr Stephen Price)

- Develop a network of trial competent sites to promote multicentre trials
    - Surgical technology trials already shown can work via the GALA-5 study and now the GALA-BIDD study (lead Colin Watts).
    - Imaging studies will develop this via the PRaM-GBM study. Advanced plans to develop an imaging substudy to the ROAM trial (called the BRAIN study) to explore mechanism of normal brain injury following radiotherapy. The latter study has advantage of a control arm (lead Stephen Price).
    - As imaging expertise is variable, the BRAIN study will explore a novel design of a two tier imaging program with a basic tier that all centres can use, and then a more explorative tier for those with research experience of advanced imaging methodology (lead Stephen Price).
    - A network of radiotherapy technology study sites will be developed with the ROAM and HIPPO studies. This will require excellent collaboration with CTRAD (lead Michael Jenkinson and Gillian Whitfield).
    - Development of a 7 Tesla imaging collaboration between Cambridge, Oxford and Nottingham. As part of this a biomarker trial of imaging 2-hydroxyglutarate in low grade gliomas has been submitted to CRUK (lead Olaf Ansorge).
- Develop a minimal imaging dataset (lead Adam Waldman)
    - We have now developed the protocol for this that aligns with EORTC and US imaging dataset.
    - Difficult is getting it into practice to prevent units requesting funding to do this 'basic' imaging. We plan to develop this as a Royal College of Radiologist guideline for brain tumour imaging (lead Adam Waldman and Gerard Thompson).

    - Once developed we could consider role of data mining to extract more information. Pilot project at Imperial has been developed and will be applying for funding (lead Matt Williams).
- Explore the James Lind Alliance Neuro-oncology priority question 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?
- Explore the James Lind Alliance Neuro-oncology priority question 10 - What is the effect of extent of resection on survival in people with a suspected glioma of the brain or spinal cord?

Novel Agents & Translational Subgroup (Chair, Professor Anthony Chalmers)

Strategic Aims:

- Increase availability of early phase clinical trials to brain tumour patients through:
    - In-house development of high quality, investigator led studies of novel agents and combinations.
    - Increasing activity and quality in pre-clinical evaluation of novel agents and combinations in clinically relevant models of brain tumours, in collaboration with the UK Radiotherapy-Drug Combinations Consortium (RaDCom).
    - Working towards multi-arm 'umbrella' studies that will enable large numbers of patients to participate in early and late phase trials testing a broad range of promising new agents and combinations.
    - Consumer provision of insights and expertise to improve the relevance and reach of the research patients and the wider public.
- Promote and facilitate translational research activity by:
    - Establishing networks of laboratories, early phase clinical trial centres and brain tumour biorepositories.
    - Increasing banking of and access to high quality brain tumour tissue with associated clinical information
    - Rolling out comprehensive molecular testing of all primary brain tumours to optimise diagnosis, facilitate translational research and maximise outputs from clinical trials.
    - Achieving effective consumer involvement through dissemination of information and the provision of a network and a community, led by consumers.

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

This Subgroup was reformatted in November 2015 with a broad representation across the care pathway from GP to palliative care encompassing key professional groups and includes voluntary charity representation (brainstrust and the IBTA). The Short-Term Aim is to build on and develop the questions related to QoL in James Lind Alliance Neuro-Oncology Top 10 Clinical Questions.

The Long Term Aims are to develop clinical studies for supportive care and quality of life. Increase accrual rates to studies in supportive care and quality of life. The Subgroup has identified the following JLA areas as the focus for studies:

1. Lifestyle factors (sleep, stress, diet)
2. Early Diagnosis
3. Early Referral to Palliative Care
4. Long term physical and cognitive effects
5. Intervention to help carers cope
6. Additional factors for managing fatigue

In addition, tumour associated epilepsy will remain a focus.
Structure: groups work with associated NCRI Groups in collaboration on questions, e.g. Primary Care; Supportive and Palliative Care; Psychosocial Oncology and Survivorship.

RDS/CTU links: Our aim is to develop and support production of a trial in that area by linking with RDS/CTU/Charities/NIHR to discuss proposals at "Incubator" days. Funding and running of these has been agreed in principle for all 10 JLA Questions supported by brainstrust/TBTC/Marie Curie/ Matthews Friends/Epilepsy Research UK.

(See the form below for more information - under Appendix 2).

4. Task groups/Working parties

N/A

5. Patient recruitment summary for last 5 years

In the Brain Tumour CSG portfolio, 5 no. of trials closed to recruitment and 3 opened.

Table 1 Summary of patient recruitment by RCT/Non-RCT

Year	All subjects		Cancer patients only		% of cancer patients relative to incidence	
	Non-RCT	RCT	Non-RCT	RCT	Non-RCT	RCT
2011/2012	560	77	534	77	12.7	1.8

Table 2 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

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

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

The Brain CSG is continuing to develop a strengthening relationship with other CSGs, in particular Breast & Lung. For example an early phase trial CamBMT1 (NCT02768337) is an open label, 3-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 Brain 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

Table 3 Funding submissions in the reporting year

Cancer Research UK Clinical Research Committee (CRUK CRC)			
Study	**Application type**	**CI**	**Outcome**
July 2015 (CTAAC)			
Sample collection associated with the PARADIGM Trial (OlaPArib And RADiotherapy In newly-diagnosed GlioblastoMa - CRUK Ref: A17870)	Sample collection	Professor Anthony Chalmers	Funded
December 2015			
Investigating the clinical utility of the branched chain aminotransferase proteins as positive predictors of patient survival in glioblastomas	Feasibility application	Professor Myra Conway & Dr Kathreena Kurian	Not funded
May 2016			
None			

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. The CSG usually has limited input into study design. To date no industry study has competed with other portfolio studies for patients.

Currently the Brain CSG portfolio consists of the following industry studies:

- 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.
- 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.

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 vs. 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 1-3 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 CSG and 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 voice makes to the research agenda; consumer engagement is in the DNA of this CSG and its subgroups.

Key drivers have been:

1. The top ten uncertainties identified by the James Lind Alliance Priority Setting Partnership, specifically:
    - 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
2. Building links with other groups and CSGs, e.g. CTRad, Proton Beam Consortium, CRUK, NCIN, Use My Data.
3. Increasing engagement across the four nations, with links to Brain Tumour Research Focus Group at Belfast Centre for Cancer Research and the Scottish Clinical Trials Units.
4. Attending conferences and presenting posters.
5. 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, the NCRI CSG held a strategy day where a panel of UK brain tumour and primary cancer specialists discussed current and potential studies for patients with brain metastases. As a result of this meeting plans were implemented develop new trial opportunities for patients with brain metastases. This has resulted in the CamBMT1 trial (NCT02768337 see above) and the HIPPO trial to evaluate 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.

A new strategy day is planned for October 2016 to develop a five year plan ahead of the CSG Chair rotation in October 2017.

12. Priorities and challenges for the forthcoming year

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.

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.

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 – Imaging & Technology Subgroup Strategy
- C – Novel Agents & Translational Subgroup Strategy
- D – Supportive & Palliative Care Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 - Publications in previous year

Appendix 5 - Major international presentations in previous year

Dr Colin Watts (Brain Tumour CSG Chair)

Appendix 1

Membership of the Brain Tumour CSG

Name	Specialism	Location
Mr Paul Brennan*	Clinical Lecturer	Edinburgh
Professor Anthony Chalmers	Clinical Oncologist	Glasgow
Dr Sara Erridge	Clinical Oncologist	Edinburgh
Dr Sarah Jefferies	Clinical Oncologist	Cambridge
Dr Catherine McBain	Clinical Oncologist	Manchester
Dr Stefan Nowicki*	Clinical Oncologist	Glasgow
Mr Peter Burchill	Consumer	Sheffield
Ms Debbie Keatley	Consumer	Belfast
Dr Robin Grant	Neurologist	Edinburgh
Dr Kathreena Kurian	Neuropathologist	Bristol
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 Adam Waldman	Radiologist	London
Dr Helen Bulbeck	Representative, Brain Tumour Charity	Isle of Wight
Dr Wendi Qian	Statistician	Cambridge
Mr Michael Jenkinson	Surgeon	Liverpool
Mr Stephen Price	Surgeon	Cambridge
Dr Colin Watts (Chair)	Surgeon	Cambridge

* denotes trainee member

Membership of the Subgroups

Novel Agents & Translational Subgroup		
Name	**Specialism**	**Location**
Professor Anthony Chalmers (Chair)	Clinical Oncologist	Glasgow
Dr Sarah Jefferies	Clinical Oncologist	Cambridge
Dr Catherine McBain	Clinical Oncologist	Manchester
Dr Stefan Nowicki*	Clinical Oncologist	Glasgow
Professor Susan Short	Clinical Oncologist	London
Dr Juanita Lopez**	Clinical Scientist	London
Mr Kismet Hossain-Ibrahim	Consultant Neurosurgeon	Dundee
Dr Helen Bulbeck	Consumer	Isle of Wight
Mr Paul Smith**	CTU Manager	London
Professor Oliver Hanemann	Neurologist	Plymouth
Professor Sebastian Brandner**	Neuropathologist	London
Dr Kathreena Kurian	Neuropathologist	Bristol
Dr Darren Hargrave**	Paediatric Oncologist	London
Ms Erica Little**	Project Officer, Brain Tumour Charity	Farnborough
Dr Tracy Warr	Reader in Neuro-Oncology	Wolverhampton
Dr Colin Watts**	Surgeon	Cambridge

Imaging & Technology Subgroup		
Name	**Specialism**	**Location**
Dr Jeremy Rees	Clinical Oncologist	London
Dr Paul Sanghera	Clinical Oncologist	Birmingham
Professor Susan Short	Clinical Oncologist	London
Dr Gillian Whitfield	Clinical Oncologist	Manchester
Dr Federico Roncaroli	Neuropathologist	London
Dr Alan Jackson	Radiologist	Manchester
Dr Rolf Jager	Radiologist	London
Dr Adam Waldman (Chair)	Radiologist	London
Dr Chris Clark	Reader in Imaging and Biophysics	London
Professor Franklyn Howe	Reader in MRI Physics	London
Dr Andrew Peet	Reader in Paediatric Oncology	Birmingham
Dr Andrew Brodbelt	Surgeon	Liverpool
Dr Paul Byrne	Surgeon	Nottingham
Mr Michael Jenkinson	Surgeon	Liverpool
Mr Stephen Price	Surgeon	Cambridge

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
Ms Charlotte Lambourn	Nurse	London
Dr Matthew Morrall	Paediatric Neuropsychologist	Leeds
Dr Martin McCabe	Paediatric Oncology	Manchester
Dr Ann Arber	Senior Lecturer, Cancer & Palliative Care	Surrey

*denotes trainee member

**denotes non-core member

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

The period 2012-14 saw the final results from several international phase III multicentre clinical trials published. Unfortunately these trials were uniformly negative and has led to a reconsideration of trials of the format "Standard of Care + X". In the same period there have been several landmark translational studies revealing the complexity of brain cancer in terms of patterns of mutations, clonal diversity and evolutionary dynamics. In parallel, data from The Cancer Genome Atlas is paving the way for a revised classification of brain tumours (WHO 2016 revision of WHO 2007 classification) that incorporates current validated biomarkers.

Set against this background the accelerating development of the NCRI Brain CSG is timely. Brain cancer has been prioritised by Cancer Research UK (CRUK) as part of its strategic planning for the next five years. The CSG needs to engage more actively through a closer and more confident dialogue with CRUK, CTAAC (now CRC) and other stakeholders including NIHR and brain tumour charities. In this way the CSG will provide clinical leadership and direction that will inform the development of translational research programmes and engagement with pharma, biotech and other potential commercial partners.

Specific priorities going forward will include:

- Promoting the collection of linked clinical and biological (especially genomic) data with the objective of establishing a stratified medicine programme for brain cancer within a three-five year time horizon.
- Developing a closer dialogue with CRUK/NIHR with the following objectives:
    - Establishing a translational infrastructure for adult glioma research
    - Embedding tumour banking into routine clinical practice
    - Developing better models for drug development that are relevant for brain cancer
    - Promoting surgical and radiotherapy trials
    - Promote the development of academic *medical* neuro-oncology in the UK to develop early phase and multi-arm multi-stage clinical trials.
- Establish a feasibility study: 'Managing tumour-associated epilepsy at the end of life: use of leviteracetam in a syringe driver versus standard care' by the Quality of Life/Supportive & Palliative Care Subgroup.
- Build on evolving collaborations with the US & Canada with priority areas including developing patient stratification paradigms through functional genomics and developing trials in rare cancers through the IRCI initiative.
- Addressing some of the barriers to trial recruitment we have identified. Particular emphasis will be placed on strategies to mitigate geographical restriction on trial participation. PPI involvement will be of particular importance with respect to this issue.
- Promoting further recruitment to subgroups with particular emphasis on academic neuro-radiology and neuro-pathology.

Work from our previous Portfolio coordinators into issues around improving recruitment has confirmed that the CSG has a year-on-year increase in the number of trials open, the number of sites recruiting to trials and the number of patients recruited. Their work has identified significant barriers including insufficient resources (such as staff and equipment), clinicians who were not engaged in research and a lack of 'exciting' trials to offer patients. A minimal dataset for MRI and

a strategy for accessing novel agents have been proposed as solutions and embraced by the respective subgroups. Examples of best practice included good communication between departments and appointment of brain tumour specific trial coordinators. Further work with the Supportive & Palliative Care Subgroup and with our PPI consumers (brainstrust) to exploit this information and develop strategies to improve patient access to trials is planned. Funding for the project officer position is no longer available and we are working with multiple stakeholders to find ways to keep the momentum in this area of CSG activity. This represents a significant challenge to the CSG going forward.

Meningiomas are the commonest primary brain tumour, but there are few study/trial opportunities. The CSG has identified this as an area for further development building on our successful development of the NIHR-unded ROAM trial, in 2015 we will explore to opportunities for further research and trials for meningiomas. The following work streams are in development:

- Development of risk stratification model for incidental meningioma (including exploration of serum biomarkers for disease monitoring).
- Development of a core outcome set for meningioma trials/studies.
- Identifying actionable mutations in aypical meningioma for re-purposing of existing drugs or the development of novel agents.
- Developing stratified therapeutics in rare meningiomas through the IRCI initiative.

This work programme (lead: Jenkinson) will exploit the following international collaborations that are in development:

- Collaboration between the Response Assessment for Neuro-Oncology (RANO) meningioma working group (Professors Rogers, Mehta, Vogelbaum) and the Core Outcome Measures in Effectiveness Trials (COMET) initiative in Liverpool.
- Collaboration between Mr Jenkinson and Professor Priscilla Brastianos (The Broad Institute, USA) for identifying actionable mutations in atypical meningiomas.

B – Imaging & Technology Subgroup Strategy

Achievements:

- PRaM-GBM trial successfully funded by CRUK Biomarker awards.
- GALA-BIDD trial recruiting well and open in multiple centres, demonstrating multi-centre working.
- ROAM and HIPPO trials have both opened.
- SJP (on behalf of the subgroup) invited to lead a NCRI Future of Surgery Workshop on Technology Trials in Surgical Oncology.

Strategy:

The strategy of this Subgroup will be further developed over this year at a strategy day organised by Adam Waldman.

- Develop a network of trial competent sites to promote multicentre trials
    - Surgical technology trials already shown can work via the GALA-5 study and now the GALA-BIDD study (lead Colin Watts).
    - Imaging studies will develop this via the PRaM-GBM study. Advanced plans to develop an imaging substudy to the ROAM trial (called the BRAIN study) to explore mechanism of normal brain injury following radiotherapy. The latter study has advantage of a control arm (lead Stephen Price).
    - As imaging expertise is variable, the BRAIN study will explore a novel design of a two tier imaging program with a basic tier that all centres can use, and then a

more explorative tier for those with research experience of advanced imaging methodology (lead Stephen Price).
    - A network of radiotherapy technology study sites will be developed with the ROAM and HIPPO studies. This will require excellent collaboration with CTRAD (lead Michael Jenkinson and Gillian Whitfield).
    - Development of a 7 Tesla imaging collaboration between Cambridge, Oxford and Nottingham. As part of this a biomarker trial of imaging 2-hydroxyglutarate in low grade gliomas has been submitted to CRUK (lead Olaf Ansorge).
- Develop a minimal imaging dataset (lead Adam Waldman)
    - We have now developed the protocol for this that aligns with EORTC and US imaging dataset.
    - Difficult is getting it into practice to prevent units requesting funding to do this 'basic' imaging. We plan to develop this as a Royal College of Radiologist guideline for brain tumour imaging (lead Adam Waldman and Gerard Thompson).
    - Once developed we could consider role of data mining to extract more information. Pilot project at Imperial has been developed and will be applying for funding (lead Matt Williams).
- Explore the James Lind Alliance Neuro-oncology priority question 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?
    - Current survey underway organized by King's Group to assess practice among health professionals will help informing this question (led by Tom Booth).
    - Need a systematic review of the topic.
    - Plan to discuss further at Strategy Day.
- Explore the James Lind Alliance Neuro-oncology priority question 10 - What is the effect of extent of resection on survival in people with a suspected glioma of the brain or spinal cord?
    - Initial survey of impact of technology on extent of resection (lead by Keymours Ashkan).
    - Plan to discuss further at Strategy Day.
    - Aim to explore early phase trial of iKnife (to be led by Babar Vaqas).

Challenges:

- Getting minimal data set into clinical practice to avoid need for it to be funded in all studies.
- Difficulties of multicentre, multivendor imaging of quantitative biomarkers. Need to learn from Paediatric Imaging Network (led by Andrew Peet).
- Lack of clarity of funding and pathway for early phase trials of new technology.
- Developing/supporting a research programme to take advantage of the newly commissioned stereotactic radiosurgery services and the developing proton beam centres.

C – Novel Agents & Translational Subgroup Strategy

Achievements:

- Sorafenib in NF, HCQ, OPARATIC and PARADIGM trials opened and recruiting; all phase I-II studies developed within the subgroup.
- ReoGlio and PARADIGM-2 phase I trials successfully funded by CRUK New Agents Committee. Due to open Q2-3 2016.

- NCRI Glioma Network established with four workstreams covering trial development, molecular stratification, pre-clinical evaluation of novel combinations and building an early phase trials network.
- Increased portfolio of Industry sponsored studies. INTELLANCE-2 currently open and recruiting very well in UK. Sativex completed recruitment. Others in set-up, including nivolumab randomised phase III studies.
- Engaged with a number of small biotech companies who had not previously worked in the brain tumour field e.g. E-Therapeutics (dexanabinol); GW Pharma (Sativex); Immunocellular Therapeutics (ICT-107); Lipopharma (Minerval).
- Worked with Brain UK to incorporate brain tumour tissue collection in this UK network of brain tissue biobanks.
- Consumer engagement has driven the collection of brain tumour tissue into a UK network and is widening the campaign for post-surgical collection.

Strategy:

- Increase availability of early phase clinical trials to brain tumour patients through:
    - In-house development of high quality, investigator led studies of novel agents and combinations.
    - Increasing activity and quality in pre-clinical evaluation of novel agents and combinations in clinically relevant models of brain tumours, in collaboration with the UK Radiotherapy-Drug Combinations Consortium (RaDCom).
    - Working towards multi-arm 'umbrella' studies that will enable large numbers of patients to participate in early and late phase trials testing a broad range of promising new agents and combinations.
    - Consumer provision of insights and expertise to improve the relevance and reach of the research patients and the wider public.
- Promote and facilitate translational research activity by:
    - Establishing networks of laboratories, early phase clinical trial centres and brain tumour biorepositories.
    - Increasing banking of and access to high quality brain tumour tissue with associated clinical information
    - Rolling out comprehensive molecular testing of all primary brain tumours to optimise diagnosis, facilitate translational research and maximise outputs from clinical trials.
    - Achieving effective consumer involvement through dissemination of information and the provision of a network and a community, led by consumers.

Challenges:

- Accessing novel agents early in the drug development process.
- Opening trials across multiple centres, each of which is likely to recruit only small numbers of patients.
- Demonstrating tumour PK and PD of novel agents in pre-clinical models and in patients.
- Obtaining programmatic research funding to support generation, validation and utilisation of clinically relevant models of primary brain tumours.
- Lack of unified strategy and funding for consistent testing of diagnostic and prognostic biomarkers, and lack of a clear strategy for the implementation of whole genome tests, such as next generation sequencing and methylome arrays.
- Obtaining institutional, financial and infrastructural support for biobanking.

- Obtaining funding and support for network activities, capacity building, pre-clinical research and early phase clinical trial activity.
- Realising potential of NCRI Glioma Network without administrative support.

D – Supportive & Palliative Care Subgroup Strategy

This Subgroup has re-structured around the experience and links required to cover the breadth of the supportive care and palliative care neuro-oncology agenda, particularly around the JLA Brain & Spinal cord tumour clinical priority areas. This includes a Primary care specialist, neurologist, rehabilitation specialist, oncologist and paediatric oncologist, palliative care physician, neuropsychologist, neuro-oncology specialist nurse and palliative care nurse, and key voluntary groups (brainstrust and the IBTA).

The supportive and palliative care questions from the 2015 JLA priority research areas will form the basis of "incubator days" to discuss possible trial protocols with the assistance of clinical trial unit and RDS support.

Incubator days have been held in:

- Epilepsy: (Seizure PRophylaxis IN Glioma – "SPRING"). A RCT of pre-operative Levetiracetam vs standard care in patients with primary brain tumours who have not had seizures (Edinburgh Jan 2016).
- Lifestyle Changes: Ketogenic Diet in patients with glioma undergoing chemo-radiotherapy (London July 2016).
- Epilepsy: "SPRING" and RCT of Levetiracetam vs other agent in patients with new onset TAE (Leeds June 2016).
- Management of Fatigue in Glioma (Leeds June 2016).
- Helping Carers Cope: Studies of methods for assisting Carers (Leeds June 2016).

Other Incubator days are planned in Studies to Improve Early Diagnosis; Early Palliative Care; Late Side Effects. All Incubator Days for JLA priority areas are being supported financially by brain tumour charities (brainstrust, The Brain Tumour Charity, Matthew's Friends/Brain Tumour Research/Astrofund).

The Subgroup has submitted four of the top 10 JLA areas for consideration for NIHR Calls for Research Funding in Oct 2015. These include: Lifestyle factors; Interval Scanning; Earlier Diagnosis and Long Term Physical and Cognitive Effects.

The Subgroup has established links with COCHRANE neuro-oncology group to prioritise JLA topics for up to date systematic reviews to help pave the way for clinical trials in these significant areas of uncertainty. Early referral to Palliative Care; Helping Carer's Cope and Extent of resection in spinal cord tumours have been accepted and allocated to gather the evidence for future research in the top 10 priority JLA areas. Ketogenic Diet and other dietary interventions in Glioma; Second Recurrence; Long term effects are also subject to current Cochrane Reviews.

The Subgroup submitted three suggestions to the NIHR Clinical Reference Group (Feb 2016) for Commissioning. Earlier diagnosis: Early Palliative Care: Molecular Subtyping – all three were taken forward by the Brain and CNS Clinical Reference Group.

A proposal from the Subgroup was presented to CTRad for comment: Protons vs Photons in CNS tumours to reduce late side effects. The CTRad proposal form has been adapted and distributed to encourage potential studies in the Supportive & Palliative Care areas and distributed via British Neuro-Oncology Society (BNOS) prior to the Leeds Meeting in June 2016.

Existing studies currently being looked at by the Subgroup:

- 'Managing tumour-associated epilepsy at the end of life: use of levetiracetam in a syringe driver versus standard care'. The aim: a feasibility study.
- 'Early Palliative Care for patients with Glioblastoma Multiforme'. Dr Anthony Byrne and the Wales CTU on the protocol development.

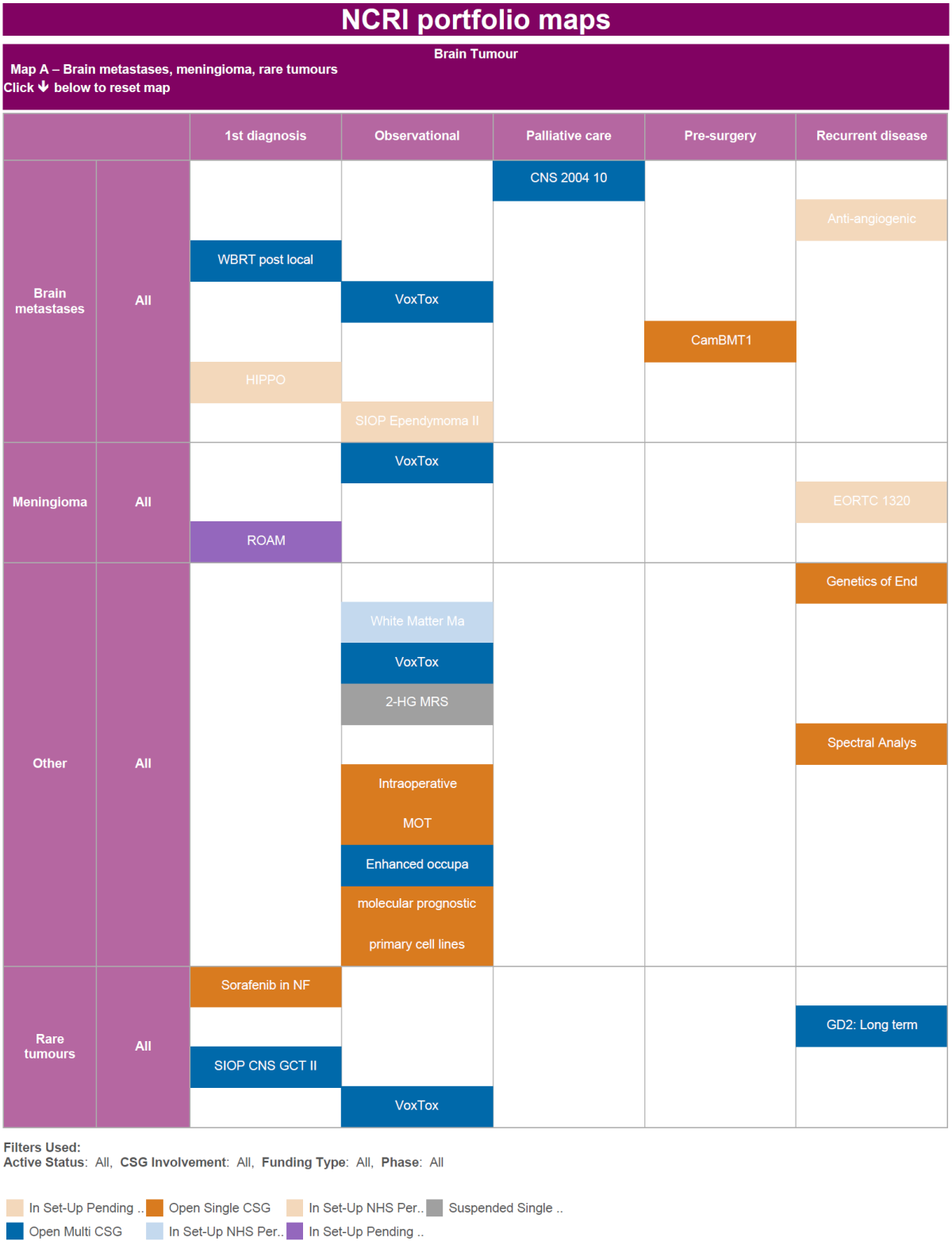
The Subgroup has submitted a workshop proposal for the NCRI Cancer Conference in Birmingham (November 2016): 'Measuring Neurocognition in brain tumour studies: current evidence and future direction'. The objective is to bring the neuro-oncology, and general communities together to encourage collaboration and research.

Two of the Subgroup members were involved in Planning the Epilepsy Research UK (ERUK) Expert Workshop on "Tumour Associated Epilepsy: Bridging the Transitional Gap (Oxford March 2016).

The Subgroup has established a website to encourage and advise researchers about Neuro-Oncology Clinical Trials - NOCTURN: Neuro-Oncology Clinical Trials UK Research Network.

Appendix 3

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 (grade 3)	**All**		MR characterisa GBM VoxTox Imaging in Trans Glioma 18F-FMC and MRS	Diffusion imagi		
Anaplastic oligo dendroglioma..	**All**		MR characterisa GBM VoxTox Imaging in Trans Glioma 18F-FMC and MRS	Diffusion imagi		
Glioblastoma	**All**	A randomised ph DCVax PARADIGM RTOG 3508/AbbVie Dexanabinol	MR characterisa GBM Prognostic and VoxTox Imaging in Trans Glioma 18F-FMC and MRS		GALA-BIDD	Phase 1 trial o ABT-414 glioblastoma
Low grade glioma	**All**		MR characterisa GBM VoxTox Imaging in Trans Glioma 18F-FMC and MRS	Diffusion imagi		

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

In Set-Up Pending .. Open Single CSG Suspended Single ..
Open Multi CSG In Set-Up Pending ..

Appendix 4

Publications in the reporting year

NIHR funded Magnetic Resonance Imaging to Characterise Invasive Phenotypes in Cerebral Gliomas
A van der Hoorn, J-L Yan, TJ Larkin, NR Boonzaier, T Matys and SJ Price (2016) Posttreatment ADC changes in the periresectional area in patients with glioblastoma. World Neurosurgery (in press).

J-L Yan, A van der Hoorn, TJ Larkin, NR Boonzaier, T Matys and 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. [Epub ahead of print].

SJ Price, Young AM, Scotton WJ, J Ching, LA Mohsen, NR Boonzaier, VC Lupson, JR Griffiths, MA McLean and TJ Larkin (2016) Multimodal MRI can identify perfusion and metabolic changes in the invasive margin of glioblastomas. Journal of magnetic resonance imaging 43(2): 487–494.

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.

ESTRO-ACROP guideline "target delineation of glioblastomas"
Niyazi M, Brada M, Chalmers AJ, Combs SE, Erridge SC, Fiorentino A, Grosu AL, Lagerwaard FJ, Minniti G, Mirimanoff RO, Ricardi U, Short SC, Weber DC, Belka C.

Radiother Oncol. 2016 Jan;118(1):35-42.

Synthesis and Evaluation of a Radioiodinated Tracer with Specificity for Poly (ADP-ribose) Polymerase-1 (PARP-1) in Vivo
Zmuda F, Malviya G, Blair A, Boyd M, Chalmers AJ, Sutherland A, Pimlott SL. J Med Chem. 2015 Nov 12;58(21):8683-93.

Selective Inhibition of Parallel DNA Damage Response Pathways Optimizes Radiosensitization of Glioblastoma Stem-like Cells
Ahmed SU, Carruthers R, Gilmour L, Yildirim S, Watts C, Chalmers AJ. Cancer Res. 2015 Oct 15;75(20):4416-28.

Abrogation of radioresistance in glioblastoma stem-like cells by inhibition of ATM kinase
Carruthers R, Ahmed SU, Strathdee K, Gomez-Roman N, Amoah-Buahin E, Watts C, Chalmers AJ. *Mol Oncol.* 2015;9(1):192-203.

Appendix 5

Major international presentations in the reporting year

There were no presentations.