APPROACH

*Analysis of **Proton** vs. **Photon** Radiotherapy in Oligodendroglioma and Assessment of Cognitive Health*

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Trial Summary

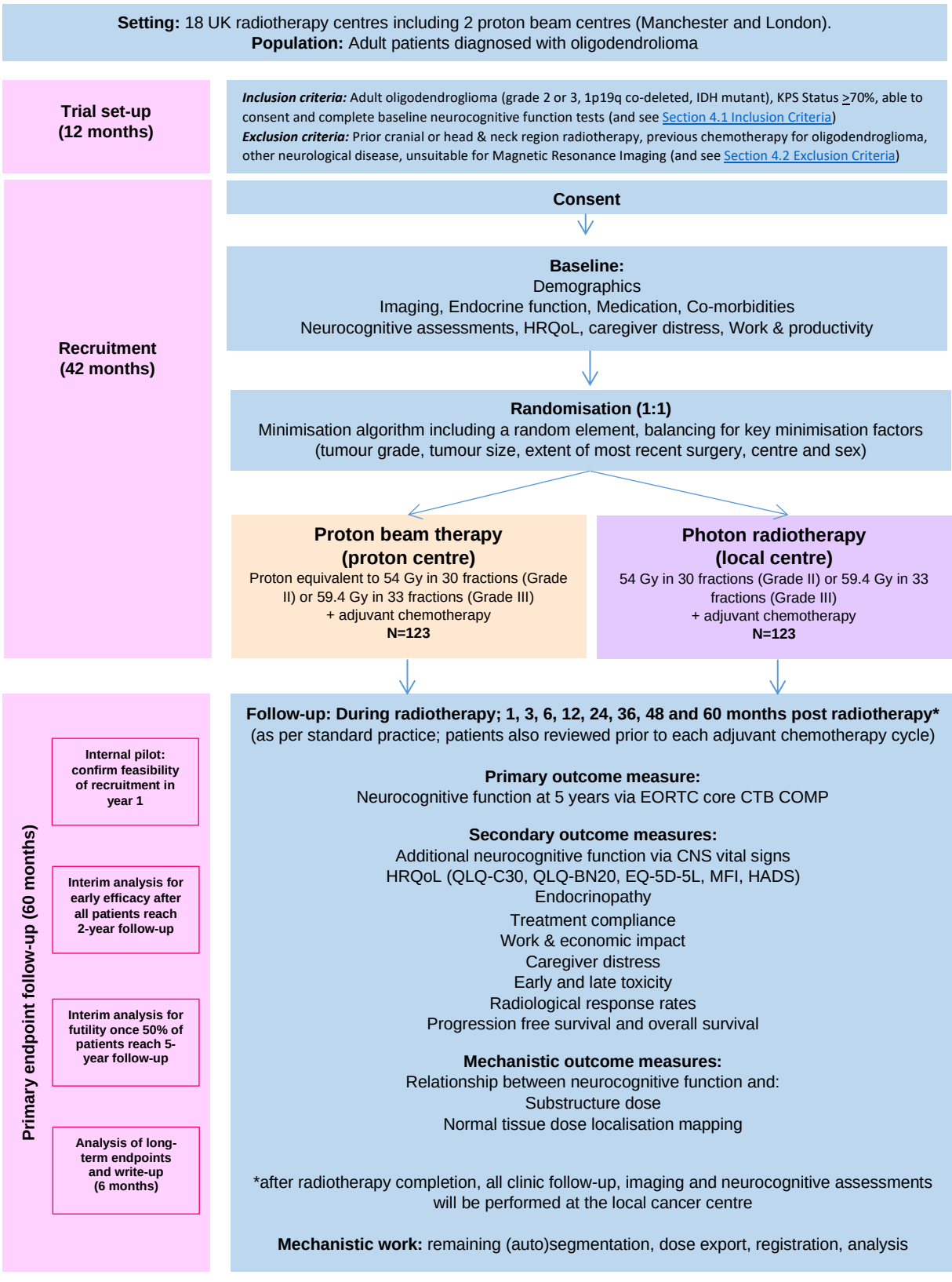
Title	**A**nalysis of **P**roton vs. **P**hoton **R**adiotherapy in **O**ligodendroglioma and **A**ssessment of **C**ognitive **H**ealth
Acronym	APPROACH
Background	Adults with oligodendroglioma (ODG) have very good prognosis brain tumours, with median survival in excess of 10 years. Radiotherapy (RT), traditionally delivered using photon radiation, is an important component of treatment. Despite controlling the tumour, photon RT can damage the healthy brain surrounding the tumour, resulting in long-term irreversible side effects. These include neurocognitive decline (NCD). Even small deficits in neurocognitive function (NCF) may have an adverse impact on quality of life (QoL) and noticeable impact on daily living, which is especially relevant for ODG patients, given their young age at diagnosis and prolonged survival. NCD may be apparent as soon as two years post-RT and becomes more obvious over time. Proton beam therapy (PBT) is an alternative type of RT that can potentially spare more surrounding healthy brain than photon RT, without compromising tumour control. The lower healthy tissue doses from PBT offer the potential for reduced long-term toxicity, including reduced NCD. PBT has recently become available in the United Kingdom (UK) but it is expensive relative to photon RT and currently only available in two NHS centres. Therefore, randomised trials of PBT are required to investigate the potential benefits of PBT over photon RT in most adult cancers, including in patients with ODG.
Population	Patients with oligodendroglioma
Design	The APPROACH trial is a Phase III, multicentre trial. Patients will be recruited from 18-25 centres and randomised 1:1 between photon RT and PBT, delivered over approximately 6 weeks. Photon RT will be delivered at the local RT centre while PBT will be delivered at one of the two NHS PBT centres in the UK (The Christie or UCLH). Neurocognitive tests will be performed at baseline, one month post end of RT and annually for 5 years. Follow up will also include clinical assessment, blood tests and brain imaging, as per standard follow up protocols. Patient QoL and productivity questionnaires and caregiver questionnaires will also be performed throughout follow-up. Interim analyses will assess the feasibility of recruitment, early efficacy at 2 years (i.e., signals of improved NCF with PBT), and assess futility. The primary endpoint will be at 5 years. 246 patients (123 per arm) are required to detect a moderate effect size difference in NCF at 2 and 5 years between PBT and photon RT.
Objectives	i) Feasibility of recruitment to a randomised trial of PBT versus photon RT, ii) Whether there are early (2 years post-RT) signals of neurocognitive benefit with PBT compared to photon RT, iii) Whether there is a long-term (5 years post-RT) neurocognitive benefit of PBT compared to photon RT.
Intervention	RT will be delivered as an outpatient on weekdays over approximately 6 weeks. Throughout this document the relative biological effectiveness (RBE) weighted dose in units of Gray(Gy(RBE)) is used to describe the product of the absorbed dose and the RBE. For PBT, the RBE should be interpreted as 1.1. For photons this should be interpreted as 1 for which Gy(RBE) is equivalent to the absorbed dose in Gy.

	The total RT dose will be 54 Gy(RBE) in 30 daily fractions for grade II tumours and 59.4 Gy(RBE) in 33 daily fractions for grade III tumours. Photon RT will be delivered using intensity modulated RT (IMRT) or rotational arc therapy (e.g. Rapid Arc, VMAT or Tomotherapy). PBT will be delivered using pencil beam scanning with optimisation, typically performed using single field optimisation (SFO). Adjuvant PCV chemotherapy will be given as per standard practice. PCV will consist of: - Lomustine 100mg/m^2, with dose banding/ capping as per the institution's usual practice, day 1, PO, on a 42-day cycle +/- - Procarbazine 100mg/m^2, with dose banding/ capping as per the institution's usual practice, once daily on days 1-10 or days 2-11, PO, on a 42-day cycle +/- - Vincristine 1.4-1.5mg/m^2 (or flat dose of 2mg if this is usual institutional practice), with dose banding/ capping as per the institution's usual practice, IV day 1, on a 42-day cycle. If a patient has a body surface area (BSA) of <1.45m^2, then dosing must be based on BSA.
Sample size	246 patients
Follow-up	Patients will be assessed during RT and 1, 3, 6, 12, 24, 36, 48 and 60 months post end of RT, as per standard follow-up schedules. Patients will also be reviewed prior to each PCV cycle.
Primary Endpoint	The primary endpoint is NCF at 5 years, assessed using a standard neurocognitive test battery - EORTC core clinical trial battery composite (CTB COMP). There are a series of assessment stages: • Stage 1 (internal pilot): Recruitment rate over 12 months (see Section 7.1 Recruitment Setting). • Stage 2 (intermediate endpoint): NCF at 2 years, to enable potential early practice-change. • Stage 3 (futility analysis): NCF once 50% of patients have completed 5 years of follow up, to assess futility. • Stage 4 (final analysis): NCF once all patients have completed 5 years of follow up
Secondary Endpoints	The secondary endpoints include: • Additional NCF outcomes • HRQoL • Endocrinopathy • Treatment compliance • Work & economic impact • Caregiver distress • Early and late toxicity • Radiological response rates • Progression-free survival • Overall survival
Main Inclusion Criteria	• Histologically proven diagnosis of ODG with 1p19q co-deletion and isocitrate dehydrogenase (IDH) mutation • Randomisation must be performed within 28 days of the magnetic resonance imaging (MRI) that leads to the decision that RT is required at that point in time. Outside of 28 days, an

	updated MRI is required to serve as a contemporaneous baseline scan to assess response to further treatment. • Karnofsky Performance Status (KPS) ≥70%. • Adequate wound healing and recovery if recent surgery. • Suitable to complete baseline neurocognitive testing (No access to translated tests, can only be administered in English). • Patients of childbearing potential should be asked to confirm that they are not pregnant to confirm trial eligibility. Formal Pregnancy testing should be performed if there is any doubt as to pregnancy status or if felt appropriate, including in circumstances such as irregular periods, unprotected sexual intercourse since the last menstrual period, missed contraceptive pill or antibiotics during the last menstrual cycle or failure of barrier contraception. See section 4.3 Birth control: contraception and pregnancy testing for further details. • Fertile participants, born male, must agree to practice methods of contraception that are considered medically acceptable for the duration of RT, adjuvant chemotherapy and for 6 months post-end of treatment if sexually active with a person of child-bearing potential. See section 4.3 Birth control: contraception and pregnancy testing for further details. • Able to swallow oral medication. • Able to provide study-specific informed consent. • Age 25 or above at the point of starting RT treatment. • No known haematological, renal or hepatic impairments making PCV chemotherapy inappropriate
Main Exclusion Criteria	• Pregnancy (positive pregnancy test) or lactating. • Prior cranial or head and neck RT. • Any previous chemotherapy for the treatment of ODG. • Comorbid neurodegenerative diseases that influence NCF. • Severe active co-morbidity making patient unsuitable for RT and/ or adjuvant chemotherapy (e.g., uncontrolled diabetes, uncontrolled hypertension). • Leptomeningeal disease. • Spinal or infratentorial disease. • Another currently active malignancy or another malignancy within the last 3 years. • Any contra-indication to procarbazine, vincristine or lomustine (see section 8.2.1 Chemotherapy contraindications for further information) including: coeliac disease; the rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption. • Any recognised genetic syndrome causing sensitivity to radiotherapy. • Patient unwilling/ unable to attend for follow up in the local radiotherapy centre. • Contraindication to MRI or gadolinium.
Randomisation	Two-arm (1:1) randomisation to either photon RT or PBT. All patients will receive adjuvant PCV chemotherapy.

APPROACH Trial Schema

Analysis of Proton vs Photon Radiotherapy in Oligodendroglioma and Assessments of Cognitive Health (APPROACH)



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Abbreviations

Table 1 Abbreviations

Abbreviation	Meaning
AEs	Adverse Events
ALT	Alanine transaminase
APL	Authorised Personnel Log
APPROACH	Analysis of Proton vs. Photon Radiotherapy in Oligodendroglioma & Assessment of Cognitive Health
ARs	Adverse Reactions
BN20	Brain Tumour module
BSA	Body surface area
CI	Confidence interval
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COWA	Controlled Oral Word Association
CP	Conditional Power
CRF	Case Report Form
CT	Computerised tomography
CTB COMP	Clinical Trial Battery Composite
CTCAE	Common Terminology Criteria for Adverse Events
CTRU	Clinical Trials Research Unit
DLM	Dose location maps
DMEC	Data Monitoring and Ethics Committee
DMPA	Depot Medroxyprogesterone Acetate
eCRF	electronic Case Report Form
EME	Efficacy and Mechanism Evaluation
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire Core 30
EORTC BN20	EORTC Brain Cancer Module 20
EQD2	Equivalent dose in 2 Gy fractions
FBC	Full Blood Count
FDA	Food and Drug Administration
FSH/LH	Follicle-stimulating hormone/Luteinizing hormone
FWER	Family wise error rate
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
GH/IGF-1	Growth hormone/Insulin-like growth factor-1
Gy	Gray
HADS	Hospital Anxiety Depression Scale
HRA	Health Research Authority
HRQoL	Health related quality of life

HVLT-R	Hopkins Verbal Learning Test - Revised
ICMJE	International Committee of Medical Journal Editors
IDH	Isocitrate dehydrogenase
IM	Intramuscular
IMRT	Intensity Modulated Radiotherapy
ISF	Investigator Site File
JLA	James Lind Alliance
IRAS	Integrated Research Application System
KPS	Karnofsky performance score
LFTs	Liver Function Tests
LGG	Low grade glioma
LSM	Lesion Symptom Mapping
MDT	Multi-disciplinary team
MFI	Multi-dimensional Fatigue Inventory
MRI	Magnetic Resonance Imaging
NCD	Neurocognitive decline
NCF	Neurocognitive function
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NHS	National Health Service
NRG	National Surgical Adjuvant Breast and Bowel Project, Radiotherapy Oncology Group and Gynecologic Oncology Joint Research Consortium
NTCP	Normal Tissue Complication Probability
OAR	Organs At Risk
ODG	Oligodendroglioma
OS	Overall survival
PBT	Proton beam therapy
pCRF	Paper CRF
PCV	Procarbazine, Lomustine, Vincristine
PFS	Progression-free survival
PI	Principal Investigator
PIS	Patient Information Sheet
PISICF	Patient Information Sheet & Informed Consent Form
PPI	Patient and Public Involvement
QA	Quality Assurance
QoL	Quality of life
RANO	Response Assessment in Neuro-Oncology
RCT	Randomised controlled trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RT	Radiotherapy

RTTQA	Radiotherapy Trials Quality Assurance
RUSAE	Related and Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard deviation
SFO	Single Field Optimisation
SFTS	Secure File Transfer Service
SNO	Society for Neuro-Oncology
SOP	Standard Operating Procedure
SmPC	Summary of product characteristics
SVZ	Sub-ventricular zones
T4/T3/TSH	Thyroxine/Tri-iodothyronine/Thyroid Stimulating Hormone
TMG	Trial Management Group
TMT-A/B	Trail Making Test A and B
TMZ	Temozolomide
TSC	Trial Steering Committee
U&Es	Urea and Electrolytes
UK	United Kingdom
ULN	Upper limits of normal
US	United States
VLSM	Voxel-based lesion-symptom mapping
WPAI	Work Productivity and Activity Impairment

1 Background and Rationale

1.1 Oligodendroglioma

Oligodendroglioma (ODG) is the third most common type of glioma and accounts for 3-5% of primary brain tumours and 5-18% of gliomas, (Koeller and Rushing 2005). Since 2016, the diagnosis of ODG is made based on the histological appearance of diffuse infiltrating glioma in the presence of 1p19q chromosomal co-deletion and isocitrate dehydrogenase (IDH) mutation (Louis *et al.* 2016; Wesseling and Capper 2018). ODG may be classified as grade 2 or grade 3, although it is now understood that this molecular make up (i.e. 1p19q co-deletion and IDH mutation) is more important in determining outcome than whether tumours are histologically grade 2 (low grade) or 3 (high grade) (Cancer Genome Atlas Research *et al.* 2015). ODG typically has a good prognosis, with median survival in excess of 10 years (van den Bent *et al.* 2013; Buckner *et al.* 2016). Around 350 patients are diagnosed with ODG each year in the United Kingdom (UK) and the median age at diagnosis is 45 years (Cancer Genome Atlas Research *et al.* 2015; Cancer Research UK. 2019). Seizures are the most common presenting symptom, followed by headache (Koeller and Rushing 2005). Over half of ODG tumours are located in the frontal lobe, with the next most common site being the temporal lobe (Koeller and Rushing 2005).

While the timing of intervention with surgery and or radiotherapy remain a matter of some controversy, standard of care treatment consists of maximal debulking surgery, radiotherapy (RT) and adjuvant chemotherapy using Procarbazine, Lomustine and Vincristine (PCV) (van den Bent *et al.* 2013; Buckner *et al.* 2016).

Given the relatively young age at presentation, many of these patients have work and/or caring responsibilities. These, together with the prolonged survival experienced by these patients, mean that the long-term consequences of treatment are a critically important survivorship issue.

1.2 Rationale for study

1.2.1 Long-term irreversible toxicity following radiotherapy for good prognosis glioma

Photon radiotherapy (RT) is a mainstay of cancer treatment but can result in long-term irreversible toxicity due to collateral damage to surrounding normal tissue. In brain tumour patients treated with photon RT, such long-term toxicity may include neurocognitive decline (NCD) (Klein 2012). This is an irreversible toxicity and is of particular importance: in patients with stable brain tumours, even small deficits in neurocognitive function (NCF) are related to worse health-related quality of life (HRQoL) and profoundly affect instrumental activities of daily living. For example, 38.5% of low grade glioma (LGG) patients have a decline in ≥1 HRQoL scale despite long-term stable disease (Giovagnoli and Boiardi 1994; Kiebert *et al.* 1998; Giovagnoli 1999; Boele *et al.* 2014; Boele *et al.* 2015). Patients with stable brain tumours following treatment report themes such as: “I feel like I’ve lost ‘me’” and “I had to quit my job as I simply couldn’t do the work because of the diminution of cognitive skills, and a lack of energy and stamina. I now feel very deflated with no job, no driving licence and little ambition” (The Brain Tumour Charity. 2015). Such changes not only impact on patients but also on their caregivers (Boele *et al.* 2013). In addition, cognitive deficits result in work limitations and loss of productivity in the brain tumour context, contributing to twice as many workdays missed per annum in brain tumour survivors compared to non-cancer patients (Feuerstein *et al.* 2007; Nugent *et al.* 2014). A brain tumour diagnosis is thought to result in an average annual productivity loss of ~£13,886 per patient (Boele *et al.* 2020), and annual caregiver income loss of €8,124-€20,196 (Bayen *et al.* 2017). This diagnosis therefore

places a disproportionately large financial burden on society (Fineberg *et al.* 2013; Boele *et al.* 2020).

NCD is a specific concern for patients with good prognosis brain tumours, including those with ODG. Given the young age at diagnosis, these patients often have work and caring responsibilities that even small declines in NCF can impair, and over 50% are affected by NCD in the long-term (Douw *et al.* 2009). Means of preserving NCF are therefore highly relevant for this patient group. The James Lind Alliance (JLA) have identified the long-term cognitive effects of RT as a Neuro-Oncology top 10 research priority (Grant *et al.* 2015; James Lind Alliance 2015).

1.3 Proton beam therapy (PBT)

Proton Beam Therapy (PBT) is an alternative form of RT. Like photon RT, PBT is delivered once daily on weekdays over a number of weeks. The physical properties of proton beams mean that a significantly reduced RT dose is deposited in the normal tissue beyond the tumour (see Figure 1 Photon RT (a) and PBT (b) radiotherapy dose distributions in a glioma patient). It is therefore hypothesised that PBT may cause less long-term normal tissue toxicity. Of almost 7500 RT centres worldwide (International Atomic Energy Agency (IAEA) 2020), there are only 92 PBT facilities (Particle Therapy Co-Operative Group 2020). Establishing a PBT facility requires major infrastructure investment including installation of a cyclotron (to generate protons). In addition to the considerable expense involved, the lack of definitive randomised controlled trials (RCTs) to demonstrate any clinical benefit of PBT over photon RT has, to date, limited wider uptake of this technology. Indeed, in the UK PBT is only commissioned for very limited, specific indications (NHS England 2018) (mainly paediatric and skull base cancers) due to the lack of a wider evidence-base to justify the increased costs. Until recently, all UK patients requiring PBT have had to travel abroad for treatment. Now, however, PBT is available in the UK with two NHS centres in England (each costing ~£125m, (BBC News 2019)). The first NHS PBT centre (Manchester) opened in December 2018 and the second (London) opened in December 2021. Two UK centres will provide sufficient capacity to treat current commissioned indications and support high quality RCTs to determine the benefits of PBT in adult malignancies, which are so far lacking. A recent systematic review of PBT trial methodology revealed that of 89 prospective studies, only 5 and 3 were phase II and III RCTs, respectively (Ofuya *et al.* 2019). High quality RCTs are therefore urgently needed to generate practice changing evidence and to inform the need for future PBT capacity in the UK and globally. Given the UK's single-payer healthcare system and the opening of two NHS centres, the UK is uniquely placed to deliver these (Jena 2018; Zietman 2018).

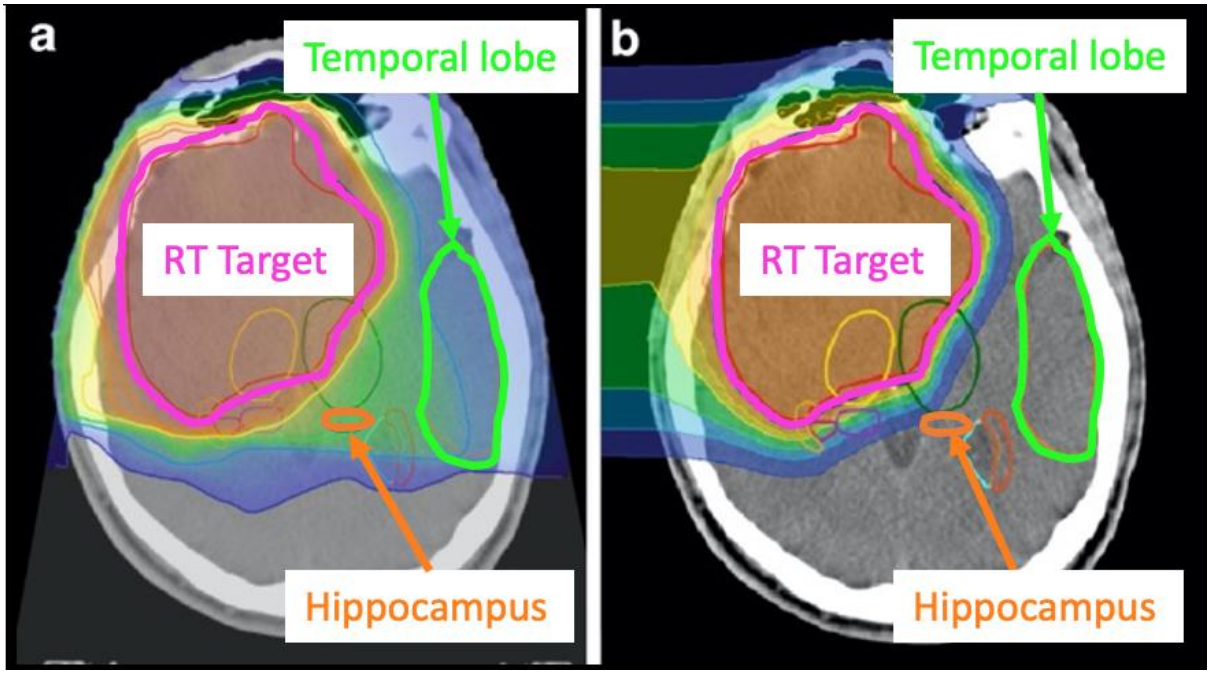

Figure 1 **Photon RT (a) and PBT (b) radiotherapy dose distributions in a glioma patient**

Image and plans from Harrabi et al, 2016. Harrabi, S.B., Bougatf, N., Mohr, A. et al. Dosimetric advantages of proton therapy over conventional radiotherapy with photons in young patients and adults with low-grade glioma. Strahlenther Onkol 192, 759–769 (2016). https://doi.org/10.1007/s00066-016-1005-9. Open access article: https://creativecommons.org/licenses/by/4.0/. Annotations and thicker contours added to image for illustration purposes. In the colourwash, warmer colours represent regions of higher dose. The radiotherapy target (which must receive treatment dose) is shown by the pink outline. Dose sparing of the normal brain structures contralateral to the tumour (in particular the contralateral temporal lobe (important for language and hearing; outlined in bright green) and hippocampus (important for memory; outlined in orange)) is apparent with the PBT plan. It is currently uncertain if this translates into a clinical improvement in neurocognition.

In silico RT dosimetry comparison studies confirm that PBT reduces dose to normal brain, including, for example, the hippocampus (which may protect memory) and pituitary gland (which may prevent irreversible hormone loss) in glioma cases (Dennis *et al.* 2013; Harrabi *et al.* 2016). PBT can reduce mean contralateral and ipsilateral hippocampal doses by 65% and 15% respectively and mean pituitary doses by 41% compared to photon intensity modulated radiotherapy (IMRT) (Harrabi *et al.* 2016). Although there are clear dosimetric benefits, it remains uncertain whether these translate into reduced normal tissue damage and thus reduced NCD, thereby supporting the use of this expensive new modality in patients with ODG. Currently there is no RCT evidence to determine whether dosimetric sparing results in patient benefit, thus representing a need to fill this knowledge gap. As with most tumour types when considering PBT, tumour control and survival outcomes are not expected to differ between PBT and photon RT, as tumour doses are equivalent (Shih *et al.* 2015; Jhaveri *et al.* 2018; Tabrizi *et al.* 2019). The major potential impact of PBT is on normal tissue damage and long-term treatment-related toxicity. Small, non-randomised clinical cohort studies of PBT in patients with ODG demonstrate the potential benefits of PBT (below) but there are no published RCTs of PBT versus photon RT. An RCT to compare PBT to photon RT in adults with ODG is therefore required i) to determine the individual patient benefit of PBT in terms of reducing NCD and preserving HRQoL and ii) to provide high-quality clinical evidence regarding the clinical benefit of PBT in ODG patients to guide future funding decisions to improve patients' long-term outcomes.

1.3.1 Current Standard of Care

The standard of care for ODG patients is maximal debulking surgery, photon RT (54 Gray (Gy) and 59.4 Gy for grade II and III ODG, respectively), delivered in 1.8 Gy fractions on weekdays over approximately 6 weeks, then 6 x 6-weekly cycles of adjuvant Procarbazine,

Lomustine and Vincristine (PCV) chemotherapy (van den Bent *et al.* 2013; Buckner *et al.* 2016). This will form the control arm in the APPROACH trial.

It should be noted that ODG patients in this trial are molecularly defined by IDH mutation and 1p19q co-deletion. This classification is relatively recent: since 2016 the diagnosis of grade II and III glioma was altered to include both phenotypic and genotypic (IDH and 1p19q) parameters (Wesseling and Capper 2018). This allows identification of a best prognosis group of patients (IDH mutant, 1p19q co-deleted), independent of grade, who stand to gain most from cognition preserving strategies. LGG studies recruiting before 2016, as discussed in the literature review below, therefore contain a proportion of grade II ODG patients but also patients who had a considerably poorer prognosis (Louis *et al.* 2021).

1.3.2 Neurocognition in post-photon RT adult patients:

The existing literature, which includes a 2019 Cochrane review focusing on NCD after photon RT in adult glioma patients (Lawrie *et al.* 2019), demonstrates that RT-related NCD is an important late side effect although the incidence, its definition, methods of assessment and time course have not been consistently defined between studies:

- In the seminal study reported by Klein et al, 39% of irradiated patients (n=104) displayed NCD at 1-12 years (mean 6.1 years) post-diagnosis, while this rose to 53% after 6-28 years (mean 12 years; n=32) (Klein *et al.* 2002; Douw *et al.* 2009). At corresponding time points, 29% (n=91) and 27% (n=33) of non-irradiated patients displayed NCD, respectively.
- A recent cross-sectional study in 48 irradiated ODG patients demonstrated that NCD impacts 27% of patients at 2-5 years, 39% at 6-10 years and 69% at >10 years post-treatment (Cayuela *et al.* 2019).
- In a recent cross-sectional study of 110 LGG patients, tested on average 7.3 years post-diagnosis, irradiated patients (n=81) scored significantly lower on tests of processing speed and executive functioning compared to non-irradiated patients (n=29); 16% of irradiated compared to 0% of non-irradiated patients had impairment in verbal fluency (Haldbo-Classen *et al.* 2019).
- In a prospective series of 27 ODG and oligoastrocytoma patients treated with (chemo)radiotherapy, at 9-14 years post-diagnosis (mean 12 years), mild to moderate and severe impairment was observed in 44% and 30%, respectively (Habets *et al.* 2014).

The observation of NCD appearing as early as two years, as observed in Cayuela *et al*. 2019, is not consistent across the literature: no significant differences in NCF between irradiated and non-irradiated LGG patients were observed in studies with small sample size at 2-3 years post-treatment in both observational and randomised studies (n=17 and 63 irradiated patients, respectively) (Vigliani *et al.* 1996; Reijneveld *et al.* 2016; Lawrie *et al.* 2019). This discrepancy may reflect differences in the neurocognitive tests used and definitions of impairment. Overall, the strongest evidence supports NCD as a very late side effect, most marked at >5 years post-photon RT (Klein *et al.* 2002; Douw *et al.* 2009; Cayuela *et al.* 2019).

There are a number of limitations in the existing literature. These include, as above, variations in types of neurocognitive tests used and the timings and definitions of NCD, which contribute to the different rates reported (van Loon *et al.* 2015; Lawrie *et al.* 2019). Loss of follow up within studies, low patient numbers and inclusion of older, less conformal, RT techniques could also contribute to variation within the literature regarding NCD. The APPROACH trial provides an excellent opportunity to address the clear problem of NCD associated with photon RT in patients with ODG. APPROACH is a prospective, randomised,

phase III trial comparing photon RT with PBT, with standardised assessments at baseline and at regular intervals up to 5 years post RT to facilitate evaluation of early and longer term NCD. Repeated, long-term neurocognitive testing has been shown to be acceptable to patients and feasible (Georg *et al.* 2019) and our own Patient and Public Involvement (PPI) work confirmed a willingness to participate in neurocognitive testing and HRQoL questionnaire completion for "as long as is necessary" (Powell *et al.* 2020).

1.3.3 Clinical outcomes from PBT in adult glioma patients

There is very limited published evidence concerning outcomes for patients with LGG/ ODG treated with PBT. Shih, Sherman and Tabrizi reported a series of prospective single arm studies which included 20 adult LGG patients (not molecularly defined) treated with PBT (Shih *et al.* 2015; Sherman *et al.* 2016; Tabrizi *et al.* 2019). After median follow-up of 5.1 years, NCF and HRQoL remained stable (Shih *et al.* 2015; Sherman *et al.* 2016). New endocrine dysfunction developed in 6 patients (Shih *et al.* 2015). A recent update, after median follow-up of 6.8 years, confirmed no overall decline in NCF, although 5 patients who reported cognitive/ mood symptoms around the time of PBT also showed progressively worse NCF on follow-up (Tabrizi *et al.* 2019). Toxicities occurring at >2 years were mainly neurological or endocrine. HRQoL remained stable or improved over time (Tabrizi *et al.* 2019). Additional small (n=19-71) non-randomised cohort studies have evaluated PBT in adult ODG patients, mainly with short follow-up and thus a focus on acute toxicities (Hauswald *et al.* 2012; Maquilan *et al.* 2014; Wilkinson *et al.* 2016; Sas-Korczynska *et al.* 2017; Nystrom *et al.* 2018; Nagaraja *et al.* 2019), which appear acceptable. These mainly consist of mild to moderate alopecia, dermatitis, fatigue and headache. In summary, the majority of published studies concerning PBT in OGD are small, single centre and non-randomised with limited follow up. RCTs are therefore urgently needed to determine if the dosimetric benefits of PBT, in comparison to photon RT, translate into clinical benefit (Thurin *et al.* 2018).

1.4 On-going studies

The APPROACH trial will contribute to global efforts to define the place of PBT in glioma patients alongside two non-UK randomised studies, described below. These compare PBT with photon RT in overlapping, but non-identical, patient populations. Outcomes from APPROACH, focusing specifically on the ODG population, using the same primary end-points, will contribute to a high impact, practice changing evidence base.

NRG-BN005 is an American phase II RCT of PBT vs. photon RT followed by adjuvant temozolomide (TMZ) chemotherapy in 120 grade II/III IDH mutant adult glioma patients (NCT03180502), (NRG Oncology 2017). The primary endpoint is NCF, with initial analysis at 2 years and follow-up to 10 years. The estimated study completion date is January 2030. The study includes worse prognosis patients (i.e. non-1p19q co-deleted), in whom TMZ chemotherapy may be more appropriate. For ODG patients, however, the evidence supports the use of adjuvant PCV, as specified in UK protocols (van den Bent *et al.* 2013; Buckner *et al.* 2016; National Institute for Health and Care Excellence 2018). TMZ and PCV may impact NCD differently but this is unknown. Given the differences in population and chemotherapy, the United States (US) results will not directly translate to the UK. We are, however, working with the US team to align assessments and increase the evidence base across molecular pathologies and treatment regimes. We are using the same neurocognitive tests and evaluating the same treatment effect for the primary endpoint. Through on-going collaboration, we aim to perform a future individual participant data meta-analysis (separately funded) and also have the potential to pool dosimetric and imaging data to further strengthen our mechanistic work. A German 80-patient trial of PBT vs. photons is also ongoing (DRKS00015160) for adult patients with IDH mutant grade II and III gliomas

(GliProPh 2018). The primary endpoint is NCF at 3 years, with annual neurocognitive testing for 6 years. As with the US trial, a higher risk group of patients are included in the German trial, meaning conclusions will not be directly applicable to the ODG patient group.

Single arm PBT studies are also ongoing:

- A Dutch single-arm PBT observational trial is recruiting 79 grade II/III IDH mutant adult glioma patients. Primary endpoints are NCF and toxicity over 4 years (NTR7993) (Erasmus MC 2019).

- A US single arm PBT phase II trial has recently recruited 63 adult grade II/III glioma patients to assess survival and toxicity over 7 years (NCT01358058) (Massachusetts General Hospital 2011).

- A German trial (DRKS00007670) includes a variety of high- and low-grade brain tumour patients requiring high dose RT (Proto-R-Hirn 2014). All patients receive PBT. The primary endpoint is grade 2+ late toxicity after 2 years.

- A phase I trial of Proton/Carbon-ion RT in combination with TMZ in adult patients with high-grade glioma is ongoing in Shanghai (Shanghai Proton and Heavy Ion Center 2017).

Single arm studies cannot provide the urgently required randomised evidence regarding the benefit of PBT over photon RT. Non-randomised evidence, however, could be included within the future planned individual participant data meta-analysis.

1.5 Patient and public involvement (PPI):

We have actively worked with, and iteratively developed this trial based on constructive feedback from, ODG patients, caregivers and our PPI co-applicant.

A focus group was held in November 2018 with 15 ODG patients and caregivers from Leeds and Manchester to discuss the potential benefits of PBT (Powell *et al.* 2020). Attendees strongly endorsed the trial proposal and opportunity to access PBT within an RCT. The group were adamant that randomisation should be 1:1 between PBT and photon RT to demonstrate clinician equipoise between modalities and so this has been adopted. Patients disliked some traditional terminology such as ‘trial’ and ‘neurocognitive tests’ and preferred research study’ and ‘neurocognitive assessments’, which will be incorporated into all patient-facing material. Patients and caregivers expressed the need for careful consideration of issues around travel and accommodation during PBT away from home. The trial will therefore endeavour to ensure that appropriate support is provided to ensure that all patients who wish to participate are able to do so. The group also highlighted that the experience of a caregiver was different to that of a patient, hence caregiver wellbeing questionnaires have been included as part of the trial. Participants considered that standard HRQoL questionnaires (European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) (Aaronson *et al.* 1993), and Brain Cancer Module (EORTC BN20), (Taphoorn *et al.* 2010) fail to address some important areas reflecting daily wellbeing, including issues related to fatigue and getting along with one’s family. As such, additional questionnaires have been included to better cover these issues. Patients considered the proposed schedule and assessments acceptable and were willing to complete questionnaires and neurocognitive tests for “as long as is necessary” (Powell *et al.* 2020).

1.5.1 Other patient groups:

The results of this trial, performed within a young, uniformly good prognosis subgroup of brain tumour patients, will inform relevant questions in a wider group of adults with other good prognosis brain tumours where RT is frequently used. Although the specific impact of treatment may differ due to different dosimetry and target volumes, data from APPROACH will help to frame the critical issues in, for example, meningioma (~1430 cases in England per annum, respectively (Maile *et al.* 2016).

1.6 Mechanistic evaluation: neuroanatomical target theory

Neuroanatomical target theory investigates potential mechanisms of radiation-induced neurocognitive dysfunction through examination of the RT dose received by different regions within the brain (Peiffer *et al.* 2013). The mechanistic hypothesis within APPROACH is that there are definable dose-response relationships for specific brain regions in adults, which impact on NCF. This hypothesis is supported by a significant literature in adult patients undergoing RT for a variety of cancers, including nasopharyngeal carcinoma in whom the temporal lobes are treated to high doses. Here, dose-response relationships have been defined for specific brain substructures (Lam *et al.* 2003; Lv *et al.* 2019; Yang *et al.* 2019). In adults with brain tumours, relationships between RT dose to the hippocampus and memory impairment have been most widely examined with a view to hippocampal RT dose sparing in an effort to preserve memory (Gondi *et al.* 2013; Brown *et al.* 2020). Neurocognition is, however, considerably more complex than hippocampal dependent memory function: individual aspects of neurocognition rely on interconnecting networks throughout the brain and the dose response relationships for the majority of relevant regions and networks remains undefined (Greene-Schloesser *et al.* 2012; Peiffer *et al.* 2013; Hart *et al.* 2019; Duffau 2020). For example, working memory requires an extensive network of communication between the hippocampus, amygdala, cerebellum and prefrontal cortex; this whole network has yet to be investigated. Indeed, a hippocampal normal tissue complication probability (NTCP) model predicting memory impairment has not been validated in LGG patients (Jaspers *et al.* 2019), necessitating a shift in attention to other brain regions/ networks involved in neurocognitive functioning (Duffau 2020).

In regard to existing data on regional dose-neurocognitive dysfunction response relationships in adults (other than the hippocampus), series are mainly small and often perform neurocognitive testing at a single, yet variable time point post-RT, making conclusions less reliable (Brummelman *et al.* 2012; Peiffer *et al.* 2013; Tabrizi *et al.* 2019; Haldbo-Classen *et al.* 2020). Furthermore, data tends to focus on specific anatomical substructures rather than allow for structural network connectivity.

Lesion Symptom Mapping (LSM) (also known as Voxel-based Lesion Symptom Mapping: VLSM) is a well-established method to relate brain location to brain function (Bates *et al.* 2003), that has been widely used in the setting of stroke and trauma. Applying LSM to map normal tissue RT dose to cognitive deficits is highly novel. By focusing on individual voxels, which may not be specific to one anatomical substructure, this allows an unbiased assessment of anatomical network contributions to cognition, beyond a pure substructure approach. An advantage of LSM is that it can be performed using the standard Magnetic Resonance Imaging (MRI) planned within this study.

Prospective data collection with consistent time points for neurocognitive testing using a fixed test battery is required to move this field forwards (Peiffer *et al.* 2013; Duffau 2020). APPROACH provides this unique and powerful opportunity. The identification of ‘at risk’ regions of normal brain will facilitate sparing of these regions from RT, which is particularly applicable for PBT as it more easily facilitates sculpting of dose away from critical regions.

This will also permit identification of patients for whom PBT will provide the largest benefit (i.e. those in whom sparing cannot be achieved by photons but can with PBT). In those in whom sparing cannot be achieved due to tumour location, improved understanding of regional dose neurocognitive dysfunction relationships will allow quantification of risks of specific deficits. This will permit more informed clinician-patient discussions regarding the risks vs. benefits of treatment and facilitate targeted neurorehabilitation, aiming to manage these complications and thus maintain HRQoL.

2 Aims and Objectives

2.1 Trial Aim

To assess whether good prognosis ODG patients treated with PBT have better NCF in comparison to those treated with standard photon RT.

2.2 Primary trial objectives

A multi-staged assessment approach is proposed:

• Stage 1 (internal pilot): To confirm feasibility of recruitment in terms of patient willingness to be randomised,

• Stage 2: To assess if there is an early neurocognitive benefit of PBT on an intermediate endpoint of NCF at 2 years compared to photon RT (the earliest time point at which chronic RT-related NCD might be expected to be identified based on the existing evidence), providing sufficient evidence in favour of PBT in ODG patients to warrant an early practice-defining decision. Regardless of the outcome at stage 2, trial follow-up will continue to 5 years to provide essential data about the long-term individual and societal impact of PBT (Lawrie *et al.* 2019),

• Stage 3: To undertake an interim futility assessment on the primary endpoint of 5-year NCF when ≥50% patients have reached 5-year follow-up, to ensure there is sufficient evidence to warrant continuation of follow-up to 5 years for all patients,

• Stage 4: To assess if there is sufficient evidence of treatment benefit based on 5-year NCF when compared to photon RT to warrant the use of PBT in patients with ODG.

2.3 Secondary trial objectives

To evaluate the impact of PBT in comparison to photon treatment for:

- Additional NCF outcomes
- HRQoL
- Endocrinopathy
- Treatment compliance
- Work & economic impact
- Caregiver distress
- Early and late toxicity
- Radiological response rates
- Progression-free survival
- Overall survival

See section 11 Endpoints for full definitions of the primary and secondary trial endpoints.

2.4 Mechanistic component

2.4.1 Mechanistic Aim

To improve understanding of RT dose-neurocognitive dysfunction relationships to facilitate future sparing of eloquent brain areas, either through changes in RT planning priorities (for photon RT or PBT) or choice of RT treatment technique (i.e., Photon RT vs. PBT).

2.4.2 Mechanistic Hypothesis

The mechanistic hypothesis is defined as:

There are definable dose-neurocognitive dysfunction relationships for specific brain regions in adults, which impact on NCF.

2.4.3 Mechanistic Objectives

The mechanistic objectives are defined as:

1. To investigate the impact of RT dose to different substructures within the brain on NCF.

2. To investigate the impact of RT dose location on NCF using LSM.

A separate mechanistic analysis plan will be developed and will be reassessed throughout the duration of the trial given that the mechanistic analysis will not take place until years nine and ten of the grant. The analysis plan will incorporate any developments in the research literature in this field over time.

3 Trial design overview

APPROACH is a phase III UK multi-centre, open-label RCT with multi-staged assessments. The two-arm RCT of PBT vs. photon RT in patients with ODG, will assess whether good prognosis ODG patients treated with PBT have better NCF in comparison to those treated with standard photon RT. Neurocognitive function will be assessed at baseline, one month post end of RT and at each annual follow-up.

A total of 246 patients will be randomised 1:1 between PBT and photon RT, with PBT being delivered in one of the two NHS PBT centres and photon RT being delivered in the local RT centre. For those randomised to PBT, during PBT, the participant will be under the care of the clinician in the PBT centre, who will be responsible for their RT planning, prescription and delivery. For those randomised to photon RT, during photon RT, the participant will be under the care of the clinician in the local RT centre, who will be responsible for their radiotherapy planning, prescription and delivery. In the lead up to RT (PBT or photon RT), during adjuvant chemotherapy and during follow up, the participant will be under the care of the clinician in the local centre. Following radiotherapy, all patients will receive adjuvant PCV chemotherapy, with clinical review and chemotherapy toxicity recorded at each cycle.

Follow up will be as standard of care, with trial-specific assessments at baseline, weekly during RT and at 1, 3, 6, 12, 24, 36, 48 and 60 months post end of RT. Secondary endpoints also include additional NCF outcomes, HRQOL, endocrinopathy, treatment compliance, work and cost impact, caregivers distress, early and late toxicity, response assessment, progression free survival (PFS) and overall survival (OS).

There are four stages of assessment to ensure trial continuation is warranted throughout. Recruitment will take place in 18-25 centres over 3½ years.

- Stage 1: (internal pilot phase) will confirm feasibility of recruitment over the first 12 months. If successful, the trial will continue to full recruitment and Stage 2 assessment.

- Stage 2: an interim analysis of NCF at 2 years as an intermediate endpoint for early signs of efficacy will be performed once all patients reach ≥2-year follow-up. If positive there is the potential to recommend change in practice; trial follow-up will continue regardless for longer term outcomes.

- Stage 3: a further interim analysis will be performed when 50% of patients reach 5-year follow-up to assess futility. If futility is concluded, follow-up may be terminated early for the remaining patients.

- Stage 4: final analysis. The primary endpoint focused on NCF at 5 years. If positive there is the potential to recommend change in practice for standard of care. All secondary endpoints will also be assessed.

Stage 1 provides an early stop if predetermined recruitment targets are not met; Stage 2 provides an early practice changing opportunity on an intermediate endpoint; and Stage 3 provides stopping rules for longer term follow-up.

3.1 Setting

3.1.1 Patients allocated to receive photon radiotherapy

Photon radiotherapy will be delivered daily on weekdays as an out-patient in the local RT centre. The participant will be under the care of the clinician in the local RT centre, who will be responsible for their radiotherapy planning, prescription and delivery as well as their ongoing care and follow up.

3.1.2 Patients allocated to receive proton beam therapy (PBT)

PBT will be delivered daily on weekdays as an out-patient in one of the two UK NHS PBT centres. The PBT centre that will be allocated for treatment will depend on participant location and centre availability.

During PBT, the participant will be under the care of the clinician in the PBT centre, who will be responsible for their radiotherapy planning, prescription and delivery. In the lead up to PBT, after completion of PBT, during adjuvant chemotherapy and during follow up, the participant will be under the care of the clinician in the local centre.

If a patient has been randomised to receive proton beam therapy, the PI or delegate must enter the patient's details on the NHS National Proton Therapy Referral Portal:

https://protons.protontherapyreferrals.nhs.uk/Login/Signin

Following confirmation that a patient has been appropriately referred and accepted for PBT they will be contacted by a 'key worker', who will be a named specialist nurse or radiographer from one of the NHS proton centres. The role of the key worker is to provide assistance and support to the patient throughout the treatment. The key worker will contact the patient and referring clinician to arrange for the patient and relative/ friend/ caregiver to attend for a pre-treatment single-assessment visit, which should be within around ten days of receipt of the referral through the Portal. The key worker will discuss the travel and accommodation arrangements during treatment and answer any practical questions that the patient may have. Further guidance related to the referral portal can be found in the **APPROACH Portal Referral Guidelines**.

3.1.2.1 Accommodation and travel for patients allocated to receive PBT

Patients allocated to PBT will need to visit one of the two national NHS proton centres for treatment planning and the treatment itself.

The proton centres are located at:

- The Christie NHS Foundation Trust in Manchester,
- University College London Hospitals NHS Foundation Trust in London.

Patients do not have to stay in the provided accommodation and if they would prefer to return home every day following their treatment, they can do so. The NHS will provide accommodation for the pre-assessment visit and duration of radiotherapy for one patient plus one partner or caregiver. The accommodation arrangements will be made by the key worker from the PBT centre and only accommodation suggested by the PBT centre will be

funded by the NHS. Further details about the accommodation will be provided to the patient once acceptance to either PBT centre has been made.

Patients will need to make their own travel arrangements. The assigned key worker should discuss the travel arrangements with the patient and answer any questions that the patient may have. The trial will not provide any reimbursement for travel provisions, though eligible participants may be reimbursed for patient travel expenses under the 'Healthcare Travel cost scheme'. More information can be found at: https://www.nhs.uk/nhs-services/help-with-health-costs/healthcare-travel-costs-scheme-htcs/

3.2 Study population

Adults (≥25 years) with ODG (PBT is already commissioned for children and young adults <25 years with ODG).

4 Eligibility

Patients meeting all of the inclusion criteria and none of the exclusion criteria will be considered for participation in the trial. Eligibility waivers to any of the inclusion and exclusion criteria are not permitted.

4.1 Inclusion criteria

- Histologically proven diagnosis of ODG with 1p19q co-deletion and IDH mutation.
- Randomisation must be performed within 28 days of the MRI that leads to the decision that RT is required at that point in time. Outside of 28 days, an updated MRI is required to serve as a contemporaneous baseline scan to assess response to further treatment.
- Karnofsky Performance Status (KPS) ≥70%.
- Adequate wound healing and recovery if recent surgery.
- Suitable to complete baseline neurocognitive testing (No access to translated tests, only English versions available).
- Patients of childbearing potential should be asked to confirm that they are not pregnant to confirm trial eligibility. Formal Pregnancy testing should be performed if there is any doubt as to pregnancy status or if felt appropriate, including in circumstances such as irregular periods, unprotected sexual intercourse since the last menstrual period, missed contraceptive pill or antibiotics during the last menstrual cycle or failure of barrier contraception. See 4.3 Birth control: contraception and pregnancy testing for further details.
- Fertile participants, born male, must agree to practice methods of contraception that are considered medically acceptable for the duration of RT, adjuvant chemotherapy and for 6 months post-end of treatment if sexually active with a person of child-bearing potential. See section 4.3 Birth control: contraception and pregnancy testing for further details.
- Able to swallow oral medication.
- Able to provide study-specific informed consent.
- Age 25 or over at the point of starting RT treatment.
- No known haematological, renal or hepatic impairments making PCV chemotherapy inappropriate

4.2 Exclusion criteria

- Pregnancy (positive pregnancy test) or lactating.
- Prior cranial or head and neck RT.
- Any previous chemotherapy for the treatment of ODG.
- Co-morbid neurodegenerative diseases that influence NCF.
- Contra-indication to MRI scan or gadolinium.
- Severe active co-morbidity making patient unsuitable for radiotherapy and/ or adjuvant chemotherapy (e.g., uncontrolled diabetes, uncontrolled hypertension)
- Leptomeningeal disease.
- Spinal or infratentorial disease.
- Another currently active malignancy or another malignancy within the last 3 years.
- Any contra-indication to Procarbazine, Vincristine or Lomustine (see section 8.2.1 Chemotherapy contraindications for further information) including: coeliac disease; and the rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption.
- Any recognised genetic syndrome causing sensitivity to radiotherapy.

- Patient unwilling/ unable to attend for follow up in the local radiotherapy centre.

4.3 Birth control: contraception and pregnancy testing

Participants, born female, of child-bearing potential, must not become pregnant during radiotherapy (using photons or PBT), in the interval between radiotherapy completion and commencement of adjuvant chemotherapy, during adjuvant chemotherapy or for six months after completion of adjuvant chemotherapy.

A participant, born female, is considered of childbearing potential following menarche and until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Fertile participants, born male, must not father a child during radiotherapy (using photons or PBT), during adjuvant chemotherapy or for six months after completion of adjuvant chemotherapy.

A participant, born male, is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

For participants of child-bearing potential or for fertile participants with partners who are of child-bearing potential:

- During radiotherapy (with photons or PBT), medically acceptable methods of contraception, as listed below, should be used to prevent pregnancy.
- During chemotherapy and for six weeks after, a barrier method of contraception must be used (i.e., condoms or the cap) to prevent transmission of chemotherapy contaminated bodily fluids and to prevent pregnancy. This may be used in conjunction with other medically acceptable methods of combination.
- From 6 weeks after chemotherapy completion until 6 months post chemotherapy completion, a medically acceptable method of contraception must be used to prevent pregnancy.

In addition, for participants of child-bearing potential:

Between completion of radiotherapy and commencement of adjuvant chemotherapy, medically acceptable methods of contraception, as listed below, should be used to prevent pregnancy.

Methods of contraception that are considered medically acceptable for the purposes of this trial include:

- Copper intra-uterine device (copper IUD)
- Levonorgestrel-releasing intrauterine system (LNG-IUS)
- Progestogen Implant
- Depot medroxyprogesterone acetate (DMPA) subcutaneous (SC) or intramuscular (IM) injections
- Combined hormonal contraceptives (pills, patches or vaginal ring) or progestogen-only pills
- Condom
- Cap
- Tubal ligation (of patient or partner)
- Vasectomy (of patient or partner)
- Sexual abstinence

For patients receiving implants, combined hormonal contraceptives and progestogen-only pills, significant interactions with any concurrent medication should be determined. Alternative methods of contraception must be used if a significant interaction exists.

For participants who are sexually active but who are not of child-bearing potential or for patients who are sexually active with partners who are not of child-bearing potential:

- During adjuvant chemotherapy and for six weeks after, any participant on chemotherapy must use barrier protection for sex (i.e., condoms or the cap) to prevent transmission of chemotherapy contaminated bodily fluids.

4.3.1 Pregnancy testing

All participants of child-bearing potential must be pregnancy screened prior to entering the APPROACH trial and before signing the main consent form. They should provide informed consent on the eligibility pregnancy screening PISICF to allow pregnancy screening. They may be required to provide a negative pregnancy result and will need to agree to continue to practice methods of contraception that are considered medically acceptable for the duration of the trial treatments (radiotherapy, between radiotherapy and adjuvant chemotherapy and during adjuvant chemotherapy) and for 6 months post-end of adjuvant chemotherapy.

All participants of child-bearing potential must have:

- Confirmed that they are not pregnant with their doctor/treatment team within 7 days prior to randomisation in order to enter the trial. Pregnancy testing should be performed if there is any doubt as to pregnancy status. A urine-based test is sufficient unless it is within 10 days of the patient's last menstrual period, when a urine-based test is unreliable. In this situation, a serum test should be performed.
- Confirmed that they are not pregnant with their doctor/treatment team within 7 days of computerised tomography (CT) simulation for RT (photon RT or PBT) in order for CT simulation to proceed. Pregnancy testing should be performed if there is any doubt as to pregnancy status. A urine-based test is sufficient unless it is within 10 days of the patient's last menstrual period, when a urine-based test is unreliable. In this situation, a serum test should be performed.
- Confirmed that they are not pregnant with their doctor/treatment team within 7 days of the first fraction of treatment in order for RT to proceed. Pregnancy testing should be performed if there is any doubt as to pregnancy status. A urine-based test is sufficient unless it is within 10 days of the patient's last menstrual period, when a urine-based test is unreliable. In this situation, a serum test should be performed.
- Confirmed that they are not pregnant with their doctor/treatment team within 7 days of **each** cycle of chemotherapy in order for chemotherapy to proceed. This should be included as part of the pre-chemotherapy assessment. Pregnancy testing should be performed if there is any doubt as to pregnancy status. A urine-based test is sufficient unless it is within 10 days of the patient's last menstrual period, when a urine-based test is unreliable. In this situation, a serum test should be performed.

5 Prior and concurrent participation in the other clinical trials

Participation in therapeutic clinical trials involving anti-tumour treatment and/ or trials that may interfere with the primary endpoint is not permitted up to the primary endpoint assessment. However, participation in non-therapeutic registry studies or questionnaire-based studies is permitted. Questions about potential clinical trials can be addressed to the Chief Investigator via Leeds Clinical Trials Research Unit (CTRU).

6 Participating Sites and Investigators

6.1 Participating sites

Each participating site must be able to comply with the following, as applicable to the trial activities taking place at the site:

- Trial treatments, imaging, clinical care, follow-up schedules, training for administration of neurocognitive tests and all requirements of the trial protocol.
- Requirements of the UK Policy Framework for Health and Social Care Research and amendments.
- Data collection requirements, including adherence to remote data capture, paper case report form (pCRF) compliance and electronic case report form (eCRF) submission timelines as per section 9 Trial assessments.
- Monitoring requirements as outlined in section 14 Trial Monitoring.

6.2 Principal Investigators and Co-Investigators

Sites must have an appropriate Principal Investigator (PI) authorised by the site and ethics committee to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. Investigators involved in the treatment and care of patients must be medical doctors and have experience of treating ODG. The trial will be registered with the NIHR Associate PI scheme and junior doctors are encouraged to apply to become an Associate PI for APPROACH.
(https://www.nihr.ac.uk/health-and-care-professionals/career-development/associate-principal-investigator-scheme.htm).

6.3 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site authorised personnel log (APL).

CVs for all staff must be kept up-to-date, signed, dated and copies (or statement of their location) held in the Investigator Site File (ISF) held at site. An up-to-date, signed copy of the CV for the PI must be forwarded to the CTRU prior to site activation.

Good clinical practice (GCP) training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials. Evidence of current GCP training for the PI must be forwarded to the CTRU prior to site activation.

Training in the administration of NCF tests is required for all staff responsible for conducting these tests. These staff may be research nurses or other assigned healthcare professionals. Refresher training must be completed annually and will also be required after a period of inactivity. Evidence of completion of training in the administration of NCF tests for site staff who will conduct these tests must be forwarded to the CTRU prior to site activation. For further information related to NCF test administration please refer to the **APPROACH NCF Test Administration Guidelines**.

6.4 Radiotherapy quality assurance

The radiotherapy quality assurance (RT QA) programme will be implemented by the National Cancer Research Institute (NCRI) Radiotherapy Trials Quality Assurance (RTTQA) group to ensure treatment is planned and delivered according to the trial protocol. Benchmarking contouring and planning cases will be completed. There will be prospective review of at least the first photon case for each centre delivering photons and the first PBT plan for centres delivering PBT. For a full summary of the RTTQA requirements these are provided in the **APPROACH Radiotherapy outlining, planning, treatment delivery and quality assurance (QA) guidelines**.

6.5 Site initiation

Before a site is activated, the CTRU trial team will arrange a site initiation. Site initiation will be an electronic process and an audio-visual recorded link with the initiation presentation will be sent to the site. This will be accompanied by the site initiation training log.

According to best practice, all staff assigned to work on APPROACH (including non-trial-specific staff) would participate in the site initiation process. As a minimum, the PI, radiotherapy physicist, research radiographer and research nurse must return their site initiation training logs before the CTRU will issue a site initiation letter confirming that the site initiation is confirmed and activated.

The site initiation process will cover all areas of the trial and management at site.

After watching the audio-visual recorded link and associated slide presentation, trial-specific staff should record on the site initiation training log that they have completed the site initiation training. The signed initiation training log must be returned to APPROACH@leeds.ac.uk.

For those staff who will perform neurocognitive testing within the trial, additional audio-visual training will be provided in addition to an online face-to-face meeting (which will need to be pre-arranged), as part of site initiation. These must be completed before a site opens to APPROACH. See **APPROACH NCF Test Training Guidelines** for further information.

A site cannot open to APPROACH without the site initiation.

6.6 Essential documentation

The following documentation must be submitted by the site to the CTRU prior to site activation:

- All relevant institutional approvals (e.g., local NHS permission).
- A completed authorised personnel log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately).
- Completed Site Contacts Form (with contact information for the PI, co-investigators, research/trial, pharmacy, radiography).
- A copy of the PI's current CV that is signed and dated.
- A copy of PI's current GCP training certificate.
- Signed PI declaration.
- RTTQA approval.
- A signed Clinical Trial Site Agreement (model Non-commercial Agreement for UK sites) between the Sponsor and the relevant institution.

- NCF Quality Assurance Log.
- Site Initiation Training Log.

Centres are asked wherever possible to make every effort to manage patients for trial purposes on one central site (usually the recruiting site), with the exception of SAR/RUSAEs experienced by participants undergoing PBT see section 10 Safety Reporting for definitions of SAR/RUSAEs). Paper back-up copies of these forms will be kept in the site file at the referral site where PBT was received instead of the recruiting site.

Sites must inform the CTRU of any additional sites involved in the patient pathway. Recruiting sites, which will be referring patients to a different site, for all or some of the trial activities, will not be activated until the relevant site involved is ready to be activated.

6.7 Site activation

Once the CTRU trial team has received all the required essential documentation, the site has received their investigator site file (ISF) and the site has been initiated and the necessary documentation has been sent to the CTRU, a site activation email will be issued to the PI and other research staff by CTRU.

Sites must not approach any potential patients until they have received an activation email from CTRU.

Any questions or queries regarding the trial can also be sent via email to the APPROACH@leeds.ac.uk inbox or a meeting can be arranged to discuss any trial specific related queries before confirmation that the site initiation has been successfully completed. The audio-visual recorded link and associated slide presentation, together with the specific training in neurocognitive testing where relevant, can be used as a further training aid for new starters who will work on the study to ensure training standardisation. These staff will need to confirm in the training log contained within the ISF that they have watched the relevant information.

A copy of the site initiation presentations will also be provided for reference in the ISF.

7 Consent, Recruitment and Randomisation

7.1 Recruitment setting

Participants will be recruited to the trial from up to 18-25 UK sites. Research sites will be required to have obtained local management approval, completed and passed all the required QA checks and undertaken a site initiation with the CTRU prior to the start of recruitment.

Participants who are randomised to photon RT will receive this at their local RT centre. Participants who are randomised to PBT will receive this at one of the two NHS PBT centres (Manchester or London). The PBT centre used for treatment will depend on patient location and PBT centre availability for treatment. As per routine practice, during PBT, participants will be under the care of the PBT clinician at the PBT centre, rather than the local (photon centre) PI. All PBT clinicians who will be involved in the care of APPROACH participants will be acting primary investigators during PBT treatment in APPROACH.

7.2 Recruitment and informed consent

Patients will be identified through clinic lists and multidisciplinary team meeting (MDTs) and approached for possible recruitment in out-patient clinics. Suitability for inclusion into APPROACH will be assessed according to the eligibility criteria for the trial. A verbal explanation of the trial and the appropriate Patient Information Sheet (PIS) will be provided by the attending medical staff (and/or the trial Clinical Research Nurse) for the patient to consider. This will include detailed information about the rationale, design and personal implications of the trial. Before a patient can enter the trial (if they are of child-bearing potential) they will be asked to read through an APPROACH specific shortened pregnancy eligibility screening PIS and then asked to sign this Informed Consent Form (ICF), if they are willing to be pregnancy screened in order to take part in the APPROACH trial. A patient of child-bearing potential cannot enter the trial unless they have confirmed that they are not pregnant with their doctor/treatment team. If there is any doubt, the pregnancy screening should be carried out prior to patient consent to the trial, but the patient should be allowed to take as much time as needed to decide about trial participation. If a patient of child-bearing potential agrees to be screened for pregnancy prior to consent, they can be provided with the main PIS/ICF and, following information provision, patients will have as long as they need to consider participation, normally a minimum of 24 hours, and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent. The formal assessment of eligibility and informed consent may only be obtained by the PI or an appropriate medically qualified doctor. The healthcare professional must have knowledge of the trial interventions and have received training in the principles of GCP and the Declaration of Helsinki, 2013. He/she must be fully trained in the trial according to the ethically approved protocol and be authorised and approved by the PI to take informed consent as documented in the trial Authorised Personnel Log. The PI retains overall responsibility for the informed consent of participants at their research site. Informed consent must be obtained prior to the participant undergoing procedures specifically for the purposes of the trial, which are out-with standard routine care at the participating site.

Where a participant is required to re-consent, or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

Site staff are responsible for:

- Checking that the correct (current approved) versions of the PISICF is used.
- Checking that information on the PISICF is complete and eligible.
- Checking that the patient has completed/initialled all relevant sections and signed and dated the form.
- Checking that an appropriate member of staff has countersigned and dated the PISICF to confirm that they provided information to the patient.
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e., information given, consent signed, etc.).

Following randomisation:

- Adding the patient trial number to the consent form and making sufficient copies and filing the original consent form in the ISF and a copy in the patient's medical notes.
- Giving the patient a copy of their signed PISICF and patient contact card.
- Sending a copy of the signed consent form to CTRU in line with the terms of the ethically approved consent form.

The participant will be provided with a local contact point where they may obtain further information about the trial.

The PI retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki 2013.

The right of the patient to refuse consent without giving reasons will be respected. Consenting participants will remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment.

After the participant has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the patient. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis.

7.2.1 Considerations for recruitment of primary caregiver

When patients are approached regarding their suitability for the APPROACH trial, their primary caregiver will also be informed about the opportunity to report caregiver HRQoL and work and productivity during the APPROACH trial. Separate caregiver information about the trial will be provided and, after the caregiver has had time to consider the trial and ask questions, separate caregiver consent will be obtained.

The right of the caregiver to refuse consent for involvement without giving reasons will be respected. Consenting caregivers will remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment or trial involvement of the participant. However, caregivers will be withdrawn from trial should the participant withdraw from further data collection for any reason.

In addition to the considerations related to recruitment stated above, when approaching a participant's primary caregiver for participation in the trial, site staff are responsible for assuring the following:

- The individual has been identified as the primary caregiver by the participant
- The individual is not currently caring for another individual (excluding children)
- The individual is above the age of 18
- Checking that the correct (current approved) versions of the Caregiver PISICF is used
- Checking that the primary caregiver has completed/ initialled all relevant sections and signed and dated the form.

7.3 Loss of capacity following informed consent

This is expected to be a very rare occurrence. Any participant who loses capacity would be withdrawn from the trial. Any data collected about up until that point would still be used as part of the trial analysis. This is explained in the PIS.

7.4 Eligibility screening

In order to determine the generalisability of the trial results, and for Consolidated Standards of Reporting Trials (CONSORT) requirements, participating research sites will be required to complete a screening log for all patients presenting with ODG and screened for eligibility for the APPROACH trial. Documented reasons for ineligibility or declining participation will be closely monitored by the CTRU as part of a regular review of recruitment progress.

Anonymised information will be collected including:

- Age
- Sex
- Ethnicity
- Additional dependents or caring responsibilities
- Employment status
    - Ability to work remotely
- The reason for non-randomisation:
    - The reason not approached, or
    - The reason not eligible for trial participation, or
    - The reason declined if eligible

However, the right of the patient to refuse consent without giving reasons will be respected. This information will be requested from participating sites on a regular basis (at least 3 monthly) by the CTRU. Once eligibility has been confirmed, participants can then be randomised.

7.5 Randomisation

Written informed consent for entry into the trial must be obtained and eligibility must be confirmed prior to randomisation.

7.6 Randomisation process

Following confirmation of written informed consent and eligibility, participants will be randomised into the trial by Leeds CTRU. Participants will be randomised on a 1:1 basis to receive either PBT or photon RT.

A computer-generated minimisation program that incorporates a random element will be used to ensure the treatment groups are well-balanced for the following important prognostic factors, details of which will be required at randomisation:

- Most recent histological tumour grade (2 or 3)
- Tumour size (< 5cm or ≥ 5cm)
- Extent of most recent surgery (biopsy only or subtotal resection or gross total resection)
- Randomising centre
- Sex

Randomisation will be performed centrally using the CTRU automated 24-hour randomisation system, which can be accessed via the web. Login details, provided by the CTRU, will be required to access the randomisation system.

The following information will be required at randomisation:

- Site code (assigned by CTRU) of the research site
- Participant details, including initials, date of birth and sex
- Confirmation of eligibility
- Confirmation of written informed consent
- Minimisation factors (as specified above)

Once randomisation is complete, the system will allocate participants a unique 5 digit trial number.

24hour Randomisation:

Web: *https://lictr.leeds.ac.uk/webrand/*

Please ensure that you have completed the following eCRFs immediately after randomisation:

- **Consent Form**
- **Eligibility Checklist**
- **Baseline assessment**
- **Randomisation**

A copy of the consent form should also be sent via the CTRU's secure file transfer service (SFTS). The HRQoL baseline questionnaire and the baseline neurocognitive function tests must be sent to the CTRU immediately after randomisation

Confirmation of randomisation, including details of treatment allocation, will be emailed automatically to the PI and research team once complete.

Following randomisation, a paper F50 Contact Details CRF should be collected and sent to CTRU via the SFTS, to confirm the participant's and primary caregiver's preferred method of questionnaire administration and completion after randomisation. Applicable contact details, email address/mobile phone number will be collected on the F50 Contact Details CRF as appropriate.

8 Trial Treatments

8.1 Radiotherapy

Radiotherapy will ideally start within 6 weeks of randomisation and must start within 10 weeks of randomisation.

Radiotherapy will also start within 21 days of the CT simulation scan.

An MRI, to assist in radiotherapy planning is required. This is ideally performed within 21 days, but must be performed within 28 days, of the CT simulation scan. The immediate post-operative MRI must NOT be used as a 'planning' MRI as immediate post-operative changes may not have had sufficient time to resolve.

For those randomised to photon RT, during photon RT, the participant will be under the care of the clinician in the local RT centre, who will be responsible for their radiotherapy planning, prescription and delivery. In the lead up to photon RT, during adjuvant chemotherapy and during follow up, the participant will be under the care of the clinician in the local centre.

For those randomised to PBT, during PBT, the participant will be under the care of the clinician in the PBT centre, who will be responsible for their radiotherapy planning, prescription and delivery. In the lead up to PBT, during adjuvant chemotherapy and during follow up, the participant will be under the care of the clinician in the local centre.

RT will be delivered as an outpatient on weekdays over approximately 6 weeks. Throughout this document the relative biological effectiveness (RBE) weighted dose in units of Gray(Gy(RBE)) is used to describe the product of the absorbed dose and the RBE. For PBT, the RBE should be interpreted as 1.1. For photons this should be interpreted as 1 for which Gy(RBE) is equivalent to the absorbed dose in Gy.

The total RT dose will be 54 Gy(RBE) in 30 daily fractions for grade II tumours and 59.4 Gy(RBE) in 33 daily fractions for grade III tumours. Radiotherapy will be delivered on weekdays over approximately 6 weeks (1.8 Gy per daily fraction for all)

Photon RT will be delivered using intensity modulated RT (IMRT) or rotational arc therapy. PBT will be delivered using pencil beam scanning with optimisation, typically performed using single field optimisation (SFO).

Please see the **APPROACH Radiotherapy outlining, planning, treatment delivery and quality assurance (QA) guidelines** for full details on immobilisation, image acquisition, outlining, planning, treatment delivery, treatment interruptions and quality assurance (QA).

All delineation will be performed at the treating centre.

Radiosensitizers should be discontinued prior to commencement of RT. Necessary washout periods should be discussed with local Pharmacy teams.

8.2 Chemotherapy

Adjuvant chemotherapy is as per standard of care and will consist of PCV (procarbazine, lomustine and vincristine).

8.2.1 Chemotherapy contraindications

Patients with contra-indications to procarbazine or vincristine or lomustine must not be included in the trial.

Lomustine is contraindicated in patients with known hypersensitivity to the drug or any of its excipients, severe bone marrow depression or renal impairment, coeliac disease or wheat allergy. It is also contra-indicated in patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption. Please refer to section 4.8 of the current approved version of the applicable summary of product characteristics (SMPC), supplied for use within the trial; (note this may not necessarily be the latest version of the SMPC).

Procarbazine is contra-indicated in patients with severe leucopenia or thrombocytopenia (from any cause), severe hepatic or renal disease and in patients with hypersensitivity to the active substance or any of its excipients. Please refer to section 4.8 of the current approved version of the applicable SMPC, supplied for use within the trial; (note this may not necessarily be the latest version of the SMPC).

Vincristine is contraindicated in patients with the demyelinating form of Charcot-Marie-Tooth Syndrome, childhood polio (CCO Formulary) or known allergy to vinca alkaloids or any of its excipients. Please refer to section 4.8 of the current approved version of the applicable SMPC, supplied for use within the trial; (note this may not necessarily be the latest version of the SMPC).

8.2.2 Chemotherapy treatment schedule

Chemotherapy should start between 4 and 8 weeks after RT completion.

Chemotherapy is scheduled at 6-weekly intervals (+ 1-week for unavoidable delays, bank holidays etc.) for a maximum of 6 cycles (depending on tolerability) or until disease progression, whichever is sooner. Patients should be treated according to this schedule, as per standard practice.

It is recommended that initial doses (in the absence of renal or hepatic impairment) will be:

Lomustine 100mg/m^2, with dose banding/ capping as per the institution's usual practice day 1, PO, on a 42 day cycle, for up to 6 cycles.

Procarbazine 100mg/m^2, with dose banding/ capping as per the institution's usual practice once daily on days 1-10 or days 2-11, PO, on a 42 day cycle, for up to 6 cycles.

Vincristine 1.4-1.5mg/m^2 (or flat dose of 2mg if this is usual institutional practice), with dose banding/ capping as per the institution's usual practice IV, day 1, on a 42 day cycle for up to 6 cycles. If a patient has a body surface area (BSA) of <1.45m^2, then dosing must be based on BSA.

Tests required within 7 days prior to Cycle 1 and within 3 days of subsequent cycles:

Full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs).

Required haematological parameters to proceed with chemotherapy are:
- Hb ≥10 g/L (may be corrected with transfusion if necessary),

- Platelets ≥100 $x10^9$/L,
- Absolute neutrophil count ≥1.5 $x10^9$/L,
- White cell count ≥3.0 $x10^9$/L,

Usual practice may be followed in terms of dose modifications for baseline renal or hepatic abnormalities or subsequent haematological toxicity, hepatic or renal dysfunction or pulmonary, neurological or other toxicity. The following guidelines may be helpful if local policies do not exist:

Dose recommendations for anticancer drugs in patients with
renal or hepatic impairment (and associated appendices). Lancet Oncol 2019; 20: e200–07 (Krens *et al.* 2019)

South West Clinical Network. PCV: Procarbazine, Lomustine and Vincristine. https://www.swagcanceralliance.nhs.uk/wp-content/uploads/2020/09/PCV-v2.pdf (South West Clinical Network 2014)

BC Cancer Monographs for individual drugs: http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index (BC Cancer)

For each cycle of chemotherapy, the pre-treatment clinical assessment must be performed within 7 days prior to Day 1 of each cycle.

8.2.3 Supportive medications, pre-medications and dietary advice

Anti-emetics and other supportive measures, such as dexamethasone, may be prescribed as per each institution's usual practice.

Constipation is common with vincristine - laxatives are recommended on a PRN basis for all patients.

For patients receiving procarbazine, dietary advice should be provided as per each institution's usual practice.

Granulocyte colony stimulating factor (GCSF) may be used as per usual hospital practice. Of note, concurrent use of GCSF and vincristine may result in severe neuropathy. Ideally GCSF should be avoided within 5 days of vincristine administration unless the clinical benefits (e.g. in cases of severe neutropenic sepsis) are considered to outweigh the risks.

Precautions
Neutropenia may occur: fever or other evidence of infection should be assessed rapidly and managed in line with institutional policy for neutropenic sepsis.

For patients receiving Lomustine, a vomited dose of Lomustine should not be repeated if it occurs more than 30 minutes after administration.

A vomited dose of procarbazine should not be repeated.

Hypersensitivity (to procarbazine) should be managed according to local hospital guidelines.

Women of child-bearing potential or men who are sexually active must use medically acceptable forms of contraception, see section 4.3 Birth control: contraception and pregnancy testing.

Missed doses

A missed dose of lomustine may be taken any time on the day that it is due. Doses of Lomustine that are missed for more than three days should be omitted.

A missed dose of procarbazine may be taken within 8 hours of the time it is due. A dose that has been missed for more than 8 hours should be omitted. The next dose should be taken on schedule. Doses should not be doubled up to make up for missed doses.

Overdoses of trial medication

A dose of Lomustine, Procarbazine or Vincristine in excess of that specified according to the protocol will constitute an overdose.

Medications to be avoided and drug interactions

All concomitant medications including any over the counter or complementary treatments should be reviewed and potential interactions considered.

Live vaccines should be avoided during and for 6 weeks after completion of chemotherapy.

Where particular medications should be avoided (see list below), necessary washout periods and required intervals to re-starting these agents, should be discussed with the local Pharmacy team.

LOMUSTINE:

- Cimetidine (enhances toxicity of lomustine): avoid
- Alcohol: avoid on the day that lomustine is taken
- Theophylline medications: avoid
- Anti-epileptics – check with your Pharmacist – there may be pharmacokinetic interactions depending on agent

PROCARBAZINE:

- Alcohol or tyramine containing foods (can result in nausea, vomiting, CNS depression, hypertension (including hypertensive crisis), changes in vision and headache): avoid. **Dietary advice regarding foods that should be avoided should be as per the institution's usual practice for patients taking procarbazine**
- Antihistamines (can result in increased CNS or respiratory depression): use with caution
- Levodopa (concurrent use causes hypertension): avoid concurrent use
- Tricyclic anti-depressants and other mono-amine oxidase inhibitors (concurrent use can cause CNS excitation, hypertension, tremors, palpitations, hypertension (including hypertensive crisis) or angina: avoid concurrent use
- Anti-diabetic agents: concurrent use may worsen hypoglycaemia: close monitoring of blood sugars required
- Anti-epileptics - check with your Pharmacist - there may be pharmacokinetic interactions depending on agent

VINCRISTINE:

- Itraconazole: avoid
- Drugs that inhibit drug metabolism via cytochrome P450: avoid
- Phenytoin: vincristine reduces plasma levels: monitor for effect
- Digoxin: vincristine reduces plasma levels: monitor for effect
- Filgrastim (GCSF): concurrent use may result in severe neuropathy: avoid within 5 days of vincristine administration unless the clinical benefits (e.g. in cases of severe neutropenic sepsis) are considered to outweigh the risks.

8.4 Withdrawal of treatment or data collection

In line with usual clinical care, cessation or alteration of treatment at any time will be at the discretion of the attending clinician or the participant themselves. If a clinician withdraws a participant or if a participant withdraws consent for further trial treatment and/or further collection of data, their data and any samples collected prior to withdrawal of consent will remain on file and will be included in the final study analysis. Data outstanding up to the point of withdrawal will be chased with site.

The PI, or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Withdrawal eCRF, in order that the correct processes are followed by the CTRU and site following the withdrawal of consent.

In addition, it is suggested that the participant is made aware of the fact that if any significant new information becomes available concerning the treatment they have received in the trial, it may be necessary to contact them in the future.

9 Assessments

9.1 Eligibility assessments

The following investigations and assessments must be carried out prior to randomisation and can be used to establish eligibility.

All investigations and assessments that are listed below and carried out before consent for APPROACH can be considered standard of care, with the exception of the pregnancy screen, which has a separate consent process (see section 7.2 Recruitment and informed consent).

No specific time limit prior to randomisation:

- Diagnostic biopsy or surgery to gain histology

Within 7 days prior to randomisation:

- Confirmed that they are not pregnant with their doctor/treatment team. Since this is an eligibility criteria and must be performed prior to consent, participants of child-bearing potential must consent using the shortened pregnancy eligibility screening PISICF, to being pregnancy screened and potentially being required to show a negative pregnancy result prior to consenting to the trial.

Within 14 days prior to randomisation:

- KPS
- Medical history
- Clinical assessment (including participant's height and weight, clinical examination including central nervous system (CNS) examination and documentation of concurrent medications of interest (including review of steroid use, anti-epileptics and hormonal therapies))

In addition, completion of the baseline neurocognitive function (NCF) tests MUST take place prior to randomisation (see section 9.10 Neurocognitive function tests).

9.2 Pre-randomisation/Baseline assessments

In addition to the above eligibility assessments, data collected on the pre-randomisation eCRFs (Baseline and Randomisation), will also include (but will not be limited to):

- Participant details and demographics including sex, date of birth, date of diagnosis of ODG, previous interventions for ODG (biopsy only or subtotal or gross total resection) and date of interventions
- Confirmation of written informed consent
- Completion date of baseline neurocognitive testing
- Confirmation of completion of HRQoL and related questionnaires (EORTC QLQ-C30 and BN20, EQ-5D-5L, MFI, HADS, WPAI, additional health resource use questionnaire), Caregiver Needs Screen
- Confirmation of the date of an up-to-date MRI scan, performed within 28 days prior to randomisation to serve as the baseline scan to assess response rates and progression-free survival
- Baseline CTCAE symptom scores
- Caregiver baseline data
- Baseline MRI: randomisation must be performed within 28 days of the magnetic resonance imaging (MRI) that leads to the decision that RT is required at that point

in time. Outside of 28 days, an updated MRI is required to serve as a contemporaneous baseline scan to assess response to further treatment

The following HRQoL questionnaires should also be completed pre-randomisation by both the participant and, if willing and consent obtained, their primary caregiver on the paper baseline QoL booklet provided by CTRU in clinic:

- EORTC QLQ-C30 and BN20 (completed by participant)
- EQ-5D-5L (completed by participant)
- Multi-dimensional Fatigue Inventory (MFI) (completed by participant)
- Hospital and Anxiety Depression Scale (HADS) (completed by participant)
- Work Productivity and Activity Impairment (WPAI) and an additional health resource use questionnaire (completed by participant and primary caregiver)
- Caregiver Needs Screen questionnaire (completed by primary caregiver)

Please see section 9.12 Participant and caregiver questionnaires below for further details.

9.3 Pre-treatment assessments

Data collected following randomisation but prior to the RT treatment start date will include (but will not be limited to):

Within 7 days prior to CT simulation for RT:

- Confirmed that they are not pregnant with their doctor/treatment team.

Within 7 days prior to start of RT:

- Confirmed that they are not pregnant with their doctor/treatment team.

Within 21 days prior to start of RT:

- CT simulation scan for RT planning

In addition:

MRI to assist in radiotherapy planning: this is performed ideally within 21 days, but **must** be performed within 28 days, of the CT simulation scan

Completion date of endocrine assessments (see section 9.11 Endocrine testing) will be collected on the Endocrine Assessment eCRF. Must be completed between randomisation and start of radiotherapy, ideally within 4 weeks of randomisation.

After randomisation and before starting PBT or photon RT, discontinuation of any radiosensitisers must be documented.

9.4 Weekly assessments during PBT or photon RT

Participants should be seen once weekly for review and assessed clinically for symptoms and toxicity, together with documentation of concurrent medications of interest (including review of steroid use, anti-epileptics and hormonal therapies) and assessment of performance status. These may be performed in the formal outpatients' clinic or as 'on-treatment' reviews. Toxicities will be assessed based on the latest National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0). A copy of the NCI-CTCAE is provided in the ISF.

Details of PBT or photon RT treatment will be collected on a weekly basis by completing the PBT Treatment or Photon RT eCRFs. Data collected during these visits will include (but will not be limited to):

- Date treatment started and ended
- Weekly number of fractions and weekly doses given
- Details of any interruptions, including reason(s)
- For patients who are randomised to PBT, any fractions delivered as photon RT, the number of photon fractions delivered and the reasons for this
- Clinical assessment (clinical examination including CNS examination, documentation of concurrent medications of interest (including review of steroid use, anti-epileptics and hormonal therapies) and assessment of KPS)
- Acute toxicity scores for adverse reactions (ARs) related to treatment using CTCAE

9.5 Assessments during final week of PBT or photon RT

The following assessments should be completed on any day the participant receives one of their 5 final radiotherapy treatments (i.e. during their final week of treatment). Data collected will include (but will not be limited to):

- As per the weekly assessment above and:
- HRQoL questionnaires (EORTC QLQ-C30, EORTC BN20, EQ-5D-5L, MFI and HADS (completed by participant)),
- WPAI questionnaire and additional health resource use questionnaire (completed by participant and primary caregiver),
- Caregiver Needs Screen questionnaire (completed by primary caregiver).

9.6 Chemotherapy pre-treatment assessments

Participants may start PCV chemotherapy at any time between 4 and 8 weeks post-end of RT. Participants will be reviewed prior to each cycle of adjuvant PCV chemotherapy. A clinical assessment should be performed **within 7 days prior to Day 1 of each cycle** of chemotherapy and blood tests should be performed **within 7 days prior to Day 1 of cycle 1 and within 3 days of all subsequent cycles** of PCV chemotherapy. Data collected will include (but will not be limited to):

Within 7 days prior to Day 1 of cycle 1 and within 3 days of Day 1 for all subsequent cycles:

- FBC, U&Es, LFTs, creatinine clearance and bilirubin (within required parameters to proceed with chemotherapy, see section 8.2.2 Chemotherapy treatment schedule for further details)

Within 7 days prior to Day 1 of each chemotherapy cycle:

- Confirmed that they are not pregnant with their doctor/treatment team.
- Clinical assessment (including participant's weight, clinical examination including CNS examination, documentation of concurrent medications of interest (including review of steroid use, anti-epileptics and hormonal therapies) and assessment of KPS)

The following will also be performed and recorded:

- Date treatment started and ended
- Chemotherapy dose details (any delays, dose reductions or interruptions that have occurred and the reason(s) for these)
- Toxicities using CTCAE

9.7 Follow-up assessments

Participants will be seen in the out-patient clinic after completion of PBT or photon RT for follow-up visits (post-end of PBT or photon RT) as follows: 1, 3, 6, 12, 24, 36, 48 and 60 months. Where relevant and possible, follow-up assessments should be performed during the closest chemotherapy pre-treatment assessment and within +/- 4 weeks of the scheduled follow up timepoint. Details of the follow-up assessments required at each of these follow-up time points are provided below.

Follow-up data will be collected at these time points by completing the relevant eCRF. At follow-up visits, data collected will include (but will not be limited to):

- Clinical assessment (clinical examination including CNS examination, documentation of concurrent medications of interest (including review of steroid use, anti-epileptics and hormonal therapies) and assessment of KPS)
- Clinician-recorded toxicities and CTCAE (until end of trial as per assessment schedule)
    - Pre-existing symptoms/side effects related to ODG or its treatment that pre-date APPROACH trial treatments should be recorded at the baseline assessment – these will not be considered as new toxicities
    - Pre-existing symptoms/side effects related to a non-ODG cause that pre-date APPROACH trial should be recorded at the baseline assessment – these will not be considered as new toxicities
- Neurocognitive function tests (see 9.10 Neurocognitive function tests)
- HRQoL questionnaires (EORTC QLQ-C30 and BN20, EQ-5D-5L, MFI, HADS, completed by participant))
- Endocrine assessment (see 9.11 Endocrine testing; not required at months 1 and 3)
- WPAI questionnaire and an additional health resource use questionnaire (completed by participant and primary caregiver)
- Caregiver Needs Screen questionnaire (completed by primary caregiver)
- MRI (not required at month 1)
- Documentation of clinical or radiological progression

Follow-up visits and assessments will continue until 60 months post-end of radiotherapy or until death, whichever is sooner.

9.8 Progression

At progression, further management will be guided by the local team. Participants should continue to be assessed for neurocognitive function, HRQoL, endocrinopathy, WPAI, health resource use questionnaire, Caregiver Needs Screen, toxicity and overall survival until 5 years of trial follow up is complete.

Neurocognitive function and endocrinopathy will continue to be assessed as scheduled in the trial protocol (+/- 2 months at each time point). Where HRQoL, WPAI, health resource use questionnaire and Caregiver Needs Screen are assessed electronically, these should also continue to be assessed as scheduled in the trial protocol (+/- 2 months at each time point).

Clinical assessments, including toxicity assessments will be recorded from the clinic visit closest in time (and ideally within 2 months) to the scheduled visit in the trial assessment schedule. Where HRQoL, WPAI, health resource use questionnaire and Caregiver Needs Screen are assessed on paper (i.e. collected/ completed at a face to face clinic visit), these

should also be assessed the clinic visit closest in time (and ideally within 2 months) to the scheduled visit in the trial assessment schedule.

The timing and frequency of MRI will be guided by clinical need, as per standard of care, but data will be collected from those MRIs performed closest in time to those scheduled in the trial assessment schedule.

9.9 MRI

MR imaging will be performed at baseline, to assist with RT planning and at 3, 6, 12, 24, 36, 48 and 60 months post-end of RT, as per standard practice. Again, as per standard practice, additional imaging may be performed outside of these intervals in light of clinical concerns over deterioration.

The baseline MRI, that determines that a patient requires RT at that point in time, must be performed within 28 days of randomisation. Outside of 28 days, an updated MRI is required to serve as a contemporaneous baseline scan to assess response to further treatment.

Imaging sequences will be as per standard (Ellingson *et al.* 2015; British Society of Neuroradiologists: BSNR Standards Sub-Committee 2015-2018) and will include:

- T2
- FLAIR
- DWI
- T1 pre-gadolinium
- T1 post-gadolinium

MRI scans will be evaluated based on response assessment in neuro-oncology (RANO) criteria (Wen *et al.* 2010; van den Bent *et al.* 2011; Chukwueke and Wen 2019).

9.10 Neurocognitive function tests

The full battery is described below, together with the domains assessed. The full battery will be performed at baseline (before randomisation), 1 month post-end of RT and at 12, 24, 36, 48 and 60 months post-end of RT.

Baseline testing must be completed before randomisation.

Those tests that contribute to the primary endpoint assessment are those included in the EORTC core clinical trial battery composite (CTB COMP), an internationally recommended (van den Bent *et al.* 2011; Wefel *et al.* 2011) for use in studies of NCD in cancer patients.

CTB COMP tests consist of:

- Hopkins Verbal Learning Test-Revised (HVLT-R)
- Trail Making Test A and B (TMT-A/B)
- Controlled Oral Word Association test (COWA)

Cognitive test	Description	Time
Hopkins Verbal Learning Test-Revised	12 words are read aloud to the patient with 2 second intervals. Direct recall is scored for trials 1-3. After a 20-25 minute interval, delayed recall (trial 4) and recognition is scored	10 minutes, plus 5 minutes

Trail Making Test Part A	Circles labelled 1 through 25 to be connected as fast as possible	2-3 minutes
Trail Making Test Part B	Circles labelled 1-13 and A-L to be connected in alternating successive order (i.e., 1-A, 2-B, etc.) as fast as possible	5 minutes
COWA	Naming as many words as possible starting with a certain letter within 1 minute	6 minutes

CTB COMP tests cover assessment of processing speed, verbal memory, and executive functioning. Tests within CTB COMP must be administered by a trained individual (see **NCF Test Administration Guidelines)** in a face-to-face setting, in a quiet uninterrupted environment (e.g. separate clinic room).

Specific NCF test forms will be provided for the completion of these tests. The printed text must not be altered in any way. Completed NCF test forms should be scanned and returned to the CTRU via the APPROACH trial specific secure file transfer service (SFTS) within 28 days of completion for QA and scoring purposes.

Training to perform the NCF tests for the primary endpoint will be delivered as part of the site initiation process. A yearly refresher of the training will be provided. More frequent refresher training may be required if any concerns are raised during the NCF QA review of completed NCF test forms. Further information related to training can be found in the **NCF Test Administration Guidelines**.

QA will be undertaken centrally through visual inspection of the raw data, ensuring that any issues with reliability and validity of assessments is recorded. Appropriate feedback to centres will be provided.

Additional tests are also included at each time point to allow a more thorough neurocognitive assessment. Additional tests will contribute to secondary NCF endpoints and will be assessed using the online electronic platform, CNS Vital Signs. Instructions regarding the execution of CNS Vital Signs will be provided. Participants will complete the electronic assessments after completing the CTB COMP tests above. These can be completed on a desktop in a quiet undisturbed environment, and must be completed under the supervision of a Research Nurse or other trained individual.

CNS vital sign tests and potential domains include (CNS Vital Signs):

Cognitive test	Description	Approx. Time
Verbal Memory Test	The VBM test measures recognition memory for WORDS. Fifteen words are presented, one by one, on the screen every two seconds. For immediate recognition, the participant has to identify those words nested among fifteen new words. Then, after six more tests, there is a delayed recognition trial. Note: the VBM within CNS Vital Signs covers visual verbal memory while the HVLT-R covers auditory verbal memory.	3 minutes
Visual Memory Test	The VIM test measures recognition memory for FIGURES or SHAPES. Fifteen geometric figures	3 minutes

	are presented, one by one, on the screen. For immediate recognition, the participant has to identify those figures nested among fifteen new figures. Then, after five more tests, there is a delayed recognition trial.	
Finger Tapping Test	The FTT requires subjects to press the Space Bar with their right index finger as many times as they can in 10 seconds. They do this once for practice, and then there are three test trials. The test is repeated with the left hand.	2 minutes
Symbol Digit Coding Test	The SDC test consists of serial presentations of screens, each of which contains a bank of eight symbols above and eight empty boxes below. The participant types in the number that corresponds to the symbol that is highlighted.	4 minutes
Stroop Test	The Stroop test has three parts. In the first part, the words RED, YELLOW, BLUE, and GREEN (printed in black) appear at random on the screen, and the participant presses the space bar as soon as the test subject sees the word. In the second part, the words RED, YELLOW, BLUE, and GREEN appear on the screen, printed in colour. The participant is asked to press the space bar when the colour of the word matches what the word says. In the third part, the words RED, YELLOW, BLUE, and GREEN appear on the screen, printed in colour. The participant is asked to press the space bar when the colour of the word does not match what the word says.	4-5 minutes
Shifting Attention Test	The SAT is a measure of ability to shift from one instruction set to another quickly and accurately. Participants are instructed to match geometric objects either by shape or by colour. Three figures appear on the screen, one on top and two on the bottom. The top figure is either a square or a circle. The bottom figures are a square and a circle. The figures are either red or blue (mixed randomly). The participant is asked to match one of the bottom figures to the top figure. The rules change at random (i.e., match the figures by shape, for another, by colour).	2.5 minutes
Continuous Performance Test	The CPT is a measure of vigilance or sustained attention or attention over time. The test subject is asked to respond to the target stimulus “B” but not to any other letter. The stimuli are presented at random.	5 minutes
Perception of Emotions Test	The POET measures how well a subject can perceive and identify specific emotions. "Social cognition" or "emotional acuity" has been defined as "the way in which people make sense of other people and themselves". It is the ability to perceive and understand social information.	2 minutes
Non-Verbal Reasoning Test	The NVRT measures how well a subject can perceive and understand the meaning of visual or	3.5 minutes

	abstract information and recognising relationships between visual-abstract concepts. The NVRT is comprised of 15 matrices, or visual analogies. The matrices are progressively more difficult. Non-verbal or visual-abstract reasoning is the process of perceiving issues and reaching conclusions through the use of symbols or generalisations rather than concrete factual information.	
Four Part Continuous Performance Test	The 4PCPT is a four-part test that measures a subject's working memory and sustained attention. PART ONE - is a simple reaction time test, PART TWO - is a variant of the continuous performance test, the reaction times that are generated are "choice reaction times". PART THREE - is a "one back" CPT. The subject has to respond to a figure only if the figure immediately preceding was the same. PART FOUR - is a "two-back" CPT. It is a difficult task and is used to measure working memory.	7 minutes

9.11 Endocrine testing

Tests of endocrine function will be performed at baseline and 6, 12, 24, 36, 48 and 60 months post-end of RT, as per standard of care. These are best performed within a dedicated Endocrinology Department.

Baseline testing must be completed after randomisation and before start of radiotherapy, ideally within 4 weeks of randomisation.

Dynamic/static testing will be performed for the following:

- GH/IGF-1
- FSH (all patients)/LH (all patients)/ testosterone & SHBG (male patients only)/ oestradiol (female patients only)
- Cortisol
- T4/T3/TSH
- Prolactin

The following protocol should be followed:

- Patients are required to fast from midnight the night before testing
- Baseline bloods are collected between 8am and 9am on the day of testing. These consist of: IGF-I, GH, LH, FSH, testosterone & SHBG or oestradiol, prolactin, TSH, fT4 and fT3
- After the baseline bloods have been collected, the patient is given 1mg glucagon IM
- Bloods are then taken every 30 minutes for the next 3 hours for GH and cortisol

9.11.1 Interpretation of endocrine function results

Endocrine function results should be interpreted by an Endocrinologist or Specialist Nurse with expertise in Endocrinology.

Cut-offs for diagnosis of hormone deficiencies will be influenced by the assays used and so may differ from the exact values described below. As a general guide, however:

- *Growth hormone (GH) deficiency*: severe deficiency suggested by a peak (at any time point) in GH <3.0 ug/l.
- *Cortisol insufficiency*: deficiency suggested by a peak (at any time point) in cortisol <450 nmol/l.
- *Gonadotropin deficiency for men*: inappropriately low gonadotropins (<9 iu/l) with a testosterone level below 8.0 nmol/l.
- *Gonadotropin deficiency for premenopausal women*: can only be diagnosed in the setting of notable oligo- or amenorrhoea when the gonadotropins would be inappropriately low for the oestrogen level.
- *Gonadotropin deficiency for post-menopausal women*: gonadotropins inappropriately low.
- *Prolactin*: There is no real definition of prolactin deficiency, but generally levels increase after cranial RT. As a pragmatic approach, a prolactin level <100 miu/l will be considered as prolactin deficiency. A prolactin above 600 miu/l is elevated.
- *Secondary hypothyroidism*: free T4 <10 pmol/l with inappropriately low TSH (usually mid-low normal). Bioinactive TSH may be observed in pituitary disease where fT4 levels fall and the TSH can be towards the upper limit of normal or even up to 6.0 miu/l.

A number of caveats exist regarding interpretation of the above endocrine function results, including medications the patient is receiving, in particular steroid, opioid and dopaminergic drugs. The use of hormonal contraceptives should also be considered when interpreting results, including those for gonadotrophins and cortisol. In addition, body composition in men is a major determinant of testosterone levels (e.g. a combination of high body mass index (BMI), low total testosterone and low SHBG, may result in a normal calculated free testosterone). The use of any other hormonal therapies should also be considered when interpreting results. Prolactin is a stress hormone, meaning that levels may be variable. The glucagon stress test fails to result in an adequate peak GH or cortisol in around 1 in 10 normal individuals. Peak GH responses are significantly attenuated by a BMI >30 kg/m^2. Renal and liver function influence the observed levels of many hormones. Acute illness attenuates almost all hormones except cortisol. What used to be considered 'sick euthyroid' syndrome is now termed non-thyroidal illness syndrome and is a confounder that can present with similar values to TSH deficiency.

Blood results, their interpretation and the use of any endocrine therapies should be recorded on the Endocrine Assessment eCRF.

9.12 Participant and caregiver questionnaires

All patients and their primary caregivers will be requested to complete questionnaires at baseline, during the final week of RT treatment and 1, 3, 6, 12, 24, 36, 48 and 60 months post-end of RT. Baseline questionnaires will be completed on paper prior to randomisation in clinic, and patient and caregiver preferred methods for all proceeding questionnaires should be recorded on the F50 Contact Details paper CRF and sent to CTRU via the SFTS.

Both participants and caregivers can choose to either: receive paper questionnaires to be completed in clinic at the appropriate time points; or electronic questionnaires that can be completed online using ‘REDCap’ which stands for Research Electronic Data Capture (see section 9.18 Trial assessments and data collection for further information).

Where a participant/caregiver has expressed a preference to complete their questionnaires on paper, questionnaires will be completed by the participant/caregiver on attendance at the scheduled outpatient appointments, prior to being seen in clinic. Questionnaires should be completed independently by the participant. If a participant requires assistance from a caregiver, this should be recorded on the form. The forms will then be sent to CTRU.

Where a participant/caregiver has expressed a preference to complete their questionnaires via REDCap online, the participant/caregiver will be sent a link to the questionnaire via text or email. They will also be sent reminders to prompt completion of the data, this includes reminders by their preferred method, either text message or email. Please note: online questionnaires can be completed on any device and do not have to be completed on a mobile phone. If participants/caregivers would prefer to complete questionnaires on a desktop computer, a prompt or reminder sent by email should be the preferred option for communication about questionnaire completion, please see Section 9.18 Trial assessments and data collection for further information.

9.12.1 Health-related quality of life

Generic HRQoL will be assessed with the **EORTC QLQ-C30** (Aaronson *et al.* 1993), Quality of Life Questionnaire Core 30. This questionnaire is comprised of five function scales (physical, role, cognitive, emotional, and social functioning), nine symptom scales (fatigue, pain, nausea and vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial impact), and a scale for overall quality of life. Items are rated on a four-point scale. Higher scores on the functional scales indicate better functioning, whereas higher scores on the symptom scales indicate more impediments of symptoms.

Disease-specific HRQoL will be assessed with the **EORTC QLQ-BN20** (Taphoorn *et al.* 2010) brain cancer specific module questionnaire. This questionnaire comprises four multi-item scales (future uncertainty, visual disorders, motor dysfunction and communication deficit) and seven single items covering other common symptoms.

The EuroQoL **EQ-5D-5L** (EuroQol 2019) questionnaire collects information about five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and is the standard questionnaire used in health economic evaluation. The results can be combined into a 5-digit number that describes the patient's health state which in turn can be assigned a utility score. The questionnaire also includes a visual analogue scale to record the patient's self-rated health on a vertical visual scale.

The **Multi-dimensional Fatigue Inventory (MFI)** (Smets *et al.* 1995), will be used to assess subjective fatigue. This instrument is a 20-item self-report that covers dimensions around general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. Scoring ranges from 1-5 to indicate how appropriately particular statements relating to fatigue represent their experiences and is scored according to the respective manuals. Higher total scores correspond with more acute levels of fatigue.

The **Hospital and Anxiety Depression Scale (HADS)** is a 14-item measure designed to assess anxiety and depression symptoms in patients. Items are rated on a 4-point severity scale. HADS produces two scales, one for depression and one for anxiety, differentiating the two states. Scores equal to 11 or more indicate a definitive case on either scale (Zigmond and Snaith 1983), and will be used to assess distress.

9.12.2 Caregiver Needs Screen

The 30-item **Caregiver Needs Screen** questionnaire will be included and completed by the participant's primary caregiver at baseline, during the final week of RT treatment and 1, 3, 6, 12, 24, 36, 48 and 60 months post-end of RT. This validated questionnaire includes subscales for neurologic and oncologic symptoms, personal communication, communication with healthcare providers, resources and caregiver health.

9.12.3 Work & economic impact

The **Work Productivity and Activity Impairment (WPAI)** questionnaire will be completed by participants and caregivers at baseline, during the final week of RT treatment and 1, 3, 6, 12, 24, 36, 48 and 60 months post-end of RT and includes six questions about employment, time off and productivity at work and during regular activities.

A **health resource use** questionnaire will be completed by participants and caregivers at baseline and annually thereafter at 12, 24, 36, 48 and 60 months post-end of RT and will collect patients' utilisation of health services related to their brain cancer including: NHS and primary health services, hospital based secondary care services and personal costs incurred. Personal costs incurred for caregivers will also be collected. The health resource use questionnaire will be administered in combination with the HRQoL chosen method (paper/REDCap), at baseline and annual follow-up. Additional information related to costs will also collect any hospital admissions and the length of stay.

9.13 Participant Transfers

If a participant is being permanently transferred to a different site, the Participant Transfer eCRF should be entered on MACRO as soon as possible to enable tracking of the participant.

9.13.1 Transfer to another site participating in APPROACH

Copies of any paper CRFs, informed consent forms and any other relevant correspondence is sent to the new site, with originals kept at the original centre. Data from before the date of transfer is questioned with the original site, data after the transfer will be queried with the new site. Both sites must ensure that the participant transfer is recorded on the participant log in the Investigator Site File.

9.13.2 Transfer to a site that is NOT participating in APPROACH

- All trial treatment will cease. Any further treatment for brain cancer received by the participant will be off trial.
- If the participant agrees to be followed up at the new site, it is the responsibility of the original site to gather follow-up data from the new site in order to complete the eCRFs. The original site will keep all trial documentation and ensure that the participant transfer is recorded on the participant ID log in the Investigator Site File.
- If the participant does not want to be followed up at the new site, a Participant Withdrawal eCRF must be entered by the original site on MACRO.
- Please note: participants will not be able to take part in any further NCF tests at a site that is not participating in APPROACH.

9.14 Death

All deaths occurring from the date of randomisation to the end of follow-up must be reported to the CTRU using the Notification of Death eCRF on the APPROACH database **within 7 days** of site becoming aware of the event. Data collected will include (but will not be limited to):

- Date of death
- Cause of death

9.15 Pregnancies

All pregnancies or suspected pregnancies in a trial participant, or their partner, occurring from the date of randomisation until 6 months after completion of adjuvant chemotherapy treatment must be reported to the CTRU **within 24 hours** of site becoming aware. All protocol treatment must be stopped immediately if a pregnancy in a participant occurs or is suspected.

The CTRU will report all pregnancies occurring during treatment to the Sponsor along with any follow-up information.

9.16 End of trial

The end of the trial is defined as the date of the collection of the last participant's last data item. Participants will be followed up until death or until the final analysis as described in section 3 Trial design overview, (whichever is sooner). Follow up and trial assessments will continue, including beyond tumour progression.

A separate mechanistic analysis plan will be developed and will be reassessed throughout the duration of the trial given that the mechanistic analysis will not take place until years nine and ten of the grant. The analysis plan will incorporate any developments in the research literature in this field over time.

9.17 Schedule of Assessments

Table 3 Assessment Schedule for both PBT and photon RT

	Baseline			Radiotherapy Treatment						Follow-up post-end of radiotherapy							
	Eligibility assessments	Pre-rand	Pre-RT trt	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	1 month	3 months	6 months	12 months	24 months	36 months	48 months	60 months
Medical history	●																
Clinical Assessment[1]	●			●	●	●	●	●	●[12]	●	●	●	●	●	●	●	●
Neurocognitive function tests[2]		●								●			●	●	●	●	●
Pregnancy test	●[3]		●[4]							●[5]	●[5]	●[5]					
Baseline CTCAE monitoring		●															
MRI scan[6]		●[16]	●[7]								●	●	●	●	●	●	●
CT scan			●[8]														
Informed consent		●															
HRQoL[9]		●							●[12]	●	●	●	●	●	●	●	●
Work & Productivity[10]		●							●[12]	●	●	●	●	●	●	●	●
Health Resource Use[10]		●											●	●	●	●	●
Caregiver Needs Screen[11]		●							●[12]	●	●	●	●	●	●	●	●
Endocrine assessment[13]			●									●	●	●	●	●	●
PBT or photon RT				●	●	●	●	●	●								
PCV Chemotherapy[14]										6 x 6-weekly cycles of adjuvant PCV chemotherapy							
CTCAE acute & late toxicity monitoring[15]				●	●	●	●	●	●[12]	●	●	●	●	●	●	●	●

[1] Comprised of clinical examination (including CNS examination), documentation of concurrent medications of interest (including review of steroid use, anti-epileptics and hormonal therapies) and assessment of Karnofsky Performance Status to be done within 14 days prior to randomisation.
Participant's height to be done for baseline only, participant's weight to be done at eligibility and prior to Day 1 of each cycle of chemotherapy

[2] Neurocognitive test. See section 9.10 Neurocognitive function tests

[3] Participant must have confirmed that they are not pregnant with their doctor/treatment team within 7 days prior to randomisation (see section 4.3.1 Pregnancy Testing)

[4] Participant must have confirmed that they are not pregnant with their doctor/treatment team within 7 days prior to CT simulation for radiotherapy AND within 7 days prior to the first radiotherapy fraction (4.3.1 Pregnancy Testing)

[5] Participant must have confirmed that they are not pregnant with their doctor/treatment team within 7 days prior to each chemotherapy cycle (section 4.3.1 Pregnancy testing)

[6] Required to assess response rates and progression-free survival and evaluated based on RANO criteria

[7] MRI for radiotherapy planning to be done ideally within 21 days prior to the start of RT, but no more than 28 days of the CT simulation scan

[8] CT simulation for RT to be done within 21 days prior to the start of RT

[9] Including: EORTC QLQ-C30, EORTC BN20, EQ-5D-5L, Multi-dimensional Fatigue Inventory (MFI), Hospital and Anxiety Depression Scale (HADS)

[10] Work & Productivity (WPAI) and Health Resource Use questionnaires will be assessed in participants and primary caregivers. The Health Resource Use will be collected at baseline and at annual follow-up only.

[11] Caregiver Needs Screen to be completed by primary caregiver for each participant. Baseline data will also be collected at time of baseline questionnaire completion.

[12] To be completed on any day the participant will receive one of their 5 final RT treatments

[13] Endocrinopathy: Endocrine function will be assessed using blood tests. Dynamic/static testing will be performed for growth hormone/insulin-like growth factor-1 (GH/IGF-1), follicle-stimulating hormone/luteinizing hormone (FSH/LH)/ testosterone (males) & SHBG (males) /oestradiol (females), cortisol, thyroxine /tri-iodothyronine/ thyroid stimulating hormone (T4/T3/TSH) and prolactin. See section 9.11 Endocrine testing

[14] Participants may start PCV chemotherapy anywhere between 4 and 8 weeks post-end of RT. For each cycle of chemotherapy, a pre-treatment clinical assessment must be performed within 7 days prior to Day 1 of each cycle. Full blood count, urea and electrolytes, liver function tests, creatinine clearance and bilirubin should be performed within 7 days prior to the first chemotherapy cycle and within 3 days prior to each subsequent chemotherapy cycle

[15] ARs and SARs should be monitored and reported, during trial treatment, up until the end of the trial

[16] Randomisation must be performed within 28 days of the magnetic resonance imaging (MRI) that leads to the decision that RT is required at that point in time. Outside of 28 days, an updated MRI is required to serve as a contemporaneous baseline scan to assess response to further treatment

Table 4 Chemotherapy Assessment Sbhedule

	PCV Chemotherapy Treatment					
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Clinical Assessment[1]	●	●	●	●	●	●
Weight	●	●	●	●	●	●
Blood tests[2]	●	●	●	●	●	●
Pregnancy test[3]	●	●	●	●	●	●
CTCAE toxicity monitoring[4]	●	●	●	●	●	●

[1] Pre-treatment clinical assessment must be performed within 7 days prior to day 1 of each cycle, comprising participant's weight, clinical examination including CNS examination, documentation of concurrent medications of interest (including review of steroid use, anti-epileptics and hormonal therapies) and assessment of Karnofsky Performance Status.
[2] Full blood count, urea and electrolytes, liver functions tests, creatinine clearance and bilirubin should be performed within 7 days prior to the first chemotherapy cycle and within 3 days prior to each subsequent chemotherapy cycle
[3] Participant must have confirmed that they are not pregnant with their doctor/treatment team within 7 days prior to each chemotherapy cycle (see section 4.3.1 Pregnancy testing)
[4] ARs and SARs should be monitored and reported throughout trial treatment, including PCV chemotherapy, up until the end of the trial

9.18 Trial assessments and data collection

Trial participant data will be collected electronically via the CTRU Remote Data Entry (RDE) database. Participants will be given the choice of completing the HRQoL questionnaires either on paper or electronically, via the electronic patient reported outcome software REDCap. REDCap is the CTRU's current solution for health-related quality of life (HRQoL) data collection and allows trial participants to directly enter data into REDCap, as an alternative to paper-based forms. REDCap has been validated for use in all CTRU trials.

For those wishing to complete the questionnaires electronically, they will be given the option of receiving an email or text message with a link to their questionnaire. Each participant's and caregiver's preferred method of questionnaire administration and completion will be collected during the consent process and applicable contact details (i.e. email address/mobile phone number) collected.

Non-responders will receive reminders by the pre-stated preferred method of communication at the following time points where HRQoL data is collected: during the final week of RT treatment and 1, 3, 6, 12, 24, 36, 48 and 60 months post-end of RT. Reminders will be sent 2 weeks and 4 weeks after the initial link to the questionnaire was sent and where records at CTRU show that it has not been completed. The CTRU will contact sites at intervals throughout the study to ensure that each consenting participant's and caregiver's contact details and status have not changed and that it is still appropriate to send links to the questionnaires.

Participant and caregiver contact details, including email address and mobile phone number (if applicable), will be provided after randomisation to be used to facilitate the administration of HRQoL questionnaires during the trial.

This personal data will only be provided following the provision of informed consent by the participant or caregiver as indicated on the informed consent form and will conform to the 2018 Data Protection Act and General Data Protection Regulation (GDPR).

9.18.1 General eCRF completion guidance

Participating sites will record trial participant data via RDE onto eCRFs, using the MACRO database system, which will be managed by the CTRU. Access to the RDE system will be provided by the University of Leeds following the site being authorised to open to recruitment; guidance on RDE and completing eCRFs will be provided.

Participating sites will be expected to maintain a file of essential trial documentation in an ISF, which will be provided by the CTRU, and keep copies of all completed paper CRFs for the trial.

It is the responsibility of the site staff to ensure the ISF is properly maintained during the duration of the trial.

9.19 Submission of trial data

Data will be entered by site research staff on trial-specific eCRFs, which will be provided by CTRU on a trial-specific database, access to which will be provided by the CTRU following sites authorisation to open to recruitment.

RDE/eCRFs must only be completed by personnel authorised to do so by the PI at site, as recorded on the trial-specific Authorised Personnel Log (APL). Login details will be provided for these personnel only and should not be shared with others.

Completed NCF test paper forms should be returned to the CTRU within 28 days of completion for quality control and scoring purposes. In addition, completed NCF forms used in practice sessions with colleagues as part of the training process must also be returned to CTRU as soon as possible for review (see **NCF Test Administration Guidelines**).

The electronic platform CNS Vital Signs, used for completion of the secondary NCF tests, automatically scores tests and produces a report, which will be sent directly to the CTRU.

9.20 Electronic Case Report Forms (eCRFs)

A number of eCRFs which require expedited reporting to the CTRU, should be entered within the time points specified below:

- A scanned copy of any consent forms must be sent to the CTRU via the in-house SFTS and the corresponding eCRF entered at the time of consent
- A paper Contact Details CRF should be sent to the CTRU via the SFTS immediately after randomisation
- SAR (serious adverse reaction) and RUSAE (related unexpected serious adverse events) eCRFs must be entered within 24 hours of the site becoming aware of the event. Please note: a paper SAR and RUSAE form will also be provided as a back-up in the event any urgent reporting is required and the MACRO database cannot be accessed
- Protocol Violations eCRFs must be entered within 24 hours of the site team becoming aware of the event
- Notification of Pregnancy eCRFs must be entered within 24 hours of the site team becoming aware
- Any Notification of Death eCRFs must be entered within 7 days of the site team becoming aware
- Any Withdrawal Request eCRFS must be entered within 7 days of the date of withdrawal
- End of treatment eCRFs must be entered within 14 days of completion of PBT or photon RT

All other eCRFs must be completed within 28 days of the data collection time points detailed in Table 3 Assessment Schedule for both PBT and photon RT.

Only the participant's trial number, date of birth and initials will be added to the eCRFs – site staff are responsible for ensuring the data returned to CTRU does not contain any other personal identifiable data. The exception to this is any copies of the consent form, where the participant/caregiver/authorised investigator name and signature must not be obliterated.

Following receipt of any completed eCRFs, the CTRU will contact sites on a regular basis to resolve any missing or discrepant data.

10 Safety Reporting

10.1 General definitions

10.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial participant which does not necessarily have a causal relationship with the treatment. Non-serious AEs which have no causal relationship with trial treatment will not be recorded in this trial, but must still be recorded in the participant's medical notes

10.1.2 Adverse Reaction (AR)

Adverse reactions (ARs) are all untoward and unintended responses to a trial treatment.

This definition implies a reasonable possibility of a causal relationship which is supported by facts, evidence or arguments to suggest a causal relationship. This definition includes medication errors and uses outside what is foreseen in the protocol (i.e. if an AR occurs as a result of a medication error).

Trial treatment in APPROACH is defined as radiotherapy (photons or protons) **and** adjuvant chemotherapy.

10.1.3 Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is any untoward medical occurrence or effect that:

- Results in death.
- Is life-threatening*.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Consists of a congenital anomaly or birth defect.
- Jeopardised the subject or required intervention to prevent one of the above.

*The term life-threatening refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical judgement should be exercised in deciding whether an SAE is serious (see protocol section. These characteristics / consequences must be considered at the time of the event.

10.1.4 Serious Adverse Reaction (SAR)

A Serious Adverse Reaction (SAR) is an SAE deemed to have been related to trial treatment. For the purposes of safety reporting trial treatment in APPROACH is defined as radiotherapy (photons or protons) and adjuvant chemotherapy. Safety monitoring of reactions to chemotherapy will be included and as such will be reported under the toxicity secondary objective (see section 13.5), however, there is no hypothesis of expected differences and no plan for formal comparisons. These events are collected for monitoring

purposes, and completeness of symptom reporting for this patient population across the course of the trial.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see section 10.4 Responsibilities). These characteristics/consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above. Important SAE/SARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one or the other outcomes listed in the definition above, should also be considered serious.

10.1.5 Related Unexpected Serious Adverse Event (RUSAE)

A serious adverse reaction which is related and unexpected (termed Related Unexpected Serious Adverse Event, or RUSAE) will require expedited reporting (see section 9.20 Electronic Case Report Forms (eCRFs)) to enable reporting to the main Research Ethics Committee (REC) and Sponsor.

The Health Research Authority (HRA) defines the terms related and unexpected as:

- Related: that is, it resulted from administration of any research procedures.
- Unexpected: that is, the type of event that in the opinion of the investigator is not considered expected.

When determining whether an SAR is expected or not, please refer to Appendix B – Treatment toxicities for a list of expected radiotherapy related side effects and, for expected chemotherapy-related toxicities, additionally refer to the relevant version of the SMPC that is used locally.

10.2 Reporting requirements for ARs

Non-serious AEs which have no causal relationship with trial treatment will not be collected in this trial, but must still be recorded in the participant's medical notes.

Information about all ARs, whether volunteered by the participant, discovered by investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the relevant eCRF and will be evaluated for duration and intensity according to the current NCI-CTCAE, see Appendix A NCI-CTCAE.

Information on all radiotherapy related ARs will be collected weekly during PBT or photon RT and until the end of trial according to the assessment schedule illustrated in Table 3. All chemotherapy related ARs will be collected during chemotherapy up to 42 days after the last cycle received.

10.3 Recording and reporting SARs and RUSAEs

Examples of events which will be classed as expected ARs and SARs within this trial and therefore will not be reportable as RUSAEs are given in Appendix B Treatment Toxicities. This is not intended to be an exhaustive list, therefore when determining whether an SAR is expected or not, please always refer to the relevant SMPC that is used locally.

10.3.2 Events classed as expected SARs

Examples of events that **will be** classed as expected SARs within this trial and therefore will not be reportable as RUSAEs unless the Investigator considers the severity to be unexpected are given in Appendix B Treatment Toxicities. In relation to chemotherapy treatment, the toxicities listed in Appendix B Treatment Toxicities are not intended to be an exhaustive list, therefore when determining whether an SAR is expected or not, please always refer to the relevant approved SMPC.

10.3.3 Expected ARs and SARs related to chemotherapy

For a full list of expected side effects for lomustine, procarbazine or vincristine please see individual drug SMPCs, which can be found on the Electronic Medicines Compendium (http://medicines.org.uk). **Please use the approved version of the SMPC when determining if toxicities are expected or not.**

Most ARs related to chemotherapy are mild to moderate (CTCAE v5.0 Grade 1-2) and reversible, but severe and life-threatening reactions (Grade 3-4) can occur.

Potential ARs are listed in Appendix B Treatment Toxicities. These may occur with any degree of severity (i.e. mild to severe). Only episodes considered as serious, as per the description above (Section 10.1.3 Serious Adverse Event (SAE) and Reaction (SAR)) should be reported as SARs.

Toxicities and dose modifications should be managed according to local guidelines.

10.3.4 Expected ARs and SARs related to radiotherapy

Potential ARs are listed in Appendix B Treatment Toxicities. These may occur with any degree of severity (i.e. mild to severe). Only episodes considered as serious, as per the description above (Section 10.1.3 Serious Adverse Event (SAE) and Reaction (SAR)) should be reported as SARs.

Toxicities related to radiotherapy should be managed according to local protocols. This may require increases in dexamethasone dose.

Toxicities related to chemotherapy should be managed according to local protocols.

10.3.5 Reporting and recording requirements for SARs and RUSAEs

All ARs (any grade), are to be reported as per the AR reporting period in section 10.2 Reporting requirements for ARs.

All SARs and RUSAEs for all participants occurring during treatment must be recorded on the appropriate SAR or RUSAE eCRF within 24 hours of the trial site team becoming aware of the event, regardless of causality. Please note: a paper SAR and RUSAE form will also be provided as a back-up in the event any urgent reporting is required and the MACRO database cannot be accessed. Selected late toxicities occurring during follow-up must also be recorded and reported as above.

SARs and RUSAEs will be collected throughout trial treatment and up until the end of the trial according to the assessment schedule, this is defined as the active trial monitoring period.

For each SAR and RUSAE the following information will be collected:

- Full details in medical terms with a diagnosis, if possible
- Case description
- Event duration (start and end dates, if applicable)
- Seriousness criteria
- Outcome
- Action taken
- Whether the event would be considered expected or unexpected

Assessment of expectedness must be made by an authorised medically qualified person. If such a person is unavailable, initial reports without causality and expectedness assessment should be submitted to CTRU by a healthcare professional within 24 hours but must be followed up by medical assessment as soon as possible thereafter.

Please ensure that each event is reported separately and not combined on one SAR eCRF.

Any change of condition or other follow-up information should be entered within 24 hours of the research team becoming aware of the information. Events will be followed up until the event has resolved or a final outcome has been reached.

All SARs assigned by the PI or delegate (or following Chief Investigator review) as unexpected will be classified as a RUSAE and will be subject to expedited reporting to the Sponsor and REC by the CTRU on behalf of the Chief Investigator in accordance with current HRA guidance, CTRU Standard Operating Procedures (SOPs) and Sponsor requirements.

10.4 Responsibilities

Principal Investigator (PI)

1. Checking for ARs when participants attend for treatment.

2. Using medical judgement in assigning seriousness and expectedness using the relevant SMPC used locally.

3. Ensuring that all SARs, (including RUSAEs) are recorded and reported to the CTRU within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SARs (including RUSAEs) are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting.

4. Ensuring that ARs are recorded and reported to the CTRU in line with the requirements of the protocol.

Chief Investigator / delegate or independent clinical reviewer

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.

2. Using medical judgement in assigning seriousness and expectedness of SARs where it has not been possible to obtain local medical assessment.

3. Immediate review of all RUSAEs within 24 hours.

4. Review of specific SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

CTRU

1. Central data collection and verification of ARs, SARs and RUSAEs, according to the trial protocol onto a MACRO database.

2. Reporting safety information to the Chief Investigator, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.

3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.

4. Expedited reporting of RUSAEs, to the REC and Sponsor within 1 working day of CTRU awareness.

5. Notifying Investigators of all RUSAEs that occur within the trial which compromise participant safety.

6. Preparing annual safety reports for the REC.

Trial Management Group (TMG)

In accordance with the Trial Terms of Reference, the Trial Management Groun (TMG) will provide clinical and practical advice on trial related matters. The TMG is accountable to the TSC and DMEC and are responsible to escalate concerns to these committees.

Trial Steering Committee (TSC)

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing blinded safety data and liaising with the DMEC regarding safety issues.

Data Monitoring & Ethics Committee (DMEC)

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

11 Endpoints

11.1 Primary endpoint

Neurocognitive function
Neurocognitive function (NCF) for the primary endpoint will be measured and assessed using the composite score of the EORTC core CTB COMP; consisting of HVLT-R, TMT-A/B and COWA. Neurocognitive assessments will be performed face-to-face on paper-based tests at baseline and 1, 12, 24, 36, 48 and 60 months post end of RT.

11.2 Secondary endpoints

Additional tests of neurocognitive function
The CNS Vital Signs test battery will be performed at baseline, and 1, 12, 24, 36, 48 and 60 months post-RT. CNS vital sign tests to be assessment include: Verbal Memory (VBM), Visual Memory (VIM), Finger Tapping (FTT), Symbol Digit Coding (SDC), Stroop Test (ST), Shifting Attention (SAT), Continuous Performance (CPT), Perception of Emotion (POET), On-Veral Reasoning (NVRT), and the 4-part Continuous Performance (FPCPT).

Participants will complete this after face-to-face testing for the primary NCF endpoints, on a desktop computer or PC with a mouse, supervised by a research nurse or other qualified individual.

Health Related Quality of Life (HRQoL)
Health related quality of life questionnaires to be completed by participants at baseline, during the final week of RT and 1, 3, 6, 12, 24, 36, 48, 60 months post-RT. These include the EORTC Quality of life questionnaire core 30 (QLQ-C30), QLQ-BN20, the EQ-5D-5L, MFI questionnaire and the HADS.

Endocrinopathy
Endocrine dysfunction will be assessed using blood tests. Dynamic/static testing will be performed for GH/IGF-1, FSH/LH/ testosterone (males) & SHBG (males)/ oestradiol (females), cortisol, T4/T3/TSH, and prolactin. These will be performed at baseline and 6, 12, 24, 36, 48 and 60 months post-RT, as per standard of care.

Treatment compliance
Data on the treatment participants receive will be collected weekly during radiotherapy. Information will be recorded on the total dose of radiotherapy received (dose and fractions), the overall treatment time (i.e. time between start and end date), details of any interruptions to the radiotherapy and the reasons for these interruptions (i.e. toxicity or other). In the case of PBT, any fractions that are given as photon treatment instead of PBT (e.g. the result of PBT machine breakdown) will also be recorded.

Adherence to the radiotherapy schedule will be defined as a participant that has completed their scheduled course of radiotherapy with no more than two treatment days of interruptions due to toxicity or any other reason.

The number of chemotherapy cycles and doses delivered will also be recorded, along with details of any modifications (delays, dose reductions, omissions) to treatment and their associated reasons.

Work & economic impact
WPAI general health (WPAI:GH) will be completed by the participant and their primary caregivers at baseline, during the final week of RT and 1, 3, 6, 12, 24, 36, 48 and 60 months

post-RT. The questionnaire includes six questions about employment, time off and productivity at work and during regular activities, assessing the impact due to overall health and symptoms.

An additional health resource use questionnaire will collect patients' utilisation of health services related to their brain cancer including: NHS and primary health services, hospital based secondary care services and personal costs incurred. Personal costs incurred for caregivers will also be collected. The health recourse utilisation will be collected at baseline and annual follow-up.

Caregiver distress
The 30-item Caregiver Needs Screen will be completed by the participant's primary caregiver at baseline, during the final week of RT and 1, 3, 6, 12, 24, 36, 48, 60 months post-RT. The questionnaire includes subscales for neurologic and oncologic symptoms, personal communication, communication with healthcare providers, resources and caregiver health.

Early and late toxicity
The acute toxicity period has been defined from start of RT to the 3 months post end of RT follow-up assessment. Clinician assessment of acute toxicities will take place on each week of treatment during clinic and during the 1 and 3 month follow-up assessments. The late toxicity period will be defined as after 3 months until the final follow-up visit at 60 months. Clinician assessment of late toxicity will take place during each of the follow-up visits and will be recorded at 6, 12, 24,36,48 and 60 months post start of radiotherapy treatment. Toxicities will also be recorded at each chemotherapy assessment.

All radiotherapy and chemotherapy toxicities will be evaluated using the CTCAE criteria (V5.0) and include all ARs, SARs and RUSAEs.

Radiological Response rates
Tumour response will be assessed using MRI scans, performed at baseline, 3, 6, 12, 24, 36, 48 and 60 months post-RT, as per standard of care. Response will be evaluated based on the RANO criteria. Additional off-schedule MRI scans may be used in the case of suspected progression.

Progression-free survival (PFS)
PFS is defined as the time from randomisation to the date of the first documented evidence of progression or death from any cause. Assessment of progression will use response data evaluated by RANO at 3, 6, 12, 24, 36, 48 and 60 months post-RT. Additional unscheduled MRI scans may be used in the case of suspected progression.

Overall survival (OS)
OS is defined as the time from randomisation to the date of death from any cause. Survival data will be collected at standard follow-up visits.

12 Statistical Considerations

12.1 Sample size

The required sample size is 246 patients, recruited over 3½ years.

NCF is measured using CTB COMP, calculated from the mean of standardized z-scores for the HVLT-R, TMT-A/B, and COWA. The sample size for NCF at 5 years is based on a two-sample t-test. A Cohen's d of 0.5 is considered a moderate effect size (Cohen 1988); assuming a common standard deviation (SD) of 1 this effect size equates to a mean z-score of 0.5, and is deemed clinically relevant in this setting given that patients are typically young and of working age, so even small deteriorations will likely result in noticeable everyday issues (Giovagnoli and Boiardi 1994; Boele *et al.* 2014). This is the same targeted difference in CTB COMP score adopted in the NRG-BN005 US PBT vs. photon RT glioma study (NCT03180502) (NRG Oncology 2017). Based on a two-sample t-test with 5% two-sided significance and 90% power, 172 patients (86 per arm) are required to detect an effect size of 0.5. Assuming 30% loss to follow-up at 5 years (Cohen 1988; Klein 2019), 123 patients will be required per arm.

12.2 Planned recruitment

A total of 246 patients will be recruited from 18-25 UK centres over 3½ years. This provides an approximate recruitment target of 5-6 patients per month.

Based on responses from centre feasibility questionnaires, the estimated potential annual trial recruitment is ~ 85 patients. The numbers selected for the pilot phase allow for lower recruitment rate during year one, and completion of recruitment during the remaining 2½ years.

13 Statistical Analysis

13.1 General considerations

Statistical analysis for the main trial endpoints is the responsibility of the CTRU Statisticians. The analysis detailed below provides an overview of the analyses to be performed for the main trial. A separate and fully detailed statistical analysis plan (SAP) will be written in accordance with CTRU SOPs, prior to any analyses being performed.

Analysis of the primary and secondary endpoints will be performed on an intention-to-treat (ITT) basis, unless specified otherwise within the SAP.

13.2 Frequency of analysis

A staged assessment approach will be used within the trial with an initial assessment of recruitment and two interim analyses for:

- Evaluating efficacy based on an intermediate endpoint, using all patients' NCF scores at 2 years. Secondary endpoints including treatment compliance and acute and late toxicities up to 2 years will also be assessed.
- Evaluating futility for the primary endpoint when 50% of patients have been followed up for 5-years.

The final primary and secondary endpoint analysis will take place once the final participant has reached their primary endpoint, i.e. 60 months post end of RT treatment, and once all data have been received and cleaned.

13.3 Interim analysis

Pilot stage – recruitment assessment
After the first 12 months of recruitment, the number of participants recruited and number of centres opened will be explored.

A 50% recruitment rate is assumed in the first 6 months, and a 100% recruitment rate in the following 36 months (3 years). Given that this is equivalent to 39 months at 100% recruitment, the 100% recruitment rate requires 6.3 participants to be recruited per month (246/39 = 6.3). In year 1, this results in a target recruitment rate of 57 patients (50% rate for 6 months and 100% rate for 6 months: ½(6.3*6) + 6.3*6 = 57).

Based on approaches described by Herbert et al (Herbert *et al.* 2019), the following traffic light system will be used to determine the pilot phase outcome.

	Number participants recruited	Number centres open	Outcome / action
Red	< 37 (<64% of year 1 target)	< 9	Full review of feasibility including TSC and EME; potential termination of trial
Amber	37-56 (64-98% of year 1 target)	9 - 11	Assess barriers to recruitment and explore remedial action
Green	57+ (>100% of year 1 target)	12+	Recruitment targets sufficiently high, continue to main phase

The internal pilot stage will be assessed on only the **number of patients recruited** within the first year, centre targets are presented and will be explored for context of remedial action, if required.

2 year early interim efficacy assessment
The first interim analysis will occur after all participants reach 2-year follow-up.

Assessment of efficacy on the intermediate endpoint of 2-year NCF will allow early dissemination and potential practice change if the clinically relevant difference of 0.5 is shown at the 1% level. The study is designed with an intermediate and final primary endpoint, whereby a significant positive treatment effect on either endpoint would warrant change in practice. As such, it is important to preserve the family wise error rate (FWER) in the trial, following the Food and Drug Administration (FDA) guidance on multiple endpoints in clinical trials. The FWER of 0.05 will be preserved using the fall-back method (U.S. Department of Health and Human Services Food and Drug Administration 2017) with alpha of 0.01 allocated to the intermediate, and 0.04 allocated to the final, primary endpoint. Should a significant effect be observed on the intermediate endpoint, the full alpha of 0.05 will be used for the final primary endpoint analysis. Irrespective of early interim assessment outcome, the trial will continue. Assuming the same sample size calculation, using a type I error of 0.04 (5 years) would provide ~89% power. At the 2 year time point, assuming a smaller dropout rate of 10%, a type I error of 0.01 would provide ~87%.

5 year futility interim assessment
The second interim analysis will be when 50% of patients reach 5-year follow-up, using stochastic curtailment to assess futility for the primary endpoint. Conditional power (CP) will evaluate the probability of achieving a significant result at the end of the trial based on accumulated data. A pre-defined non-binding stopping boundary will be decided with the DMEC, as per FDA adaptive designs guidance (U.S. Department of Health and Human Services Food and Drug Aministration 2019). Assessing futility, assuming an estimated CP bound of 20%, will reduce overall power to ≥87.5% while not inflating type I error (Sully *et al.* 2014).

13.4 Primary endpoint analysis

The number and proportion of participants completing the CTB COMP will be presented at baseline, 1, 12, 24, 36, 48 and 60 months post end of RT. The reasons for missingness will be presented where available. Summary statistics will be presented for NCF scores at each time point, including raw scores and Z-scores for each test and composite mean score, overall and by treatment arm.

A mixed effects repeated measures model will be used to assess the difference in mean NCF scores between the treatment arms. The model will adjust for the minimisation factors, baseline NCF score, time point, treatment group, and treatment group by time point interaction as fixed effects. Participant and (if appropriate) participant-time interaction will be fitted as random effects.

The difference between treatments arms will use contrasts to represent the final estimated treatment effect with associated 95% confidence intervals (CIs), and additional 96% (4% level) CIs if there is no significant effect at the interim analysis. The differences will be presented for 1, 12, 24, 36, 48 and 60 months post end of RT, however, the analysis of primacy will focus on the 60 months / 5-year treatment effect.

The effect size, accounting for standard deviation, will also be estimated in line with the sample size assumptions.

The missing data mechanism will be explored and, if appropriate, multiple imputation may be considered.

13.5 Secondary endpoint analysis

Additional tests of neurocognitive function
The CNS vital signs battery tests which will form cognitive domains. Summary statistics for the raw scores and z-scores for cognitive domains will be presented, for each time point, overall and by treatment arm. Similar mixed effects repeated measures models used for the primary outcome will also be used for the additional NCF outcomes. The difference between treatment arms of each cognitive domain with associated 95% confidence intervals (CIs) will be presented for 1, 12, 24, 36, 48 and 60 months post end of RT.

Health Related Quality of Life (HRQoL)
Questionnaires will be scored using respective scoring manuals. Summary statistics will be presented overall and by treatment arm for the HRQoL questionnaires including all the domains for the EORTC QLQ-C30 and EORTC BN20 module, the EQ-5D-5L, MFI and HADS scores. Change in mean score from baseline with 95% CIs will also be reported. Summaries will be presented for each treatment group and overall, at each follow-up time point.

The same mixed effects repeated measures model used for the primary outcome will also be used for HRQoL outcomes.

Endocrinopathy
Summary statistics will be presented for each specific endocrinopathy overall and by treatment arm. This will include: growth hormone deficiency, cortisol deficiency, secondary hypothyroidism, gonadotrophin deficiency in males, gonadotrophin deficiency in pre- and post-menopausal women and prolactin abnormalities. The need for any endocrine replacement or blocking therapies will also be presented using summary statistics.

Treatment compliance
Summary statistics will be presented by treatment arm for the total dose of radiotherapy received and the duration of treatment. Number of participants withdrawing from treatment and reasons for interruption to PBT or photon radiotherapy schedules or for PBT patients needing to receive fractions of photon radiotherapy will be summarised.
The number of chemotherapy cycles received, doses, the proportion of participants experiencing modifications and associated reasons will be reported. The effect of radiotherapy dose and type (i.e. photon RT or PBT) on chemotherapy compliance will be explored.

Work and economic impact
Summary statistics of the participant and caregiver WPAI:GH scores will be presented overall and by treatment arm for each of the follow-up time points. Each of the four types of scores will be calculated and summarised for:

- Absenteeism (work time missed)
- Presenteeism (impairment at work / reduced on-the-job effectiveness)
- Work productivity loss (overall work impairment / absenteeism plus presenteeism)
- Activity Impairment

The additional health utilisation data will be presented with summary statistics. Additional analysis of cost effectiveness may be explored, however, this will be funded by a separate grant and proposal.

Caregiver distress
The number and proportion of caregivers completing the 30-item Caregiver Needs Screen will be presented for each follow-up time point. Summary statistics of the scores will also be presented overall and by treatment arm for each follow-up time point.

Early and late toxicity
Summary statistics of safety data on ARs/SARs/RUSAEs experienced will be presented overall and by treatment arm for the acute and late toxicity period. The number and proportion of participants experiencing each CTCAE grade of acute and late toxicities will be summarised.

The long-term collection of clinician recorded toxicities will capture a level of symptom burden as a result of treatment. CTCAE grades of patients over time will be assessed to explore the time dependence of ARs in a population that can often experience chronic conditions. Additionally, this longitudinal data will be explored in relation to other endpoints over time e.g. HRQoL.

Safety monitoring of reactions to chemotherapy will be included and as such will be reported under the toxicity secondary objective, however, there is no hypothesis of expected differences and no plan for formal comparisons – this is being used to inform the safety of

the radiotherapy comparison. These events are collected for monitoring purposes, and completeness of symptom reporting for this patient population across the course of the trial.

Radiological response rates
Summary statistics will be presented for the proportion of participants within each clinical response status, as assessed by the RANO criteria, at baseline, 12, 24, 36, 48 and 60 months post end of RT.

Progression-free survival (PFS)
The proportion of participants who have progressed or died at 60 months post-randomisation will be reported along with 95% CIs. PFS will be presented using Kaplan-Meier (KM) curves. The median PFS estimates and 95% CIs will be presented along with the log-rank test statistic (and associated p-value) which tests for a difference in the median PFS. PFS at 60 months post-randomisation will be compared between the treatment arms using Cox's Proportional Hazards (PH) model, adjusting for the minimisation factors. The hazard ratio (HR) for the experimental arm versus the control arm (where a HR < 1 would indicate the experimental arm is better than the control) will be presented along with 95% CIs and associated p-value testing for the difference between the arms.

Participants who have not progressed/died at the time of analysis, including those lost to follow-up, will be censored at the last date they were known to be alive and progression-free. Participants who withdraw consent for data collection will be censored at the date of withdrawal if they have not progressed/died by this date.

The assumptions of the Cox PH model will be tested.

Overall survival (OS)
The proportion of participants who have died at 60 months post-randomisation will be reported along with 95% CIs. OS will be presented using Kaplan-Meier (KM) curves. The median OS estimates and 95% CIs will be presented along with the log-rank test statistic (and associated p-value) which tests for a difference in the median OS. OS at 60 months post-randomisation will be compared between the treatment arms using Cox's PH model, adjusting for the minimisation factors. The HR for the experimental arm versus the control arm (where a HR < 1 would indicate the experimental arm is better than the control) will be presented along with 95% CIs and associated p-value testing for the difference between the arms.

Participants who are still alive at the time of analysis, including those lost to follow-up, will be censored at the last date they were known to be alive. Participants who withdraw consent for data collection will be censored at the date of withdrawal if they have not died by this date.

The assumptions of the Cox PH model will be tested.

14 Trial Monitoring

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the Consent Form.

CTRU will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

14.1 The Trial Steering Committee (TSC) and the Data Monitoring and Research Ethics Committee

The trial will be overseen by an independent TSC & DMEC.

The DMEC will monitor the trial data, safety including SARs and RUSAEs, treatment related mortalities and the associated ethics of the trial. Listings of SARs, and RUSAEs will be provided to the DMEC on a regular basis. The DMEC will be provided with detailed unblinded reports containing the information agreed in the data monitoring analysis plan, by the CTRU, at approximately 12-monthly intervals.

Trial progress will be closely monitored by the independent DMEC, who will report to the TSC, and the overall direction overseen by the TSC (ensuring regular reports to the NIHR Efficacy and Mechanism Evaluation (EME) Programme).

14.2 Data monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis.

The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

14.3 Clinical governance issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC, Sponsor and, where applicable, to individual NHS Trusts.

15 Quality Assurance Processes

15.1 Quality assurance

The trial will be conducted in accordance with the principles of GCP in clinical trials, as applicable under UK regulations, the UK Policy Framework for Health and Social Care Research and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006, and through adherence to CTRU SOPs.

15.2 Serious breaches

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to **immediately** notify the CTRU of a serious breach (as defined in the latest version of the HRA SOP) that they become aware of. A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree-

a) the safety or physical or mental integrity of the trial subjects, or

b) the scientific value of the research

In the event of doubt or for further information, the Investigator should contact the Senior Trial Manager at the CTRU.

16 Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. Informed written consent will be obtained from the participants prior to randomisation into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

16.1 Ethical Approval

Ethical approval will be sought through the HRA. The trial will be submitted to and approved by a REC, the HRA and the appropriate Site-Specific Assessor for each participating research site prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, participant information sheets, consent forms and all other relevant trial documentation.

17 Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 2018 Data Protection Act and operationally this will include:

- Consent form from participants to take part in the trial.
- Appropriate storage, restricted access and disposal arrangements for participant personal and clinical details.
- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation.
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- Copies of participant consent forms, which will include participant names, will be sent to the CTRU when a participant is randomised into the trial. All other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.
- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent from further trial treatment and / or further collection of data their data will remain on file and will be included in the final trial analysis.

18 Archiving

18.1 Trial data and documents held by CTRU

At the end of the trial, data and the Trial Master File will be securely archived by CTRU in line with the Sponsor's procedures for a minimum of 5 years. When there is no longer a lawful basis for retaining the data, it will be securely destroyed.

18.2 Trial data and documents held by research sites

Research sites are responsible for archiving all trial data and documents (ISF and all essential documents therein, including CRFs) at the participating research site until authorisation is issued from the Sponsor for confidential destruction.

18.3 Participant medical records held by research sites

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

19 Statement of Indemnity

The University of Leeds is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

20 Funding

This project is funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme.

21 Publication Policy

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Authorship decisions will be guided by standard requirements for authorship relating to submission of manuscripts to medical journals. These state that authorship credit should be based only on the following conditions being met (http://www.icmje.org):

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Substantial contribution to drafting the article or revising it critically for important intellectual content
- Substantial contribution to final approval of the version to be published.

In light of this, the Chief Investigator, other grant co-applicants, and relevant senior CTRU staff will be named as authors in any publication, subject to journal authorship restrictions. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial. Where possible publications will also acknowledge the APPROACH Group' which will include the PIs and APIs from participating sites.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

On completion of the research project a draft final report will be submitted to the EME programme (trial funder) by the CTRU, within 14 days. This will be peer reviewed and then published on the EME website. The CTRU is obliged to provide NIHR/EME with advanced notice of any publication relating to the trial. Copies of any materials intended for publication will be provided to NIHR/EME at least 28 days prior to submission for publication.

22 Information Governance and Confidentiality

University of Leeds are data controllers for the trial. Participating sites will be data processors for any trial data processing (while remaining data controllers of data processing required for patient care).

All data processing for the trial will be in accordance with the 2018 Data Protection Act. Personal data will be processed under a lawful basis of 'task in the public interest' (GDPR Article 6, 1(e)) and special categories of personal data (in this case, data about health, racial or ethnic origin and genetic data) will be processed for scientific research purposes (GDPR Article 9, 2(j)).

All trial participants (and any patients considered for the trial) are provided with detailed information about how their data will be processed before any trial data processing. Any material changes to how data will be processed will be communicated to trial participants in a timely manner (prior to the changes, if reasonably possible).

Personal data will only be processed for specified, explicit and legitimate purposes, and will be adequate, relevant and limited to those purposes. Data will be stored and transferred securely for all processing. The trial will undergo an information governance risk assessment at the CTRU to ensure its proposed processing is compliant with data protection laws.

Confidentiality of participant data will be maintained at all times, with access to data granted only to those who need it for legitimate reasons (i.e. to conduct the trial, or to ensure the trial has been conducted lawfully). Participants will allow access to their confidential data through the informed consent process. Copies of participants' consent forms, which will include participants' names, will be collected when a participant is randomised into the trial by the CTRU. In addition, participant name and address may be collected for questionnaire posting or email address/phone number if the participant chooses to complete the questionnaires electronically. All other data collection forms that are transferred to or from the CTRU will be coded with a unique participant trial number and will include two participant identifiers, usually the participant's initials and date of birth. Data will be held securely on paper and electronically at the CTRU. The CTRU will have access to the entire database for monitoring, co-ordinating, and analysis purposes.

Sites are responsible for maintaining this pseudonymisation on any data sent to the CTRU. Any exceptions (e.g. collecting unredacted consent forms at the CTRU for central monitoring of informed consent) will only be for legitimate reasons and will be explained fully to participants in advance of data processing. Where central monitoring of source documents, or copies of source documents, is required by CTRU, the participant's name must be obliterated by site before sending. Any breach of confidentiality or of participants' personal data will be handled and reported (if required) in line with relevant laws.

Data will be made available for secondary research once the main trial objectives are complete.

If a participant withdraws consent from further trial treatment and/or further collection of data, their data will remain on file and will be included in the final trial analysis.

23 References

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24 APPENDIX

Appendix A – NCI CTCAE

NCI-CTCAE
Toxicities will be assessed based on the latest NCI-CTCAE version 5.0
A copy of the NCI-CTCAE is provided in the ISF.

Appendix B – Treatment toxicities

Table B1. Expected ARs or SARs following radiotherapy

Tablc B1 Expected ARs following radiotherapy (RTOG 1205 2016; Scoccianti et al. 2018)

Expected early (during treatment and within 3 months of treatment)

• Fatigue
• Lethargy
• Headaches
• Nausea
• Vomiting
• Weakness
• Dizziness
• Transient worsening of existing neurological deficits (including seizures and focal neurological symptoms)
• Hydrocephalus
• Hair loss
• Seizures
• Skin reaction
• Reactions in ear canals (which can lead to temporary hearing impairment)
• Dry mouth
• Taste changes
• Prolonged steroid requirements
 	
• Cerebral oedema (may result in)
  ○ fatigue,
  ○ headaches,
  ○ nausea,
  ○ vomiting,
  ○ weakness,
  ○ dizziness,
  ○ transient worsening of existing neurological deficits (including seizures and focal neurological symptoms),
  ○ seizures and
  ○ prolonged steroid requirements.

Late toxicities (more than 90 days following radiotherapy completion)

• Fatigue
• Lethargy
• Weakness
• Hair loss may persist form the acute phase
• Prolonged steroid requirements
• Radionecrosis (may occur months after re-irradiation; may be asymptomatic or may result in)
  ○ fatigue,
  ○ headaches,
  ○ nausea,
  ○ vomiting,

- weakness,
- dizziness,
- transient worsening of existing neurological deficits (including seizures and focal neurological symptoms),
- seizures,
- cerebral oedema and
- prolonged steroid requirements.

Very late toxicities (one year to several years after radiotherapy)

- Neurocognitive impairment
- Endocrine dysfunction
- Cataracts
- Dry eye
- Permanent damage to the vision or hearing (very rare)
- Development of a second primary cancer
- Increased risk of stroke

Table B2 Common Expected Side Effects for Lomustine (BC Cancer 2018), Procarbazine (BC Cancer, 2011) and Vincristine (BC Cancer, 2022)

	Lomustine	Procarbazine	Vincristine
Dermatology/ Skin			
Alopecia	✓		✓
Gastrointestinal			
Nausea	✓	✓	
Vomiting	✓	✓	
Stomatitis	✓		
Constipation			✓
Metabolism & Nutrition Disorders			
Anorexia		✓	
Musculoskeletal & Connective Tissue Disorders			
Myalgia			✓
Myositis			✓
Psychiatric Disorders			
Insomnia		✓	
Hallucinations		✓	
Nervous System Disorders			
Peripheral neuropathy		✓	✓
Reproductive System & Breast Disorders			
Amenorrhoea		✓	
Azoospermia		✓	
General Symptoms			
Myelosuppression	✓	✓	✓
Fatigue	✓	✓	
Nightmares		✓	
Rash		✓	
Flu like symptoms		✓	
Jaw pain			✓
Infusion site extravasation			✓

Lomustine – Marrow toxicity may be delayed or prolonged.

These drugs may also cause alterations in liver function tests.

Less common but potentially severe side effects from PCV include: pneumontitis/ pulmonary fibrosis (acute or delayed), nephrotoxicity, secondary leukaemia or myelodysplastic syndrome, hypersensitivity, haemolytic anaemia, thromboembolism, myocardial infarction, SIADH (Syndrome of Inappropriate Anti-diuretic Hormone secretion), gastrointestinal tract perforation, pancreatitis.