STUDY PROTOCOL

REVISED Strategy-based cognitive rehabilitation for childhood brain tumour: Protocol for an acceptability and feasibility trial of the Fatigue, Learning, and Memory Enrichment (FLaME) intervention

[version 2; peer review: 2 approved, 2 approved with reservations]

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Abstract

Background

Medical treatments have improved survival rates for paediatric brain tumour (PBT), but the condition and treatment continue to be associated with significant cognitive morbidity. Nearly all survivors will experience some degree of cognitive impairment (neurocognitive 'late effects') that has a cascading impact on the development of intellectual and academic skills, quality of life, mental health, vocational attainment, and functional independence. Longstanding cognitive fatigue is also a prevalent symptom for survivors of PBT and further impacts engagement with therapeutic interventions and quality of life. Cognitive rehabilitation is recommended in national healthcare guidance and frequently requested by patients and families but rarely implemented due to a limited evidence base and poor feasibility and acceptability. There are currently no therapeutic interventions for cognitive fatigue for PBT survivors.

Open Peer Review

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Aims & Objectives

We aim to establish feasibility, acceptability, and preliminary efficacy for strategy-based cognitive rehabilitation for PBT. The study will determine if there is benefit to feasibility and acceptability when cognitive fatigue management is integrated to cognitive rehabilitation.

Methods

Thirty-six 7-17 years olds diagnosed with PBT will be recruited from Great Ormond Street Hospital. Participants will be randomised to either 1) a 12-week cognitive rehabilitation intervention with integrated cognitive fatigue management, 2) a 6-week cognitive rehabilitation intervention alone, or 3) standard care. All participants will have received neuropsychological assessment identifying difficulties with cognition and fatigue. Feasibility (e.g., attrition, retention, adherence) will be assessed through the trial. Acceptability will be measured throughout using questionnaires and interviews based on the Theoretical Framework for Acceptability and satisfaction rating scale. Preliminary effectiveness data will be gathered pre- and post-intervention using standardised measures of cognitive skills, fatigue, quality of life, % school attendance, and goal-based outcomes.

Outcome

The findings will be used to determine the appropriate rehabilitation intervention for a larger, multicentre randomised controlled trial.

Plain Language Summary

Medical treatments have improved survival rates for children with brain tumours. However, most children experience long-term difficulties with 'cognition' (thinking skills such as memory and paying attention) and cognitive fatigue (excessive mental tiredness) after treatment. Thinking difficulties and fatigue can affect a child's ability to learn, and their social and emotional wellbeing. National guidance recommends treatment called 'cognitive rehabilitation' which teaches skills to improve or manage cognitive difficulties. Families often request this, but it is not usually available due to little research. Fatigue may also get in the way of children using and benefiting from cognitive rehabilitation. No research study yet has offered a fatigue treatment for children recovering from brain tumours. The study aims to see if it is practical and helpful to families to provide cognitive rehabilitation for children affected by brain tumours. The treatment focuses on strategies to help cognition. We will see if adding strategies to manage fatigue helps. We will include thirty-six 7–17-year-olds who have been cared for at Great Ormond Street Hospital for brain tumour. All participants will have had an assessment describing cognitive strengths and weaknesses as part of usual care.

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Any reports and responses or comments on the article can be found at the end of the article.

Participants will be randomly allocated to one of three groups: 1) cognitive rehabilitation with fatigue management (12 weeks), 2) cognitive rehabilitation only (6 weeks), or 3) usual care. Each child and their carer will complete questionnaires before, during, and after the treatment, and an interview at the end of the treatment. This information will help the researchers see if families find the treatment helpful and practical to take part in, and if adding fatigue strategies is beneficial. Researchers will look at information such as the number of appointments attended, feedback about the treatment, and information about fatigue levels, cognition, and wellbeing. The findings will be used to develop a UK-wide study.

Keywords
Paediatric brain tumour, cognitive rehabilitation, cognition, fatigue, feasibility, acceptability

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REVISED **Amendments from Version 1**

The changes made in the most recent article version address the comments of two peer reviewers. The changes include clarification of 1) standard care at the study site, 2) Neuropsychology service eligibility criteria, 3) oncology surveillance with the multidisciplinary team, 4) a typical neurocognitive assessment protocol for paediatric neuro-oncology at the trial site. The '*Introduction*' section was updated to include nuanced discussion and current citations for risk factors for neurocognitive impairment after paediatric brain tumour, a reference to a systematic review on broader interventions to mitigate neurocognitive impairment, and a more explicit statement on the lack of research distinguishing cognitive fatigue and fatigue in general in the paediatric brain tumour population. Further details of how the intervention is adapted by age is provided in the '*Intervention*' section. Additional discussion on the selection and evaluation of the Multidimensional Fatigue Scale was added to the '*Primary outcome measures*' section.

Any further responses from the reviewers can be found at the end of the article

Introduction

Background & rationale

Treatment advances for paediatric brain tumour (PBT) in recent decades have substantially improved mortality rates but come at significant cost in cognitive morbidity alongside the long-term effects of the tumour itself. Up to 100% of children treated for PBT experience some degree of cognitive difficulty despite most having achieved typical cognitive development prior to diagnosis[1,2]. Risk factors for neurocognitive impairment are varied and continue to be investigated. The most consistent risk factors for neurocognitive impairment have included provision and dose of cranial radiation, younger age at treatment, shunted hydrocephalus, and cerebellar mutism syndrome[2,3]. Most children experience a constellation of long-term cognitive impairments that impact quality of life, mental health, access to education, academic and vocational attainment, and functional independence in adulthood. The most common neurocognitive impairments are in processing speed, attention, working and long-term memory, and visual-motor function which increase with time since treatment and result in the insidious secondary slowing of intellectual and academic progress over time (neurocognitive 'late effects'), with an average loss of 18 Full-Scale IQ points by early adulthood following cranial irradiation[2,4]. Despite developments in oncology treatment protocols, survivors of common malignant tumours (e.g., medulloblastoma) remain at risk of significant neurocognitive and functional impairment into adulthood[5].

The well documented neurocognitive late effects inform the strong emphasis on neurorehabilitation in national guidance for PBT[6,7]. Interventions aimed to alleviate the burden of cognitive impairment are paramount but rarely implemented[8]. Interventions to mitigate neurocognitive impairment have included lifestyle changes, pharmacological intervention, and cognitive rehabilitation[9]. Cognitive rehabilitation typically involves systematic interventions to restore and/or compensate for cognitive impairment[10] including 1) massed practice on computerised cognitive training tasks (drill-based practice, e.g., Cogmed), 2) internal and metacognitive strategy-use to optimise cognition (e.g., generalisable elaborative encoding techniques such as mnemonics), and/or 3) external compensatory aids (e.g., visual reminders). Cognitive rehabilitation is almost entirely unavailable for PBT[11] with a paucity of research and poor feasibility and acceptability of trialled interventions. Drill-based computerised rehabilitation has been the focus of the small number of available studies, however, the feasibility and acceptability of this approach for PBT is low[12] and has well documented problems in poor generalisation to skills beyond the trained task (e.g., academic skills) and poor maintenance of improvements[13]. The focus of drill-based interventions is typically to remediate specific cognitive deficits which can neglect the broader profile of multiple co-occurring neuropsychological difficulties common after PBT.

Rehabilitation in paediatric acquired brain injury has greatest potential when it includes internal and metacognitive strategy-use, is adapted for developmental level, and delivered within a systemic context[10]. There is currently one good quality randomised controlled trial (RCT) of a cognitive rehabilitation intervention that incorporates strategy-use for PBT[14]. The intervention resulted in improvements in parental report of child inattention and academic attainments, albeit with small effect sizes. The program involved strategy-use training, but also included a demanding drill-based practice component (requiring 40 hours of practice), with only 60% of participants completing the intervention. A subsequent study[15] omitted the drill-based practice and extended the strategy-use component (15 sessions, 20 hours in total), combining it with systemic support in a smaller pilot study. The power and generalisability of the findings are limited by a small sample size, however significant improvement for written expression was found along with trends towards improvement on neurocognitive measures. Participants also rated high levels of satisfaction, particularly because the intervention improved their understanding of their cognitive strengths and weakness.

Despite some promising findings for strategy-based cognitive rehabilitation, poor feasibility is reflected in generally low completion rates. Cognitive fatigue (extreme mental tiredness) is one of the most frequently reported and distressing chronic symptoms after PBT[16]. Cognitive fatigue can impact adherence to interventions, as well as participation in settings where children make most use of rehabilitation strategies such as in education and activities of daily living. Despite cognitive fatigue being both common and impairing, it has been significantly overlooked in both research and clinical interventions for PBT, with very few studies conceptually distinguishing cognitive fatigue from fatigue in general. No cognitive rehabilitation intervention for PBT has addressed the high prevalence of cognitive fatigue that could predictably limit engagement and completion of rehabilitation.

There have been no published trials to date of cognitive rehabilitation interventions for child survivors of brain tumour in the United Kingdom and within the National Health Service

(NHS). The Department of Health and Social Care 'Brain tumour research: task and finish working group' report[17] strongly advocates that research should focus on quality of life, including "living with the long-term cognitive effects of surgery and radiotherapy" (pg.21); a priority that should be "embraced by the research community and funders" (pg. 21). The proposed research study addresses this public health priority by trialling the acceptability and feasibility of an intervention to address the long-term cognitive effects of brain tumour and treatment that impact on multiple facets of survivorship and quality of life. The study will 1) assess the acceptability and feasibility of a novel cognitive rehabilitation intervention for PBT, and 2) determine whether incorporating cognitive fatigue management improves feasibility, acceptability, and patient-reported benefit.

Theoretical approach to acceptability

Acceptability will be evaluated using the Theoretical Framework for Acceptability (TFA[18,19]). The TFA offers a robust framework for evaluating theoretically informed components of acceptability throughout and after an intervention by those who receive and deliver it. Examples of component constructs include affective attitude (the individual's feelings about the intervention), burden (how effortful it is to participate), and perceived effectiveness (how the individual perceives the intervention to have achieved its goal).

Theoretical approach to outcome measurement

A major aim of cognitive rehabilitation is to improve everyday functioning and quality of life. Prevailing drill-based rehabilitation seeks to achieve this through remediating specific cognitive impairment. This approach naturally lends itself to selecting performance-based neuropsychological tests as the primary outcome measure. Impairment on performance-based tests is typically identified at pre-intervention and the test is repeated post-intervention to measure the extent of remediation. This approach has been found to yield either non-significant results or small effect sizes on measures other than those very similar to the drilled task[13], and practice effects from repeated cognitive testing can confound study results[14]. Strategy-based cognitive rehabilitation shifts the focus of rehabilitation away from remediating impairment to developing metacognitive and compensatory mechanisms to better manage the impact of the cognitive impairment on everyday life. Studies focused on strategy-based rehabilitation in paediatric brain injury therefore have included outcome measures related to everyday function. On recent systematic review[10], strategy-based rehabilitation predictably does not produce change on performance-based cognitive tests. However, these studies demonstrate significant and powerful improvement on functional measures such as everyday executive function skills, problem-solving, goal-directed behaviour, daily living skills, individual rehabilitation goals, and quality of life. The findings have informed the focus of outcome measurement in the current study.

Study objectives

The overarching study aim is to establish feasibility and acceptability for a strategy-based cognitive rehabilitation intervention for PBT, and any benefit to feasibility and acceptability by integrating cognitive fatigue management. The findings will be used to determine whether the cognitive rehabilitation intervention alone, or the same intervention with integrated fatigue management should be taken forwards to a definitive RCT.

Objectives include:

1. To assess whether the proposed cognitive rehabilitation intervention design is feasible to implement and acceptable to patients.
2. To assess whether feasibility and acceptability differ when fatigue management is incorporated to determine which intervention arm to take forwards to the definitive RCT.
3. To measure preliminary/limited-efficacy patient reported benefit and outcomes of the intervention arms relative to standard care.
4. To identify the optimal outcome measures for a larger scale RCT.
5. To document any barriers to recruiting a representative sample and acceptability of randomisation.
6. To identify any practical barriers to conducting an RCT intervention at the designated NHS site.

Methods

Patient and Public Involvement

Pre-study PPI

The study has been informed by over 20 years of feedback from families affected by childhood brain tumour referred to the Neuropsychology service at GOSH. The intervention was initially developed for a patient and their carer at GOSH who reported favourable outcomes. Twelve families who had recently received care within the GOSH Neuropsychology service provided feedback on the funding proposal. The feedback was highly positive and indicated a high level of demand with 11 of 12 families indicating they would be interested in taking part. Most families said that they would find it beneficial to have options for online participation and/or support with travel costs, and for sessions to fit around school hours. All feedback has been incorporated into the study design and budget. The study was also informed by a recent North Thames survey[11] of forty-five families of childhood survivors of PBT where only 2% reported being able to access dedicated cognitive rehabilitation support, and 69% stating they either definitely would have liked their child to receive it (47%) or were unsure (22%).

The Participants Information Sheets (PISs) for the study were developed using guidance and templates from the Sponsor's Patient and Public Involvement (PPI) department and GOSH Young Person Advisory Group (YPAG) for research. The GOSH YPAG provided advice on the acceptability of the study design, use of plain English for study documents including the PIS, and recruitment practices. All advice from the YPAG has been incorporated into the study and protocol. A

carer for someone treated for childhood brain tumour and healthcare service user provided further suggestions through NIHR Research for Patient Benefit (RfPB) peer review.

PPI during the study

A Patient/Public Advisory Group (PAG) will be established at the start of the project and chaired by the PPI lead for the research study. The PAG has been appropriately costed for the study using NIHR payment guidance. A Stakeholder Mapping exercise under the Theory of Change model[20] was completed with the Chief Investigator and PPI study lead to identify stakeholders with relevant lived experience and knowledge of brain tumour diagnosis and treatment. The PAG will include 6 members. Nine 3-hour quarterly meetings will take place across the lifecycle of the study. The content of each PAG meeting will be dependent on the project stage. The group will be involved in providing advice and/or co-production for the study, including recruitment practices, creation of materials during the study, analysis, and dissemination of research.

Ethics and dissemination

The study (Protocol number 22BO24 version 2, 16.12.2024) has been approved by the Camden & Kings Cross Research Ethics Committee and NHS Health Research Authority (REC reference: 24/LO/0844, IRAS Project ID: 327316, date of approval: 16/01/2025). The study is registered on ClinicalTrials.gov registry (ClinicalTrials.gov Identifier: NCT06770335, 13/01/2025: https://clinicaltrials.gov/study/NCT06770335).

Consent

Documented informed consent or assent will be sought by trained and delegated members of the research team for all participants after a discussion session based on the PIS. A copy of the PIS will be provided to participants. Special considerations for informed consent with children include PISs adapted for different ages (7–11 years, 12–15 years, and age 16+ years and a parent/carer version), assent forms for under age 16 (with parental consent) and consent form for 16+ years, and new PISs (and consent where appropriate), when children move into a new age bracket during the study. Participants will be informed that participation in the study is entirely voluntary, they can decline participation without giving a reason, they can withdraw at any time without giving a reason, and not taking part will have no consequences for their ongoing healthcare. Capacity will be presumed in the first instance (as stated in the Mental Capacity Act, 2005). For adolescent participants who can provide informed consent or where a parent consenting for their child loses capacity, the participant will not continue in the study and only de-identified data will be retained.

Study design and setting

The feasibility study employs a randomised, parallel arm design with a standard care control group (see Figure 1: Study Flowchart).

Thirty-six participants will be recruited and randomised to either 1) a 12-week block of intervention (cognitive rehabilitation with fatigue management), 2) a 6-week block of intervention (cognitive rehabilitation alone), or 3) 12 weeks of standard care. Randomisation will be undertaken centrally by the study team using GraphPad random assignment. Participants will be young people aged 7 years to 17 years, 11 months who have been diagnosed with a childhood central nervous system (CNS; brain) tumour, or received oncology treatment to the brain, and are current patients at Great Ormond Street Hospital for Children (GOSH). The study is a single-site study. All participants will be recruited at GOSH, with each participant completing a 14-week study period. All study procedures will take place at GOSH. Standard care at the study site consists of 1) a single feedback session on the neuropsychological assessment findings and recommendations, and 2) continuation of routine oncology medical care, as appropriate for the patient, without any neuropsychological intervention.

Eligibility criteria

Potential participants will be invited to take part based on the following inclusion and exclusion criteria:

Inclusion criteria

1. Age range: 7 years to 17 years, 11 months.
2. Received diagnosis and/or treatment/surveillance at GOSH for a childhood tumour that involved the CNS (brain) and/or oncology treatment to brain.
3. Received or receiving a neuropsychological assessment/consultation at GOSH over the course of the study period or in the 48 months prior to the study period, or under active surveillance with the neuro-oncology multidisciplinary team during the study period.
4. At least 6 months post-diagnosis/acute treatment (surgery and/or radiotherapy), and 3 months post-return to school, with stable disease.
5. One or more scores outside of normal limits (i.e. 1 SD above or below the mean in the direction indicating difficulty) in at least one neuropsychological domain (on performance-based tests or questionnaire-based rating scales).
6. Report impairment (z-score > -0.67) in fatigue on one or more subscales of the PedsQL Multidimensional Fatigue Scale.
7. Capacity/competence of patient or parent/carer to provide informed consent.

Exclusion criteria

1. Completed or having another targeted formal psychological intervention for cognitive rehabilitation or fatigue in the past 6 months.
2. Sensorimotor (e.g., visual-motor) impairment only on neuropsychological assessment without additional cognitive difficulty.
3. Current substance misuse from self-report.
4. Currently receiving formal psychiatric care for a diagnosed mental health disorder (including active

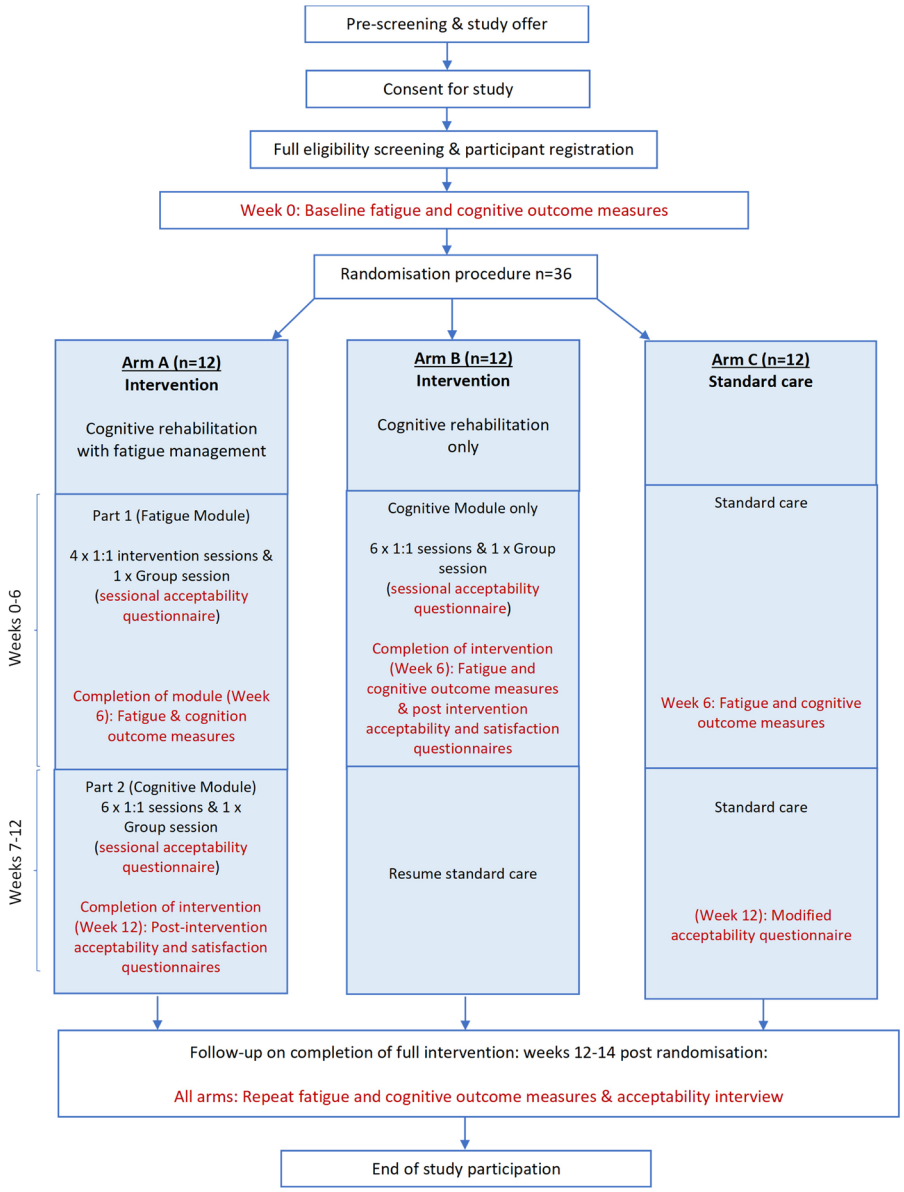

Figure 1. Study Flowchart.

suicidal ideation), excluding ADHD treatment (if a child has a diagnosis of ADHD they should be treated).

5. Intellectual Disability based on a standard score of more than 2 standard deviations below the mean on a general adaptive behaviour composite and, where available, the General Ability Index of intellect.

6. Patient and parent/carer is unable to communicate verbally and in written form in English.

Intervention

The Fatigue, Learning, and Memory Enrichment ('FLaME') program was developed by members of the research team by incorporating strategies that have been trialled and found successful in fatigue[21–23] and cognitive rehabilitation[14,15,24–28] interventions for children. Strategies for cognitive fatigue include pacing, activity scheduling and monitoring, behavioural strategies to regulate stress, and basic psychoeducation (e.g., sleep hygiene). Strategies for cognition focus on regulating attention to information and optimising encoding and retrieval (e.g. chunking and elaborative semantic encoding strategies such as the PQRST method and mnemonics), age-appropriate problem-solving strategies, and compensatory strategies such as visual reminders. A paediatric neurocognitive interventions model (PNI model[24]) informed the theoretical development of the intervention. In the PNI model, skills are targeted sequentially based on a developmental hierarchical model where

foundational factors (e.g., psychosocial needs) are addressed first, followed by adult-supported compensatory strategies, with independent use of strategies for specific impairments delivered only once these earlier levels have been addressed. This approach was recently piloted to deliver strategy-based rehabilitation for memory impairment in children with paediatric traumatic brain injury, finding large effect sizes for improvements in everyday memory difficulties[29]. Extending the PNI model for childhood brain tumour, cognitive fatigue is a common co-occurring difficulty that plausibly benefits from intervention at the foundation stage before subsequent levels of cognitive rehabilitation are delivered.

All interventional components are delivered by a Psychologist under the supervision of a senior Clinical Psychologist & Neuropsychologist. The full intervention is delivered over 12 weeks, inclusive of 10, 1-hour individual sessions (child and parent attends) and a separate parent and peer psychoeducational group session during each block (i.e. during the fatigue and cognitive intervention blocks). The group sessions reinforce the same psychoeducational components of individual sessions and are primarily to facilitate peer support. The cognitive rehabilitation-only intervention is delivered in a 6-week block consisting of 6 individual sessions (child and parent attends) and a parent and peer group session. Psychoeducational webinars for each block of cognitive fatigue and cognitive rehabilitation are provided to the child's teacher/Special Educational Needs Co-ordinator (SENCo) to enhance systemic support and maximise generalisation of strategies. The intervention is delivered hierarchically with cognitive fatigue management introduced first (in the full intervention), followed by cognitive rehabilitation strategies with consideration to developmental stage of the child. The programme content and concepts (e.g., PQRST, chunking, pacing) per session are consistent across age groups, but the delivery (e.g., wording, supporting images, and consolidation activities) is adapted by age. Degree of involvement of an adult in intervention activities can be adapted according to the child's level of development and independence.

The intervention can be delivered in face-to-face or remote format depending on participant preference. Meta-analysis[30] and review[31] of similar remote skills-based neuropsychological interventions for young people with diverse neurological conditions have recently found remotely delivered interventions have high levels of feasibility and acceptability without compromise to fidelity and efficacy. They also have the advantage of greater geographical reach and access for families who may otherwise be unable to participate[15,32]. Criteria for discontinuing the intervention includes patient request, disease relapse requiring urgent medical treatment, and where the participant becomes ineligible based on the eligibility criteria.

Study data and outcome measures

Demographic and clinical data

- Demographic data: age, date of most recent neuropsychological assessment, sex, ethnicity, living location, parental education and occupation.
- Clinical data: primary oncology diagnosis/tumour type, tumour location, tumour WHO grade, oncology treatment type (surgery, chemotherapy, and/or radiotherapy), co-morbid health conditions, diagnoses, and treatments.

Neuropsychological assessment data

All children will have received protocol-based neuropsychological assessment/consultation within the clinical service prior to commencing the intervention. This includes standardised measures such as direct measures of intellectual function (e.g., Wechsler Intelligence Scale for Children – 5th Edition), attention (e.g., Conners Continuous Performance Task – 3d Edition), memory (e.g., Children's Memory Scale), and indirect measures of everyday skills (e.g., Adaptive Behaviour Assessment – 3rd Edition, Behaviour Rating Inventory of Executive Function – 2nd Edition). Specific measures are administered according to the age of the child and presenting needs (see https://doi.org/10.6084/m9.figshare.29376176 for a typical neurocognitive assessment battery for paediatric neuro-oncology in the service). This takes place as part of standard care and will be used to characterise the cognitive needs of the participant sample.

Feasibility measures

Demand

1. Acceptance/refusal rates for potentially eligible participants.
2. Documentation of ineligibility and refusal reasons.
3. The completed number of sessions out of the total planned and attrition rate across the lifecycle of the study.
4. Record of any bias in dropout (i.e. by demographic and clinical characteristics).
5. Length of time to recruit participants within the study recruitment window.
6. A qualitative logbook of any unanticipated challenges or 'lessons learned'.

Implementation, practicality, adaptation, and integration

1. Fidelity: Clinician and observer report of fidelity using a checklist for the content coverage of the specific intervention session.
2. Participant adherence: Adherence to intervention strategies through completion rate of a brief home learning task related to the individual session content of the week. Adherence will also be discussed at post-intervention interviews.
3. Estimated cost analysis of resource required for the RCT and/or sustainability in the organisation.
4. Feasibility of data collection time points as indicated by attrition, missing, and unusable data.
5. Documentation of obstacles to recruitment in the organisation.
6. Mode of intervention delivery.

Acceptability measures

The study will triangulate qualitative and quantitative data through TFA-informed questionnaire[19] and qualitative interviews. The TFA-questionnaires were developed for the study using a published template[19] as a session-by-session and post-intervention measure for each trial arm. Questionnaires were adapted according to the age of the child. Semi-structured interview schedules were also developed for children, parents/carers, and therapists delivering the intervention using the same template and research[33]. The questionnaires and interview guides were independently evaluated by two researchers with advanced experience in psychometrics for paediatric health. To assess the construct validity of each item a process of 'back coding'[33,34] was employed. Each researcher was sent the questionnaire and interview schedule items in a random order with a list of TFA constructs and were required to match each question to the correct construct and rate their confidence on a five-point scale (1=not at all confident, 5 = completely confident). This process indicated strong construct validity where 95% of items were correctly matched to their construct with a high degree of certainty (average 5 of 5 for each construct across both researchers). The only items not correctly matched on one occasion and by one researcher were the 'affective attitude' and 'general acceptability' items which were interchanged. A second researcher rated certainty of 4 out of 5 for the 'affective attitude' and 'general acceptability' items of the questionnaires, where all other items yielded certainty of 5/5 across all questionnaires and interviews. On discussion with the researchers, it was agreed that these two items had a high degree of conceptual overlap in questionnaire format and would likely be highly correlated. A decision was made to eliminate the general acceptability item from the questionnaires which is an optional item[19]. The item was retained for the interviews however where it was a more distinct and could be explored with prompt questions.

The following TFA-measures will be used:

1. Session-by-session TFA-Questionnaire for parents & child.
2. Post-intervention or standard care TFA-Questionnaire for parents & child.
3. TFA-informed qualitative interview with participants on experience and acceptability of intervention or standard care, and acceptability of randomisation.
4. Post-intervention TFA-Questionnaire with qualitative feedback for education staff.
5. Post-intervention feasibility and acceptability interview with the therapist delivering the intervention.

The Satisfaction Questionnaire after Cognitive Skills Training Interventions – parent[15] will be used as a comparison to another published study.

Preliminary outcome measures

The inclusion of outcome measures in the feasibility trial is for 'limited-efficacy testing' to inform a future fully powered RCT and for descriptive analysis of patient benefit by assessing 1) the measures' sensitivity to change in the PBT population within the context of a feasibility trial, and 2) to estimate effect sizes of the measures[35]. Outcome measures are administered at baseline, week 6, and weeks 12–14 before acceptability interviews (see Figure 1: Study Flowchart):

1. Fatigue measures
    a. Primary outcome measure: Goal Based Outcome (GBO) for management of cognitive fatigue - parent & child[36]
    b. Secondary outcome measures: Multidimensional Fatigue Scale – parent and child[37], individual daily fatigue analogue scale (child), % school attendance (from school report)
2. Cognitive measures
    a. Primary outcome measure: GBO for management of cognitive difficulty – parent and child[36].
    b. Secondary outcome measures: Behaviour Rating Inventory of Executive Function – second edition (BRIEF-II) – parent and teacher, PedsQL Core + Brain Tumour Cognitive Problems module – child and parent[38], The Brief Illness Perceptions Questionnaire – child[39]

These outcomes measures were selected due to their psychometric properties, suitability to the aims of strategy-based cognitive rehabilitation, and precedence and sensitivity to detecting change after rehabilitation interventions[22,29,40–44]. The MDFS was selected as an outcome measure for cognitive fatigue as it is the only fatigue measure that compartmentalises fatigue into subdomains. In our clinical experience of this population, sequelae of cognitive fatigue are often reflected across the domains of the MDFS (e.g., problems starting and finishing activities, feeling tired or napping after cognitive activities) but with higher scores within the cognitive domain. We will evaluate this profile in the final sample to inform if and how this measure should be used in an RCT. Where measures are protected by copyright (PedsQL Multidimensional Fatigue Scale, Core module, and Brain Tumour module, and the BRIEF-II) the appropriate license agreement has been obtained for use within the study.

Participant timeline

A schedule of participant procedures is shown in Table 1.

Data recording, storage, and access

A Case Report Form (CRF) will be assigned for all participants entering the study. The CRF will be depersonalised and the participant and CRF will be assigned an anonymised code (Patient Identification Number; PID). All data recorded will meet the standards set out by the Sponsor's local policies. An electronic Study Site File will be maintained on a secured GOSH Trust drive which will only be accessible to members of the research team at GOSH. All study source data (e.g., from patient records and study measures) will be documented in the electronic CRF. No data fields will be left blank. Where there is

Table 1. Schedule of Participant Procedures. Key: A = Arm A (Full intervention), B = Arm B (Cognitive rehabilitation only), C = Arm C (Standard care)

Procedure	Screening	Baseline	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12	12–14
Informed consent	A,B,C														
Collect demographics	A,B,C														
Collect clinical information	A,B,C														
Full eligibility screen	A,B,C														
GBO for fatigue		A,B,C	Arms A & B at each 1:1 intervention session					A,B,C	Arms A at each 1:1 intervention session						A,B.C
MDFS		A,B,C						A,B,C							A,B.C
Fatigue VAS		A,B,C	A,B	A,B	A,B	A,B	A,B	A,B,C	A	A	A	A	A	A	A,B.C
School attendance %		A,B,C													A,B.C
GBO for cognition		A,B,C	Arms A & B at each intervention session					A,B.C	Arms A at each intervention session						A,B.C
BRIEF II		A,B,C						A,B,C							A,B.C
PedsQL core & BT modules		A,B,C						A,B,C							A,B.C
BIPQ		A,B,C						A.B.C							A,B.C
Group intervention session			Arm A & B 1 x session						Arm A = 1 session						
Individual intervention session			Arm A = 4 x sessions, Arm B = 6 sessions						Arm A = 6 sessions						
TFA sessional measure			Arms A & B at each intervention						Arms A at each intervention session						
TFA post intervention questionnaire								B							A/C
Satisfaction with Cognitive Skills Training Questionnaire								B							A
TFA interview															A,B,C

GBO=Goal Based Outcome, MDFS=PedsQL Multidimensional Fatigue Scale, VAS=Visual analogue scale, BRIEF II=Behaviour Rating Inventory of Executive Function second edition, PedsQL=Pediatric Quality of Life Inventory, BT=Brain Tumour, BIPQ=Brief Illness Perceptions Questionnaire, TFA=Theoretical Framework for Acceptability

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missing data, this will be coded with a pre-specified key. All data from the CRF will be transferred to an electronic study file in depersonalised format when the participant completes the study. The CRFs and study file will be held in duplicate in a secure GOSH Trust drive and Trust approved encrypted storage device and only accessible to the GOSH site research team. Where data is transferred from source data to CRFs, and from the CRF to study file, this will be checked for accuracy by a second member of staff (named in the CRF). The Chief Investigator (CI) or delegated individual from the research team will perform random regular audit of CRFs and the study file for accuracy (checking a minimum of a randomly identified 15%).

Data processing and analyses

Quantitative data

A detailed statistical analysis plan will be produced prior to data analyses. All demographic, clinical, and neuropsychological assessment data will be summarised by group. Quantitative feasibility data will also be summarised for the sample. Quantitative data from TFA-questionnaires will also be used to compare and rank individual intervention sessions, the overall intervention, and compare to acceptability measures in the standard care arm. Means and standard deviations (or alternative as appropriate) for the satisfaction questionnaire will be described according to intervention arm.

Statistical analyses will mainly focus on change detected in the outcome measures (e.g., GBO, PedsQL, BRIEF-II). Means and standard deviations (or equivalent) will be described for the outcome measures for each group at each time point (baseline, week 6, and weeks 12–14), and compared using repeated measures ANOVA to address these two aspects of limited efficacy testing. The focus of the statistical analyses will be to estimate effect sizes (e.g., partial eta squared, Cohen's d, or non-parametric equivalents as needed) for each measure. Effect sizes will then be ranked across the outcome measures to determine which is most sensitive to change to inform the future clinical trial. The 95% confidence intervals for the effect sizes will also be considered.

Qualitative data

Qualitative data generated by feasibility outcomes will be grouped into themes. Frequency rates for each theme will be calculated if this is appropriate. It will be used to accompany description of quantitative feasibility data.

The primary qualitative data will be generated by the TFA-informed interviews. This data will be analysed using thematic analysis[45], an analytic method that explores patterns and themes in qualitative data. Themes will be analysed according to the TFA. The final analyses will be shared with two participants to provide a member check of final themes and discussed with the Patient and Public Involvement Advisory Group.

Sampling and sample size

Thirty-six participants in total will be recruited into the study via convenience sampling of the current and retrospective (past 48 months prior to study start date) patient pool from the Neuropsychology service. All children with a diagnosis of brain tumour under GOSH Neuro-Oncology medical care can be referred to the Neuropsychological service on a combination of prospective and bespoke protocols. Children treated curatively for high-grade solid tumours (including head and neck tumours with brain irradiation), or low-grade brain tumours with radiotherapy, are assessed at baseline, 2 years, and 5 years post treatment. Children with low-grade tumours without radiation are referred based on known risk factors for cognitive impairment (e.g., shunted hydrocephalus, midline tumours) and/or presenting cognitive concerns. All children treated for brain tumour remain under surveillance with the multidisciplinary team until they transition to adult services.

Participants will be recruited continually until the sample is reached. Continual recruitment involves offering the study to potential participants as they come through the clinical service systematically, and by searching the service database backwards systematically (in reverse order of assessments completed) over the past 48 months and applying the inclusion and exclusion criteria to invite potential participants. Priority will also be given in this order to patients who are either due to turn 18 years old, transition to another service, or would become ineligible for another reason within the next 6 months. All potential participants will be contacted initially by a member of their healthcare team via telephone, letter, patient messaging, or by discussion with their neuropsychology clinician on completion of their neuropsychological assessment. The GOSH neuro-oncology multidisciplinary team will be made aware of the study objectives, inclusion, and exclusion criteria and can inform potential participants of the study. Only trained and delegated members of the healthcare team can discuss the study in detail or provide Patient Information Sheets (PIS). The rationale for this sampling strategy is to maximise recruitment of a broad range of potential participants who meet the essential inclusion criteria to answer key questions of feasibility and acceptability in this population to inform the future RCT.

The justification for the sample size comes from the NIHR Research Design Service (RDS) London evidence for sample sizes for feasibility studies (https://www.rds-london.nihr.ac.uk/resources/justify-sample-size-for-a-feasibility-study/) and associated evidence for estimating a standard deviation to power the future definitive trial. There is no formal way to power a standard deviation estimate which is a measure of variability, therefore various rules of thumb have been developed that the sample size for a feasibility trial should be between 24–50[46,47]. A sample size of 36 (12 participants per arm of the study) is further justified by the feasibility and the precision this provides in estimating the mean and the variance[46]. This can then be used to calculate power for a more precise hypothesis for a definitive randomised controlled trial.

Recruitment

Pre-screening will include screening potential participants according to the inclusion and exclusion criteria 1) on completion of prospective neuropsychological assessment, and

2) retrospectively over the 48 months prior to study date. Neuropsychological assessment reports and patient electronic records will be screened to determine if participants potentially meet the inclusion and exclusion criteria. This screening will be conducted by a member of the healthcare team within the neuropsychology service. Sources of identifiable information are the referrals record for neuropsychological assessment, electronic patient record system, and neuropsychological assessment reports. Potential participants' will only be approached by a member of the healthcare team initially. A comprehensive screening of inclusion and exclusion criteria will take place once potential participants consent to study inclusion. Participants will be advised to take a minimum of 24 hours to consider participation before giving consent. Participants may wish to take longer to decide, and the study will remain open to opt in to as long as they remain eligible and can complete the 14-week participation period within the timeframe of the study completion. Participants are not paid to participate in the study but will have access to a travel budget of £100 to compensate for travel expenses.

Confidentiality

All investigators and study site staff must comply with the requirements of the Data Protection Act 2018. A password protected Site Enrolment and Participant Log will be stored in duplicate on a secure GOSH Trust drive and encrypted external device and only accessible to members of the research team directly involved in recruitment, data quality control, and audit. The Site Enrolment and Participant Log will be stored in a separate location to the CRFs and other study data. Every participant will be allocated a unique Participant Identification Number (PID) on study entry. The PID consists of an unrelated random sequence of characters. The Site Enrolment and Participant Log will be the only document that will link the participants name and NHS number with the PID. At no point in presentations or publications of study data will individual patients be identified. Any direct quotes used will be anonymised and will not contain potentially identifiable information. Personal data will be stored for no longer than 12 months after study completion and will only be accessed where this is essential to the study.

Study monitoring

The Chief Investigator will be responsible for the day-to-day management of the study with support from the study management group. The study is a low risk non-CTIMP and does not require a data monitoring committee (DMC). A Trial Steering Committee (TSC) has been established to provide overall supervision for the study on behalf of the study's Sponsor and Funder and to ensure that it is conducted to the rigorous standards set out in the UK Policy Framework for Health and Social Care and the Guidelines for Good Clinical Practice. The conduct of the research will be subject to monitoring and auditing according to the Joint Research & Development Office for GOSH/University College London - Institute of Child Health standard research operating procedures.

Risk and safety monitoring and reporting

The NIHR 'Decision Tree for Adverse Event Reporting – Non-CTIMPS', including standard definitions of an Adverse Event (AE) and Serious Adverse Event (SAE) will guide study monitoring. It is highly unlikely that a serious adverse event/reaction would be attributable to this low-risk non-CTIMP trial. However, all AEs and SAEs will be documented in an Adverse Event Reporting log and CRF. Where an SAE occurs, this will be reported to the Sponsor within 24 hours. Participants will be notified of relevant events within 7 days or prior to their next study contact if this is sooner. If during any study activity a participant or their carer discloses risk or safeguarding concerns (i.e., their intention to harm themselves or others), the local GOSH Trust risk assessment and safeguarding policy will be immediately followed.

Dissemination

The NIHR and Success Charity will be acknowledged in any dissemination. A full report of the study findings will be submitted for publication within 2 years of study completion. The formal findings will be submitted to peer-reviewed scientific journals and, where possible, presented at relevant conferences and shared with relevant stakeholders. A lay summary of the findings will be co-produced with our PAG for dissemination amongst service-users, charities, and relevant social media. We aim to use the findings from this project to apply for funding for a multicentre RCT. Participants who request results from the CI will be provided with this information after the results of the study have been published.

Authors will be individually named on the final study report. Authors will have made a substantive intellectual contribution to the report and guided by The International Committee of Medical Journal Editors recommended authorship criteria: https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

Conclusions

There is a stark discrepancy between the high level of cognitive morbidity for childhood survivors of brain tumour and available rehabilitative support. An essential first step is to better understand feasibility and acceptability of cognitive rehabilitation for this population, particularly with reference to highly prevalent co-morbidities such as cognitive fatigue. Efficacy measures should clearly map to the aims and purpose of the interventions and play an iterative role in the development of theoretical frameworks for developing and trialling rehabilitation interventions. As is the case in many areas of paediatric acquired brain injury, we are in the early stages of understanding if and how cognitive rehabilitation interventions could work for this population and how this may be implemented within the NHS. The current study aims to meet a substantial evidence gap and answer these essential questions for this vulnerable population of children.

Data availability

Figshare: 'Typical neurocognitive assessment battery for paediatric neuro-oncology. Supplemental upload for Malcolm *et al.*, (2025)' https://doi.org/10.6084/m9.figshare.29376176

Reporting guidelines

Figshare: SPIRIT_checklist for 'Strategy-based Cognitive Rehabilitation for Childhood Brain Tumour: Protocol for an Acceptability and Feasibility Trial of the Fatigue, Learning, and Memory Enrichment (FLaME) intervention' https://doi.org/10.6084/m9.figshare.28225142.v1[48]

Acknowledgements

We thank Dr Sophie Thomas for the review and advice provided on the initial research plan. We thank the GOSH YPAG and Deirdre Leyden (GOSH Patient and Public Involvement and Engagement (PPIE) Manager, Research and Innovation), our neuro-oncology service users at GOSH, and NIHR peer reviewers for their invaluable contributions.

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Open Peer Review

Current Peer Review Status: ? ✓ ? ✓

Version 2

Reviewer Report 12 September 2025

https://doi.org/10.3310/nihropenres.15248.r36582

✓ **Ailish Malone**
RCSI University of medicine and health sciences, Dublin, Ireland

This is a much-needed, rigorously planned and comprehensive study of feasibility and acceptability of a novel rehabilitation intervention for cognitive fatigue in children 7-17 years who have been diagnosed with a brain tumour. The paper makes a clear and convincing case for the need to evaluate acceptability of this intervention, due to the nuances of cognitive impairment and fatigue after a childhood brain tumour and the fact that other interventions have either been burdensome or haven't reckoned with the unique impact of fatigue. The method of a feasibility trial is appropriate and the aims / objectives map mostly clearly to the detail in the methods. The study has been constructed with best evidence and public involvement, and adheres to rigorous standards for a feasibility trial.
I commend the authors for their work and I wish them well with this study.

I see this paper has been reviewed by three colleagues already and the authors have made the requested revisions. I offer the following points as suggestions / clarifications:

1. For me, the sections in introduction "Theoretical approach to acceptability" and "theoretical approach to outcome measurement" were out of sync in their placement before the study aims and objectives. I think it would read more clearly if these moved to Methods, after stating the objectives.

2. Objectives 1-5 are mostly clearly addressed with the proposed methods. I wondered about objective 6, "To identify any practical barriers to conducting an RCT intervention at the designated NHS site." Is this in relation to the intervention taking place at GOSH as distinct from another setting, e.g., community care? How will this be evaluated, e.g., interview?

3. Consent
   - Inclusion criteria point 7 – it is good that capacity to consent will be assumed but where cognitive impairment is severe enough that there is a question about capacity (for older participants who can consent in their own right), what decision supports are in place? This is important for all studies but particularly when the intervention is cognitive rehabilitation, as

young people with moderate to severe cognitive impairment could stand to benefit.
- Consent section - The last sentence “For adolescent participants who can provide informed consent or where a parent consenting for their child loses capacity, the participant will not continue in the study and only de-identified data will be retained.” – If the adolescent participant indicates assent, could it be possible to identify another parent or responsible adult who could support their consent? (I realise these scenarios are unlikely.)

4. Recruitment: do you have an indicator of the feasibility of the sample size, e.g., how many children with a diagnosis of a CNS brain tumour attend GOSH annually? Over what timeframe will recruitment be open (feasibility measures – demand – mentions a specific study recruitment window but I don’t see it specified)? Do you have criteria to stop recruitment to the trial? I note the adverse event and serious adverse event protocol and agree with the judgment of low risk of such events, but there may still be red-amber-green criteria worth considering based on slower than anticipated recruitment or low numbers of eligible patients.

5. Eligibility: I note the inclusion criteria requires a threshold of severity on neuropsychological scales and fatigue scales and that these are done as part of usual care. To clarify, do all children with CNS tumours attending GOSH routinely complete these assessments, or only those referred to neuropsychology based on clinical indication? If the latter, is there a risk that some eligible children could be missed?

6. PPI – it’s great to see public involvement from multiple approaches and throughout the project.

7. Intervention – The intervention is described in detail and has been rigorously developed from published evidence and clinical expertise. The terms used to describe the groups differ slightly throughout the paper, e.g., Figure 1 describes “Arm A: intervention (cognitive rehabilitation with fatigue management)” and “Arm B: intervention (cognitive rehabilitation only)”, whereas in the text, subheading “intervention” uses the terms “FLaME programme”, “full intervention” and “cognitive rehabilitation-only intervention”. Is the FLaME programme the novel intervention and only delivered in Arm A / “full” intervention? If so, for clarity I suggest referring to this group as the FLaME intervention group throughout, to be clear that it is the novel intervention. This could be made even clearer by creating a graphic showing the extent to which the groups overlap and differ (this could have value in your participant information sheets too).

8. Data collection
TFA – I commend the rigorous development of this study’s TFA questionnaire.
Table 1 is most helpful in explaining the outcome measurement procedures. All instruments have been rigorously chosen and have value, though I wonder about the time this will take for children and parents during an already busy intervention. This may become evident throughout the study, both in feasibility indicators and the exit interviews, and I encourage the team to consider the burden for a full-scale trial.
I note objective 4 – “To identify the optimal outcome measures for a larger scale RCT” – do you have pre-defined criteria based on feasibility / acceptability findings for choosing these optimal measures? (This can also be a judgement at the end, upon integration of quant / qual findings).

9. Data processing and analyses, quantitative data – for such a small sample size, I wonder if there is merit in a purely descriptive approach to statistical analysis, instead of the planned inferential approach with ANOVAs etc. I would be more interested in whether the changes exceeded MCID, for example, than the p value. You can still use the data to power a larger study.

Congratulations on constructing this important study.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Physiotherapy, rehabilitation, childhood-onset disability, neuro-oncology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 05 September 2025

https://doi.org/10.3310/nihropenres.15248.r36576

?

Florien Boele
University of Leeds, Leeds, UK

This is a protocol for a well-designed feasibility trial aiming to enhance cognitive rehabilitation for children with a brain tumour diagnosis.

Answers to the NIHR Open Research questions: The rationale and objectives are clearly described and the design is appropriate for the research question. The details on methods and the interventions are described, but not to the extent that others might be able to replicate the study. However, that would be hard to do with two complex interventions being offered – to replicate the study, all intervention materials would need to be provided which is not appropriate for this protocol publication.

I do have some other comments the authors might consider to enhance the report, listed below:
-Abstract: here, define what cognitive fatigue is? It is explained in the plain language summary but not the scientific abstract.
-Study objectives: '*3. To measure preliminary/limited-efficacy patient reported benefit and outcomes*

of the intervention arms relative to standard care.' Above, the theoretical approach to outcome measurement is explained, but up to this point the actual outcomes included in the study are not clear. I would advise to clarify the outcomes you will measure in objective 3.
-Pre-study PPI: '*The study was also informed by a recent North Thames survey11 of forty-five families of childhood survivors of PBT where only 2% reported being able to access dedicated cognitive rehabilitation support, and 69% stating they either definitely would have liked their child to receive it (47%) or were unsure (22%).*' Explain how this has impacted on the study design?
-Consent: '*For adolescent participants who can provide informed consent or where a parent consenting for their child loses capacity, the participant will not continue in the study and only de-identified data will be retained.*' Will this be assessed? How would it be known if a participant or their parent loses capacity?
-Intervention: Would add subheadings to clearly indicate the different interventions delivered in each arm (with Arm A receiving both FLaME and cognitive rehab interventions, arm B only cognitive rehab, and arm C standard care). Standard care should also be described in a separate paragraph, as there is a lot of variability in what standard care looks like for this patient group, even across NHS settings.
-Acceptability measures: the method described to determine the validity of items makes sense for the questionnaires, but not for qualitative interviews. Can you confirm/explain whether this method was truly applied to the interview topic guides?
-Preliminary outcome measures: can you indicate, where applicable, which scores you intend to use for the outcome measures listed? Total scores, specific (sub)scale scores?
-Data analysis: quantitative data. Here you state that repeated measures ANOVA will be used. Probably good to clarify what will be done if scores are not normally distributed.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: adult neuro-oncology, family caregiving, quality of life and cognitive outcomes, clinical trials

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Reviewer Report 08 April 2025

https://doi.org/10.3310/nihropenres.15060.r34982

Ingrid Tonning Olsson
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This is a study protocol for an acceptability and feasibility trial of a strategy-based cognitive rehabilitation intervention for survivors of pediatric brain tumors, an area of research where well-designed studies is severely needed. The proposed study has a well worked-through design with three treatment arms: cognitive rehabilitation and fatigue intervention, cognitive rehabilitation only, and standard care. Strengths of the study are the combination of both theoretical and clinical knowledge, and the inclusion of comprehensive patient and public involvement when developing the intervention. Another strength is the inclusion of several good measures of feasibility.

Is the rationale for, and objectives of, the study clearly described?

The authors argue that many previously researched interventions for these patients have had a drill-based, reductionistic focus with low completion rates. They aim to address this by designing a more comprehensive intervention that targets both cognitive late effects and fatigue. Finding factors associated with successfully conducted strategic rehabilitation interventions is of utmost importance in strengthening the quality of life for survivors.

The objectives of the study are clearly described, and the background is comprehensive and clear. The overall objective of the proposed study is to establish feasibility and acceptability for a strategy-based cognitive rehabilitation intervention, and this is further broken down into six different sub-aims in a very clear and consistent way.

Is the study design appropriate for the research question?

Strengths of the study design are a solid and comprehensive patient and public involvement during the development of the intervention, a very well-designed assessment of feasibility and acceptability, and the use of individualized rehabilitation goals. These methods are appropriate for answering research questions. The proposed intervention combines previously tested intervention methods used for fatigue and acquired brain injury for children, although untested in this population.

A convenience sample is used, meaning that the study might suffer from bias, for example related to ethnicity or tumor type. Having received a neuropsychological evaluation at Great Ormond Street Hospital (GOSH) is an inclusion criterion, but it is not described what the criteria are for such an evaluation. Of course, a stratified sample would be preferable for this aim, but it is likely not possible.

A comment on why the cut off-variables are different for fatigue and cognitive sub domains would be helpful – why the authors apply different cut-offs for impairment: z<-.67 for fatigue and z<-1 for

cognition.
One of the aspects missing in the analysis is the comparison of participants receiving the intervention remote compared to face-to-face. The authors suggest that this can be done without compromising the fidelity or efficacy of the intervention. Even though this is likely, given previous research regarding remote interventions of cognitive rehabilitation, an analysis of this would be helpful in future tailoring of the intervention and of importance when conducting the following RCT.
Another strength of the study is the theoretical framework of the pediatric neurocognitive intervention model,[1] stating that every intervention needs to start with addressing psychosocial and systemic needs first, e.g., a family with a very heavy workload or a family with inadequately treated mental illnesses, might not be able to benefit from rehabilitation. I cannot see that this is addressed in the intervention program, e.g., by administering the Psychosocial Assessment Tool [2] before starting the intervention. Since psychosocial obstacles might be difficult to eliminate or alleviate, such screening might lead to the exclusion of families whose psychosocial status might compromise their participation, which would have benefited the study.

Are sufficient details of the methods provided to allow replication by others?
In an otherwise well-described method section, the listed seven inclusion criteria would benefit from some clarification (and these are very minor remarks, probably typos):
Criterion 2: The text states that survivors of brain tumors are eligible, but the text says "...and/or oncology treatment to brain", which might imply inclusion of survivors of leukemia and non-Hodgkin.
Criterion 3: states that survivors should have received a neuropsychological assessment or be under active surveillance with the multidisciplinary team. The latter is neither defined nor given a cut-off. The neuropsychological assessment is not described, e.g., how many subtest should be included. Given that the probability of having at least one score <=-1z-score is very high if you are taking 10 subtests (about 82%), this is of importance. Also, wording is a bit unclear: "one or more scores outside the normal limits (i.e. 1 SD above or below the mean in the direction indicating difficulty) in at least one neuropsychological domain...". I guess the authors want to say that any score <=-1SD would be an inclusion criterion. Or do they want to include survivors with very uneven profiles, e.g., those with an average overall performance and one or two very high scores?
Criterion 6: Impairment=z>-0.67. PedsQL MFS has a scale with higher scores indication less fatigue. I guess it should be z<-0.67 here, or (if the scale is reversed): z<0.67
Given that the study compares interventions to standard care, a description of what standard care consists of would provide more insight into the differences in being included in one of the other study arms. This also affects the replicability of the study. Given that the study is conducted at a single center, the standard treatment might be specific to that site. A description of the standard treatment would therefore also increase the replicability of the study.

Are the datasets clearly presented in a useable and accessible format?
This is a strength of the proposed study with well-designed graphs and tables depicting the workflow. The different measurement methods are clearly presented. It is easy to follow which data will be collected and in which way it will be analyzed.

Conclusions
This is a well-needed and well-designed study that will fill a research gap, and we are looking forward to the results. The proposed methods are suitable for the aims, the intervention is well described and founded in both clinical and theoretical knowledge, as well as guided by patient and

public involvement. Some minor aspects of the method could be clarified. We recommend the authors to:
1) Clarify of how the interventions differentiate from standard care.
2) Clarify inclusion criteria and provide a rationale for the proposed cut-off limits.
3) Include some form of standard screening of psychosocial and systemic factors before the intervention following the pediatric neurocognitive intervention model.
3) Inclusion of an analysis of differences when the intervention is remote vs on-site.

References

1. Limond J, Adlam AL, Cormack M: A model for pediatric neurocognitive interventions: considering the role of development and maturation in rehabilitation planning.*Clin Neuropsychol*. 2014; **28** (2): 181-98 PubMed Abstract | Publisher Full Text
2. Kazak AE, Scialla M, Deatrick JA, Barakat LP: Pediatric psychosocial preventative health model: Achieving equitable psychosocial care for children and families.*Fam Syst Health*. 2024; **42** (1): 76-89 PubMed Abstract | Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neuropsychology, neurocognitive late complication following childhood cancer

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 21 Jun 2025

Charlotte P. Malcolm

AUTHOR RESPONSE: Thank you very much for reviewing the manuscript and for the positive comments which we were very pleased to receive. We were particularly pleased to hear the positive feedback on the design of the study. We fully agree with the important need to develop strategic rehabilitation interventions for childhood brain tumour survivors for strengthening quality of life, and we hope this research trial will add useful evidence towards this. We look forward to sharing the results from the study. This is a study protocol for a feasibility trial which will inform the design of a future Randomised Controlled Trial

(RCT). The feasibility trial allows us to trial certain aspects of the design to inform the RCT.

We provide clarifications as requested below:

REVIEWER COMMENT: This is a well-needed and well-designed study that will fill a research gap, and we are looking forward to the results. The proposed methods are suitable for the aims, the intervention is well described and founded in both clinical and theoretical knowledge, as well as guided by patient and public involvement. Some minor aspects of the method could be clarified. We recommend the authors to:

REVIEWER COMMENT: 1) Clarify of how the interventions differentiate from standard care.

AUTHOR RESPONSE: We have now clarified standard care in the manuscript on pages 10-11 ('Study design and setting') as:

"*Standard care at the study site consists of 1) a single feedback session on the neuropsychological assessment findings and recommendations, and 2) continuation of routine oncology medical care, as appropriate for the patient, without any neuropsychological intervention".*

The primary difference between standard care and treatment arms in the study is that patients will receive a neuropsychological intervention in the trial, which is not available within the current service for children with brain tumour.

REVIEWER COMMENT: 2) Clarify inclusion criteria and provide a rationale for the proposed cut-off limits.

AUTHOR RESPONSE: Clarification for each criterion requested is provided below. Please note that eligibility criteria have been peer-reviewed and approved by a research ethics committee in advance of opening the trial. The eligibility criteria will be evaluated as part of the feasibility trial to inform a definitive RCT.

- **REVIEWER COMMENT: Criterion 2: The text states that survivors of brain tumors are eligible, but the text says "…and/or oncology treatment to brain", which might imply inclusion of survivors of leukemia and non-Hodgkin.**

AUTHOR RESPONSE: This criterion was to include patients with brain tumour and those who have head and neck tumours (e.g., rhabdomyosarcoma) with radiation fields to the brain who access the Neuropsychology service. These children present with a similar level of cognitive deficit and late effects to those with a primary brain tumour on account of radiation doses to the brain. These patients are very rare (0-2 cases referred per year). On ethical review we could not exclude these patients given their cognitive needs which have the same aetiology as children with primary brain tumours. We will describe the clinical demographics of the final sample as part of the feasibility trial. Survivors of leukaemia and non-Hodgkin do not access our service and therefore will not be recruited into the trial. We have provided clarification in the manuscript about our Neuropsychology service eligibility criteria as below (pg. 18, 'Sampling and sample size'):

"*All children with a diagnosis of brain tumour under GOSH Neuro-Oncology medical care can be referred to the Neuropsychological service on a combination of prospective and bespoke protocols. Children treated curatively for high-grade solid tumours (including head and neck tumours with brain radiation), or low-grade brain tumours and radiotherapy, are assessed at baseline, 2 years, and 5 years post treatment. Children with low-grade tumours without radiation are referred based on known risk factors for cognitive impairment (e.g., shunted hydrocephalus, midline tumours) and/or presenting cognitive concerns.*"

- **REVIEWER COMMENT: Criterion 3: states that survivors should have received a neuropsychological assessment or be under active surveillance with the multidisciplinary team. The latter is neither defined nor given a cut-off. The neuropsychological assessment is not described, e.g., how many subtest should be included. Given that the probability of having at least one score <=-1z-score is very high if you are taking 10 subtests (about 82%), this is of importance. Also, wording is a bit unclear: "one or more scores outside the normal limits (i.e. 1 SD above or below the mean in the direction indicating difficulty) in at least one neuropsychological domain…". I guess the authors want to say that any score <=-1SD would be an inclusion criterion. Or do they want to include survivors with very uneven profiles, e.g., those with an average overall performance and one or two very high scores?**

AUTHOR RESPONSE: We have now added to pg. 18 ('Sampling and sample size') that "*All children treated for brain tumour remain under surveillance with the multidisciplinary team until they transition to adult services".* We have now also included details of the cognitive tests included in a typical neuro-oncology neuropsychology assessment battery as supplementary extended data to the manuscript (https://doi.org/10.6084/m9.figshare.29376176, referenced on page 18 '*Neuropsychological assessment data*'). As described in the eligibility criteria, the focus of eligibility is on cognitive measures (i.e. not visual-motor). We intentionally kept the inclusion open to explore feasibility and it is consistent with previous cognitive rehabilitation studies in this population (references 11 and 12). Given the paucity of research, it is unclear which children would benefit from intervention and it is important to acknowledge that we are working with a condition where emerging cognitive late effects are very common and could potentially be mitigated with earlier intervention. We trialled our inclusion criteria in advance of our ethics review submission and found that it was very rare to have only one or two scores an SD below the mean. In only 1 of 57 cases (1.7%) did a child have only one score of 1 SD below the mean and they reported associated functional difficulties with this that would benefit from intervention. In most cases, if a child had one score in this range, this was accompanied by several other scores in this range across multiple cognitive domains. The cognitive profile of the feasibility sample recruited will be described with the feasibility study findings.

- **REVIEWER COMMENT: Criterion 6: Impairment=z>-0.67. PedsQL MFS has a scale with higher scores indication less fatigue. I guess it should be z<-0.67 here, or (if the scale is reversed): z<0.67.**

AUTHOR RESPONSE: We confirm that where z>-0.67 PedsQL MDFS is stated, this is indicating the direction below the mean (0) where a minus score indicates greater difficulty.

REVIEWER COMMENT: A comment on why the cut off-variables are different for fatigue and cognitive sub domains would be helpful – why the authors apply different cut-offs for impairment: z<-.67 for fatigue and z<-1 for cognition.

AUTHOR RESPONSE: We used a cut-off of 1 SD above or below the mean for cognition as this is conventional and has precedence for neuropsychological measures. As there is no similar convention or standardisation for fatigue symptoms using the MDFS in this population, we selected a more clinical and conservative cut-off score that indicates the 'below average' range, indicating children who might benefit from the intervention.

REVIEWER COMMENT: 3) Include some form of standard screening of psychosocial and systemic factors before the intervention following the pediatric neurocognitive intervention model.

AUTHOR RESPONSE: There are two elements to this point which relate to the PNI model and psychosocial factors. Firstly, whilst we drew on aspects of the PNI model, the intervention was not designed to follow it exactly. We developed the FLaME intervention to include a common co-morbidity in paediatric brain injury (i.e. fatigue) as a foundational factor in the intervention. Therefore, the FLaME intervention is a bespoke adaptation of the model for the study. Secondly, we agree that psychosocial factors are important to consider but they ae separate to the content of the FLaME trial. Within the healthcare system of this study, psychosocial factors are independently screened by a multidisciplinary team and referred for intervention to a Clinical Psychology and Social Work team rather than the Neuropsychology service, which leads this trial. As part of our trial screening visit, we document other psychological interventions the child and family may have received in the 6 months prior to the trial and we will describe this as part of the feasibility assessment to inform consideration for the definitive RCT. We also document any psychosocial factors given as a reason for declining or withdrawing from the study as part of the feasibility analysis to inform the RCT.

REVIEWER COMMENT: 4) Inclusion of an analysis of differences when the intervention is remote vs on-site.

AUTHOR RESPONSE: We agree this will be beneficial and is included in the analyses plan for the feasibility and acceptability measures, if possible. Feasibility trials are not intended to generate sufficient quantitative data to statistically compare outcomes for efficacy, which is instead the aim of the definitive RCT. We will include descriptive analysis of the outcome measures between remote and in-person delivery, if there are sufficient data and variability in modality to do this.

With many thanks again for the helpful comments.

Competing Interests: None.

Reviewer Report 08 April 2025

https://doi.org/10.3310/nihropenres.15060.r34981

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Jurgen Lemiere
Pediatric Oncology,, KU Leuven, Belgium

Given the significant impact of neurocognitive problems on pediatric brain tumor patients and the current lack of effective interventions, this study is of great importance.
The authors state that up to 100% of children treated for PBT experience some degree of cognitive morbidity. However, the reference used pertains only to PBT located in the Fossa Posterior, which is not fully representative of the broader claim made.
Additionally, the authors mention that neurocognitive problems increase over time since treatment, with an average loss of 18 FSIQ points by early adulthood. One of the references supporting this claim is over 20 years old, and the 18 FSIQ points drop is not applicable to all types of PBT. Therefore, a more nuanced and up-to-date paragraph on the neuropsychological impact of PBT is warranted.
The paragraph on neurorehabilitation is missing some potential intervention methods, such as medication and lifestyle changes. I am aware of at least one systematic review on this topic that could be included to provide a more comprehensive overview.
Regarding cognitive fatigue, the paragraph could benefit from a broader framework on fatigue. Since fatigue is multimodal, the authors should maintain consistency across the manuscript by specifically referring to cognitive fatigue rather than general fatigue.
A positive aspect of the study is the active involvement of patients and the creation of a Patient Advisory Group (PAG).
The age range for participants is quite large, spanning from 7 to 18 years. It is important to clarify whether the program is similar for all age ranges, as younger children may require more parental involvement. Additionally, will the randomization process account for the different age ranges in the treatment arms?
In the inclusion criteria, it is mentioned that an impairment score on one or more subscales of PEDSQL is required. This implies that the study is not solely focused on cognitive fatigue but on general fatigue. While it is challenging to disentangle different aspects of fatigue, the authors should be precise about the domain of fatigue being investigated and ensure coherence between the introduction (cognitive fatigue) and the study's focus (all aspects of fatigue).
Could the authors provide more details on the neuropsychological assessment and how the scores will be handled? For instance, if multiple scores for a neuropsychological domain are available and these scores are discrepant, how will this be managed? For example, the CPT includes many scores; will all scores be considered?
Regarding the intervention, the focus is on strategies for cognitive fatigue. Please refer to my previous remarks on this topic.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neuropsychology in pediatric cancer, behavioural therapy

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 21 Jun 2025

Charlotte P. Malcolm

REVIEWER COMMENT: Given the significant impact of neurocognitive problems on pediatric brain tumor patients and the current lack of effective interventions, this study is of great importance.

AUTHOR RESPONSE: Thank you for reviewing the manuscript and for the positive comments on the study which we were very pleased to receive. We were particularly pleased that the importance of rehabilitation studies in this population is recognised.

REVIEWER COMMENT: The authors state that up to 100% of children treated for PBT experience some degree of cognitive morbidity. However, the reference used pertains only to PBT located in the Fossa Posterior, which is not fully representative of the broader claim made. Additionally, the authors mention that neurocognitive problems increase over time since treatment, with an average loss of 18 FSIQ points by early adulthood. One of the references supporting this claim is over 20 years old, and the 18 FSIQ points drop is not applicable to all types of PBT. Therefore, a more nuanced and up-to-date paragraph on the neuropsychological impact of PBT is warranted.

AUTHOR RESPONSE: Reference 3 (below) has been added to support the point about the high prevalence of neurocognitive morbidity for children with a range of brain tumours and associated treatments. The authors review a large body of evidence in support of neurocognitive impairment being the most pervasive late effect.

Pancaldi A, Pugliese M, Migliozzi C, et al.: *Neuropsychological outcomes of children treated for brain tumors.* Children (Basel). 2023; 10(3): 472.

We have amended the introductory paragraph to include further nuance on risk factors for neurocognitive impairment supported by citations from 2025 as below:

Treatment advances for paediatric brain tumour (PBT) in recent decades have substantially improved mortality rates but come at significant cost in cognitive morbidity alongside the long-term effects of the tumour itself. Up to 100% of children treated for PBT experience some degree of cognitive difficulty despite most having achieved typical cognitive development prior to diagnosis [1 3]. Risk factors for neurocognitive impairment are varied and continue to be investigated. The most consistent risk factors for neurocognitive impairment have included provision and dose of cranial radiation, younger age at treatment, shunted hydrocephalus, and cerebellar mutism syndrome[3, Horne et al., 2025]. Most children experience a constellation of long-term cognitive impairments that impact quality of life, mental health, access to education, academic and vocational attainment, and functional independence in adulthood. The most common neurocognitive impairments are in processing speed, attention, working and long-term memory, and visual-motor function which increase with time since treatment and result in the insidious secondary slowing of intellectual and academic progress over time (neurocognitive 'late effects'), with reported average loss of 18 Full-Scale IQ points by early adulthood following cranial irradiation [2, 3]. Despite developments in oncology treatment protocols, survivors of common malignant tumours (e.g., medulloblastoma) remain at risk of significant neurocognitive and functional impairment into adulthood [Papini et al., 2025].

Additional citations:

Horne, B. M., Attanayake, A. A., Aquilina, K., Murphy, T., & Malcolm, C. P. (2025). The Neurocognitive Profile of Post-operative Paediatric Cerebellar Mutism Syndrome: A Systematic Review. *medRxiv*, 2025-02. doi.org/10.1101/2025.02.21.25322700

Papini C, Mirzaei S, Xing M, Tonning Olsson I, Salloum R, de Blank PMK, Lange KR, King TZ, Srivastava D, Leisenring WM, Howell RM, Oeffinger KC, Robison LL, Armstrong GT, Krull KR, Brinkman TM. Neurocognitive outcomes and functional independence in adult survivors of childhood medulloblastoma diagnosed over 3 decades. *Neuro Oncol*. 2025 Jan 12;27(1):254-266. doi: 10.1093/neuonc/noae119. PMID: 38963825; PMCID: PMC11726255.

REVIEWER COMMENT: The paragraph on neurorehabilitation is missing some potential intervention methods, such as medication and lifestyle changes. I am aware of at least one systematic review on this topic that could be included to provide a more comprehensive overview.

AUTHOR RESPONSE: As the focus of the study is on cognitive rehabilitation interventions it is beyond the scope of the introduction to discuss in detail other interventions such as pharmacological or exercise interventions. We have provided a citation to the systematic review in case readers wish to read about these interventions in paragraph 2 of the *Introduction*:

"*Interventions to mitigate neurocognitive impairment have included lifestyle changes, pharmacological intervention, and cognitive rehabilitation [Bullens et al., 2024]*".

Additional citation:

Bullens, K., Sleurs, C., Blommaert, J., Lemiere, J., & Jacobs, S. (2024). A systematic review of interventions for neurocognitive dysfunctions in patients and survivors of a pediatric brain tumor. *Pediatric Blood & Cancer*, *71*(12), e31327. DOI: 10.1002/pbc.31327

REVIEWER COMMENT: A positive aspect of the study is the active involvement of patients and the creation of a Patient Advisory Group (PAG).

AUTHOR RESPONSE: Thank you.

REVIEWER COMMENT: The age range for participants is quite large, spanning from 7 to 18 years. It is important to clarify whether the program is similar for all age ranges, as younger children may require more parental involvement. Additionally, will the randomization process account for the different age ranges in the treatment arms?

AUTHOR RESPONSE: As described in the manuscript, the intervention is delivered according to a developmental hierarchical model. Given the level of cognitive difficulty typically found in this population we anticipate that parental/adult support will be beneficial for implementing and transferring interventional strategies for all age groups and this is planned for in the intervention. We describe on pg. 12 under ('*Intervention*'), that sessions are delivered with the child and their parent/caregiver, with strategies also shared with their teacher. We have further added: "*The programme content and concepts (e.g., PQRST, chunking, pacing) per session are consistent across age groups, but the delivery (e.g., wording, supporting images, and consolidation activities) is adapted by age. Degree of involvement of an adult in intervention activities can be adapted according to the child's level of development and independence*".

As this is a small n feasibility trial, we do not include any stratified randomisation. The need for this is instead evaluated as a feasibility outcome to inform the definitive RCT which will both focus on and be powered to assess efficacy and effectiveness.

REVIEWER COMMENT: Regarding cognitive fatigue, the paragraph could benefit from a broader framework on fatigue. Since fatigue is multimodal, the authors should maintain consistency across the manuscript by specifically referring to cognitive fatigue rather than general fatigue. In the inclusion criteria, it is mentioned that an impairment score on one or more subscales of PEDSQL is required. This implies that the study is not solely focused on cognitive fatigue but on general fatigue. While it is challenging to disentangle different aspects of fatigue, the authors should be precise about the domain of fatigue being investigated and ensure coherence between the introduction (cognitive fatigue) and the study's focus (all aspects of fatigue).

AUTHOR RESPONSE: This is a complex area with limited sensitivity in measurement. There are few measures of fatigue or cognitive fatigue for the paediatric population, and the sensitivity and specificity of the measures in identifying cognitive fatigue in the paediatric brain tumour population have not been studied. There is an absence of literature on the differences between cognitive and general fatigue, especially for paediatric brain injury and

brain tumour population, that limits detailed discussion. We have made this point more explicit in the manuscript on pg. 7 (‘*Introduction*’) where we also discuss the absence of literature generally on cognitive fatigue in paediatric brain tumour: “*with very few studies conceptually distinguishing cognitive fatigue from fatigue in general*”. We selected the MDFS as this is the only measure that at least facilitates compartmentalising fatigue, but an important element of the study is to evaluate change in these domains pre- and post- an intervention that focuses on *cognition and cognitive fatigue*. In our clinical experience of this population, sequelae of cognitive fatigue are often reflected across the domains of the MDFS (e.g., problems starting and finishing activities, feeling tired or napping after cognitive activities) but with higher scores within the cognitive domain. We will evaluate this profile in the final sample to inform if and how this measure should be used in an RCT and to guide recommendations for future research for conceptual study of cognitive versus general fatigue in this population. We have added this point to the manuscript in the justification for selecting the MDFS (pages 14-15 ‘*Primary outcome measures*’) to provide further context on both terminology/conceptualisation and measurement.

REVIEWER COMMENT: Could the authors provide more details on the neuropsychological assessment and how the scores will be handled? For instance, if multiple scores for a neuropsychological domain are available and these scores are discrepant, how will this be managed? For example, the CPT includes many scores; will all scores be considered?

AUTHOR RESPONSE: We have now included details of the cognitive tests included in a typical neuro-oncology neuropsychology assessment battery as supplementary extended data to the manuscript (https://doi.org/10.6084/m9.figshare.29376176, referenced on page 18 ‘*Neuropsychological assessment data*’). We will recruit participants according to the stated eligibility criteria of one or more scores 1 SD above or below the mean in the direction indicating difficulty in cognitive domains rather than by discrepancy. We intentionally kept the inclusion open to explore feasibility and it is consistent with the inclusion criteria in previous cognitive rehabilitation studies in this population (citations 11 and 12). Given the paucity of research, it is unclear which children would benefit from intervention and it is important to acknowledge that we are working with a condition where emerging late effects are very common and could potentially be mitigated with earlier intervention. We trialled our inclusion criteria in advance of our ethics review and found that it was very rare to have only one or two scores an SD below the mean. In only 1 of 57 cases (1.7%) did a child have only one score of 1 SD below the mean and they reported associated functional difficulties with this that would benefit from intervention. In most cases, if a child had one subtest or index score in this range, this was accompanied by several other subtest and index scores within and across cognitive domains. The cognitive profile of the feasibility sample recruited will be described with the feasibility study findings.

Citations:

11. Butler RW, Copeland DR, Fairclough DL, et al.: A multicenter, randomized clinical trial of a cognitive remediation program for childhood survivors of a pediatric malignancy. J Consult Clin Psychol. 2008;76(3):367–78. 18540731 10.1037/0022-006X.76.3.367 2827251

12. Patel SK, Katz ER, Richardson R, et al.: Cognitive and problem solving training in children with cancer: a pilot project. *J Pediatr Hematol Oncol.* 2009;31(9):670–7. 19707159 10.1097/MPH.0b013e3181b25a1d

With many thanks again for the thoughtful comments and review.

Competing Interests: None.