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The neurocognitive benefits of proton beam therapy for patients with oligodendroglioma

Submission date 22/02/2023	**Recruitment status** Recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 21/03/2023	**Overall study status** Ongoing	
Last Edited 19/11/2024	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
The study is called the APPROACH study. APPROACH stands for Analysis of Proton versus Photon Radiotherapy in Oligodendroglioma & Assessment of Cognitive Health. Oligodendroglioma is an uncommon brain tumour with an excellent outlook. Standard treatment involves surgery to remove as much tumour as possible, radiotherapy (RT) and then chemotherapy. RT helps stop the tumour from re-growing. Standard RT for adult patients in the UK uses photon RT. Photon RT is given as lots of small treatments on weekdays over about six weeks. This is the best way to control the tumour whilst minimising side effects in normal brain tissue. Unfortunately, photon RT for oligodendroglioma can cause long-term side effects. These can develop years after RT and can include memory problems and difficulties in processing information. These can have a negative impact on quality of life. Proton beam radiotherapy (PBT) is an advanced type of RT, also given on weekdays over about six weeks. It requires expensive technology but can reduce the dose of RT delivered to the normal brain, including parts of the brain used for memory and information processing. We do not know, however, if these lower doses result in fewer long-term side-effects. We do not expect any difference in controlling the growth of the tumour as the same dose of RT is given to the tumour whether photon RT or PBT is used. To do this we will compare the long-term side effects of photon RT or PBT for patients with oligodendroglioma. We want to find out which is the best treatment for patients with oligodendroglioma to reduce long-term side effects.

Who can participate?
Patients with oligodendroglioma from across the UK

What does the study involve?
Participants in our study will be randomly assigned (by computer) to receive photon RT or PBT, with an equal chance of either. We will gather information on long-term brain function, quality of life, other side effects and tumour control. As part of the study we will look at whether travelling to a distant RT centre is acceptable to patients.

Patients receiving photon RT will have this at their local RT centre. PBT is only available in Manchester and London, so patients having PBT will need to stay in Manchester or London for the treatment period (accommodation is provided).

To assess long-term side effects, we will monitor patients for five years after RT. This will involve: - Carrying out short practical tasks and memory assessments to measure brain function - Completing questionnaires about quality of life and work - Having Magnetic Resonance Imaging (MRI) scans to monitor the tumour - Having blood tests to track hormone levels- these can also be affected by RT We will also ask carers to complete questionnaires, to assess carer experiences.

What are the possible benefits and risks of participating?:
By taking part in this study, the researchers hope to understand better the effects of lower dose of RT delivered to healthy brain, if side effects can be reduced and how it may impact a patient's quality of life. This will help hospitals in choosing the best treatment for future patients diagnosed with oligodendroglioma. Participants have a risk of side effects in both the radiotherapy groups.

Because RT is given over several weeks it can disrupt to day-to-day life for patients and carers, especially as this condition often involves people of working age who are not allowed to drive due to their diagnosis. Possible side effects of chemotherapy are tiredness, nausea, vomiting, taste changes, sore mouth or mouth ulcer, infections, bruising and bleeding, poor appetite, diarrhoea, constipation, abdominal pain, anaemia, skin changes and allergic reactions. Possible side effects from radiotherapy could include; tiredness, patchy hair loss, headaches, dizziness, swelling in the brain, nausea, vomiting, skin redness or irritation on the scalp, weakness, seizures and dry mouth or taste changes.

Patient and Public Involvement (PPI) has played a key role in the study: patients and carers supported the research question and follow-up plan and advised on study design. At least three PPI representatives will sit on the Trial Management Group to ensure the patient voice is represented. The PPI group will have an active role throughout and will contribute to the final scientific report and in the dissemination of the findings, that will be shared with trial participants and the wider public.

Where is the study run from?
University of Leeds (UK)

When is the study starting and how long is it expected to run for?
February 2021 to July 2031

Who is funding the study?
National Institute for Health and Care Research - Efficacy and Mechanism Evaluation Programme (NIHR) (UK)

Who is the main contact?
Dr Samantha Noutch, artemis@leeds.ac.uk (UK)

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-proton-beam-therapy-for-people-with-a-brain-tumour-called-oligodendroglioma

Contact information

Type(s)
Public

Contact name
Mr Jaike Belgrave

Contact details
Trial Coordinator
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds
United Kingdom
LS2 9JT
+44 (0)113 343 3275
approach@leeds.ac.uk

Type(s)
Principal investigator

Contact name
Dr Louise Murray

ORCID ID
https://orcid.org/0000-0003-0658-6455

Contact details
Level IV Bexley Wing
Beckett Street
Leeds
United Kingdom
LS9 7TF
-
L.J.Murray@leeds.ac.uk

Type(s)
Scientific

Contact name
Dr Samantha Noutch

Contact details
Leeds Institute of Clinical Trials Research (LICTR)
Level 10, Worsley Building
Clarendon Way
University of Leeds
Leeds
United Kingdom
LS2 9NL
+44 (0)113 343 1486
approach@leeds.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
306432

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 306432, CPMS 54825

Study information

Scientific Title
Analysis of proton versus photon radiotherapy in oligodendroglioma and assessment of cognitive health

Acronym
APPROACH

Study objectives
To assess the feasibility of recruitment to a randomised trial of proton beam therapy versus photon radiotherapy and whether there are early (2 years post-radiotherapy) signals of neurocognitive benefit with proton beam therapy compared to photon radiotherapy. The main aim will be to establish whether there is a long-term (5 years post-radiotherapy) neurocognitive benefit of proton beam therapy compared to photon radiotherapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/01/2023, Newcastle North Tyneside Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44(0)20 7104 8057; newcastlenorthtyneside1.rec@hra.nhs.uk), ref: 22/NE/0232

Study design
Multicenter interventional unblinded randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Brain cancer, oligodendroglioma

Interventions

The APPROACH trial is a Phase III, multicentre trial. Patients will be recruited from 18-25 centres and randomised 1:1 between photon radiotherapy (RT) and proton beam therapy (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 quality of life (QoL) and productivity questionnaires and caregiver questionnaires will also be performed throughout follow-up. Interim analyses will assess the feasibility of recruitment, and early efficacy at 2 years (i.e., signals of improved neurocognitive function (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.

The required sample size is 246 patients, recruited over 3.5 years.

NCF is measured using Clinical Trial Battery Composite (CTB COMP) scoring, calculated from the mean of standardized z-scores for the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT)-A/B, and Controlled Oral Word Association (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; 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. This is the same targeted difference in CTB COMP score adopted in the NRG-BN005 US PBT versus photon RT glioma study (NCT03180502). 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 a 30% loss to follow-up at 5 years, 123 patients will be required per arm.

Participants completing CNS vital sign tests will do 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. 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.

Additional tests of neurocognitive function comprises the 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.

Treatment compliance measures include information 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.

The Work & economic impact, WPAI general health (WPAI:GH) will be completed by the participant and their primary Caregivers. 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. The questionnaire includes subscales for neurologic and oncologic symptoms, personal communication, communication with healthcare providers, resources and caregiver health.

Early and late toxicity, including the acute toxicity period has been defined from start of RT to the 3 months post end of RT follow-up assessment. The late toxicity period will be defined as after 3 months until the final follow-up visits at 60 months. All radiotherapy and chemotherapy toxicities will be evaluated using the CTCAE criteria (V5.0) and include all ARs, SARs and RUSAEs.

Tumor response will be evaluated based on the RANO criteria. Additional off-schedule MRI scans may be used in the case of suspected progression.

Intervention Type
Device

Phase
Phase III

Drug/device/biological/vaccine name(s)
Photon radiotherapy (RT), proton beam therapy (PBT)

Primary outcome(s)
Neurocognitive function (NCF) at 5 years measured using the standard neurocognitive test battery - EORTC core clinical trial battery composite (CTB COMP) during baseline and at 1, 3, 6, 12, 24, 36, 48 and 60 months post end of RT, as per standard follow-up schedules

Key secondary outcome(s))
1. Additional tests of neurocognitive function measured using the CNS Vital Signs test battery (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-Verbal Reasoning (NVRT), and the 4-part Continuous Performance (FPCPT)) at baseline, and 1, 12, 24, 36, 48 and 60 months post-RT

2. Health-Related Quality of Life (HRQoL) measured using the EORTC Quality of life questionnaire core 30 (QLQ-C30), QLQ-BN20, the EuroQol EQ-5D-5L, and Multidimensional Fatigue Inventory (MFI) questionnaire and the Hospital Anxiety and Depression Scale (HADS) at baseline, during the final week of RT and at 1, 3, 6, 12, 24, 36, 48, 60 months post-RT
3. Endocrinopathy measured using dynamic/static testing in blood for GH/IGF-1, FSH/LH /testosterone (males) and SHBG (males)/oestradiol (females), cortisol, T4/T3/TSH, and prolactin at baseline and at 6, 12, 24, 36, 48 and 60 months post-RT, as per standard of care
4. Treatment compliance measured using patient records with data on the treatment participants receive collected weekly during radiotherapy
5. Work and economic impact measured using the WPAI general health (WPAI: GH) questionnaire completed by the participant and their primary caregivers at baseline, during the final week of RT and at 1, 3, 6, 12, 24, 36, 48 and 60 months post-RT
6. Caregiver distress measured using the 30-item Caregiver Needs Screen completed by the participant's primary caregiver at baseline, during the final week of RT and at 1, 3, 6, 12, 24, 36, 48, and 60 months post-RT
7. Early (acute) and late toxicity: acute toxicity period, defined from the start of RT to the 3 months post end of RT follow-up assessment, measured by clinician assessment each week of treatment during clinic and during the 1 and 3 month follow-up assessments; late toxicity period, defined as after 3 months until the final follow-up visit at 60 months, measured by clinician assessment 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.
8. Radiological tumour response meaured 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.
9. Progression-free survival (PFS), defined as the time from randomisation to the date of the first documented evidence of progression or death from any cause measured using 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.
10. Overall survival (OS), defined as the time from randomisation to the date of death from any cause collected at standard follow-up visits

Completion date
17/07/2031

Eligibility

Key inclusion criteria
1. Histologically proven diagnosis of oligodendroglioma (ODG) with 1p19q co-deletion and isocitrate dehydrogenase (IDH) mutation
2. Randomisation must be performed within 28 days of the magnetic resonance imaging (MRI) that leads to the decision that radiotherapy (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.
3. Karnofsky Performance Status (KPS) ≥70%.
4. Adequate wound healing and recovery if recent surgery.
5. Suitable to complete baseline neurocognitive testing (No access to translated tests, can only be administered in English).
6. 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.
7. 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.
8. Able to swallow oral medication.
9. Able to provide study-specific informed consent.
10. Age 25 or above at the point of starting RT treatment.
11. No known haematological, renal or hepatic impairments making PCV chemotherapy inappropriate

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
25 years

Sex
All

Key exclusion criteria
1. Pregnancy (positive pregnancy test) or lactating.
2. Prior cranial or head and neck radiotherapy (RT).
3. Any previous chemotherapy for the treatment of oligodendroglioma (ODG).
4. Comorbid neurodegenerative diseases that influence neurocognitive function (NCF).
5. Severe active co-morbidity making patient unsuitable for RT and/ or adjuvant chemotherapy (e.g., uncontrolled diabetes, uncontrolled hypertension).
6. Leptomeningeal disease.
7. Spinal or infratentorial disease.
8. Another currently active malignancy or another malignancy within the last 3 years.
9. Any contra-indication to procarbazine, vincristine or lomustine including: coeliac disease; the rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption.
10. Any recognised genetic syndrome causing sensitivity to radiotherapy.
11. Patient unwilling/ unable to attend for follow up in the local radiotherapy centre.
12. Contraindication to MRI or gadolinium.

Date of first enrolment
18/09/2023

Date of final enrolment
21/03/2027

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
University Hospital Bristol
Bristol Royal Infirmary
Marlborough Street
Bristol
United Kingdom
BS2 8HW

Study participating centre
Charing Cross Hospital
Fulham Palace Road
London
United Kingdom
W6 8RF

Study participating centre
The Christie
550 Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

Study participating centre

Clatterbridge Cancer Centre
Clatterbridge Hospital
Clatterbridge Road
Wirral
United Kingdom
CH63 4JY

Study participating centre
Guy's & St Thomas Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
Castle Hill Hospital
Entrance 3
Castle Road
Cottingham
United Kingdom
HU16 5JQ

Study participating centre
Maidstone Hospital
Hermitage Lane
Maidstone
United Kingdom
ME16 9QQ

Study participating centre
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Queens Medical Centre
Nottingham University Hospital
Derby Road
Nottingham

United Kingdom
NG7 2UH

Study participating centre
Oxford University Hospitals
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Derriford Hospital
Derriford Road
Derriford
Plymouth
United Kingdom
PL6 8DH

Study participating centre
University Hospital Birmingham
Queen Elizabeth Hospital
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
Royal Marsden Hospital
Royal Marsden Hospital
Downs Road
Sutton
United Kingdom
SM2 5PT

Study participating centre
University Hospital Southampton
Southampton University Hospital
Tremona Road
Southampton

United Kingdom
SO16 6YD

Study participating centre
St. Bartholomews Hospital
West Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre
St James' University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Singleton Hospital
Sketty Lane
Sketty
Swansea
United Kingdom
SA2 8QA

Study participating centre
University College London Hospital
235 Euston Road
London
United Kingdom
NW1 2BU

Study participating centre
Velindre Cancer Centre
Velindre Road
Cardiff
United Kingdom
CF14 2TL

Study participating centre
Weston Park Hospital
Whitham Road
Sheffield
United Kingdom
S10 2SJ

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the

end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing and believes it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree on suitable requirements for release.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No