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Title

ERNIE - Evaluating Response to an individualized Neuropsychological IntervEntion for children with brain tumors: study protocol for a randomized controlled trial

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Abstract

Background

Although survival rates for children with brain tumors have improved, many face neuropsychological challenges that can affect quality of life and daily functioning. Existing interventions are typically standardized, with limited evidence supporting their effectiveness, and often do not explicitly target individual or systemic needs. The ERNIE study aims to address these gaps by evaluating the efficacy and process of an individualized, family-centered neuropsychological intervention. The primary research question is to evaluate the efficacy of an individualized versus standardized neuropsychological intervention immediately after treatment completion.

Methods:

The ERNIE study is a single-center, prospective, superiority randomized controlled trial at the Princess Máxima Center for Pediatric Oncology in the Netherlands. Eligible participants are children aged 8 to 17 years with cognitive problems following completion of brain tumor treatment. Enrollment began in November 2024 and will continue for two years, with study team aiming to recruit 144 participants. Participants and parents are randomly assigned (1:1) to an individualized or a standardized neuropsychological intervention, each comprising six sessions of psychoeducation and strategy training over three months. Randomization is stratified by age (8–12/13–17 years) and cognitive impairment (mild/severe). Outcome assessors and families are blinded to allocation, whereas therapists cannot be blinded due to the nature of the intervention.

The primary outcome is Goal Attainment Scaling (GAS), assessed through a patient and parent interview post-intervention. Other outcomes are goal satisfaction, cognitive and psychosocial outcomes and measures of the intervention process, including recruitment feasibility, intervention completion, data collection, and implementation factors such as facilitators and barriers. A six-month internal pilot will provide an early assessment to inform study procedures. Assessments occur pre-intervention, post-intervention (~3 months), and follow-up (~12 months). Safety monitoring aligns with low-risk studies.

Discussion:

The ERNIE study compares an individualized neuropsychological approach with a standardized approach.

By integrating outcome assessment with process evaluation, the study seeks to generate evidence on both efficacy and implementation feasibility. Findings may help shape future clinical practices by investigating the impact of individualized neuropsychological interventions to improve daily functioning in this vulnerable group of children.

Trial registration

ISRCTN trial registry ISRCTN30985676, registered 04 October 2024.

https://www.isrctn.com/ISRCTN30985676

Keywords

Brain Neoplasms; Child; Cognition, Neuropsychology; Intervention Studies; Rehabilitation; Study Protocols; Randomized Controlled Trials

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	ERNIE - Evaluating Response to an individualized Neuropsychological IntErvention for children with brain tumors: study protocol for a randomized controlled trial
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Role of sponsor {5c}	The funder and sponsor are not involved in collection, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Introduction

Background and rationale {6a}

It is estimated that cancer impacts approximately 400,000 children around the world each year, making it a major global health challenge. Among these, brain tumors account for approximately a quarter of cases (1, 2). For children with brain tumors, advances in treatment have led to 5-year survival rates of approximately 75% and thus the number of survivors is increasing worldwide(3). However, up to 50% of patients and survivors have neuropsychological(4-10) difficulties that can impact their daily functioning and quality of life. For example, they may have attention or memory difficulties that impact their ability to complete schoolwork,

interact with peers, or participate in activities across home, school, and community settings(11-13). These difficulties may arise from several factors, including the tumor's direct impact on the brain, treatment (e.g. surgery, radiation and chemotherapy), related complications, and the developmental vulnerability of the maturing brain. Some challenges manifest shortly after treatment; others may emerge or worsen as children mature and encounter more complex academic and social demands(8, 14, 15). Given the large impact of neuropsychological difficulties on the brain tumor survivor and family, interventions that decrease the burden of these challenges are essential for improving quality of life for these children.

Previous intervention studies have attempted to improve elements of children's neuropsychological functioning, such as through computerized cognitive training(16) or medications(17) to improve attention skills. However, these interventions have important limitations, such that computerized training may not generalize to real-world tasks(18) or parents may be hesitant to use medications for their child(17, 19, 20). Other studies have examined cognitive or cognitive-behavioral approaches, such as through psychoeducation(21), cognitive remediation(22), social skills training(23), or stress/coping skill training(24). These studies have shown short-term benefits of these interventions, including medium improvements in attention (d= -0.48, 95% CI -0.74 to -0.22 (22)) or social skills (f=0.30, CI not available (23)) when compared to control groups. These studies provide some evidence for the efficacy of neuropsychological intervention in pediatric groups, which could be potentially implemented into the clinic.

Most of the aforementioned interventions have targeted one specific neuropsychological domain, such as attention or working memory. However, it is well established that pediatric brain tumor survivors have difficulties in several neuropsychological domains (e.g., attention, memory, fatigue(4-10)), which suggests that a more comprehensive intervention approach is needed. For example, studies that have targeted multiple neuropsychological outcomes or have used multiple methods for treatment (e.g., teaching attention, memory, or metacognitive strategies) have also been associated with improved cognitive outcomes in pediatric cancer(22, 25). These interventions have been time-intensive, which may not be needed for all survivors and may lead to non-completion of the intervention. Therefore, there is an urgent need to evaluate comprehensive interventions that can also be conducted in a more efficient (or targeted) format.

Another notable gap is the inconsistent inclusion of parents or caregivers in intervention studies(25-27), despite evidence showing that their involvement adds value beyond the child-focused components. Parents can play an essential role in supporting treatment adherence, as well as generalization and

maintenance of skills in children(28-33). The strongest evidence for efficacy in pediatric brain injury populations comes from studies that have actively included the family in the intervention(28), such as parents being involved in the intervention sessions with the child and/or supporting the completion of homework. This type of approach aligns with systemic theory and family-centered approaches in pediatric health care(34, 35). Overall, these studies highlight the importance of including parents or caregivers in interventions with children, including those with brain tumors.

In recent years, there has been an increased focus on personalized or precision treatment, particularly in oncology and rehabilitation. Personalized treatment may also be important in pediatric(36) or adult(37) neuropsychological care, such as matching treatments to the personal characteristics of an individual patient and family. Rehabilitation approaches emphasize using individualized goals and treatments that are tailored to the person's needs(31, 38); for example by developing treatment plans collaboratively with patients and families to reflect their priorities and daily life needs. These approaches also enable evaluating treatment efficacy based on individual goals. Individualized goals are increasingly being used as an outcome measure in rehabilitation studies with adults(39) and children(40). For example, neuropsychological rehabilitation research using psychoeducation, metacognitive and/or compensatory strategy-training approach with brain injury groups provides some evidence that individualized goals and treatment are also associated with increased attainment of goals and potentially neuropsychological performance (e.g., (41, 42)). Through actively involving families in the development of goals and treatment, the individualization may help to increase adherence to the treatment and improve maintenance of skills. These results suggest that an individualized approach may be useful for addressing neuropsychological difficulties in children with varied needs, including acquired brain injury and brain tumors.

Taken together, a family-centered and personalized approach that targets neuropsychological difficulties may be the most effective method for improving outcomes for children with varied needs, including pediatric brain tumors. Building on this rationale, recent reviews also highlight the need for multicomponent interventions that include family members(28, 43). However, this type of family-centered and comprehensive neuropsychological intervention has not been systematically evaluated in pediatric brain tumors. Additionally, despite growing theoretical support, empirical studies are needed to determine whether individualized approaches offer advantages over standardized approaches in this population. This is not only in terms of goal attainment or neuropsychological outcomes, but there may also be differences in broader implementation-related factors such as acceptance, costs and facilitators/barriers.

In response, the ERNIE study, detailed in this study protocol, aims to advance neuropsychological care for pediatric brain tumor patients by addressing existing limitations in intervention approaches. Using a randomized controlled trial (RCT) design, the study will evaluate the efficacy and process of an individualized (vs. standardized), comprehensive and family-centered neuropsychological intervention. Results are expected to inform best practices for tailoring interventions to individual needs, with the goal of improving daily functioning and quality of life in this vulnerable group of children.

Objectives {7}

The primary research question of the ERNIE study is to examine how the efficacy of an individualized neuropsychological intervention compares to a standardized intervention, in terms of goal attainment and goal satisfaction immediately post-intervention (~3 months after baseline). We will also examine differences between intervention groups on domains of daily functioning, fatigue, cognitive functioning, social-emotional functioning, and parent/family outcomes at the immediate post-intervention phase.

The secondary research question is to examine how the effects of an individualized neuropsychological intervention compare to a standardized intervention, in terms of the maintenance of goal attainment and goal satisfaction at follow-up (~12 months after baseline, after a period of ~9 months without intervention). We will also examine differences between groups on domains of daily functioning, fatigue, cognitive functioning, social-emotional functioning, and parent/family outcomes at the follow-up phase.

The tertiary research question is to examine the process of the neuropsychological interventions, including completion of the intervention according to intended protocol, dose, reach, costs of the intervention, experiences of families and therapists, and facilitators and barriers to implementation. Additionally, an exploratory analysis will examine whether there are factors (e.g., patient or treatment variables) that impact the completion of intervention materials, dose, reach, costs of the intervention, experiences of families and therapists, and facilitators/barriers to implementation.

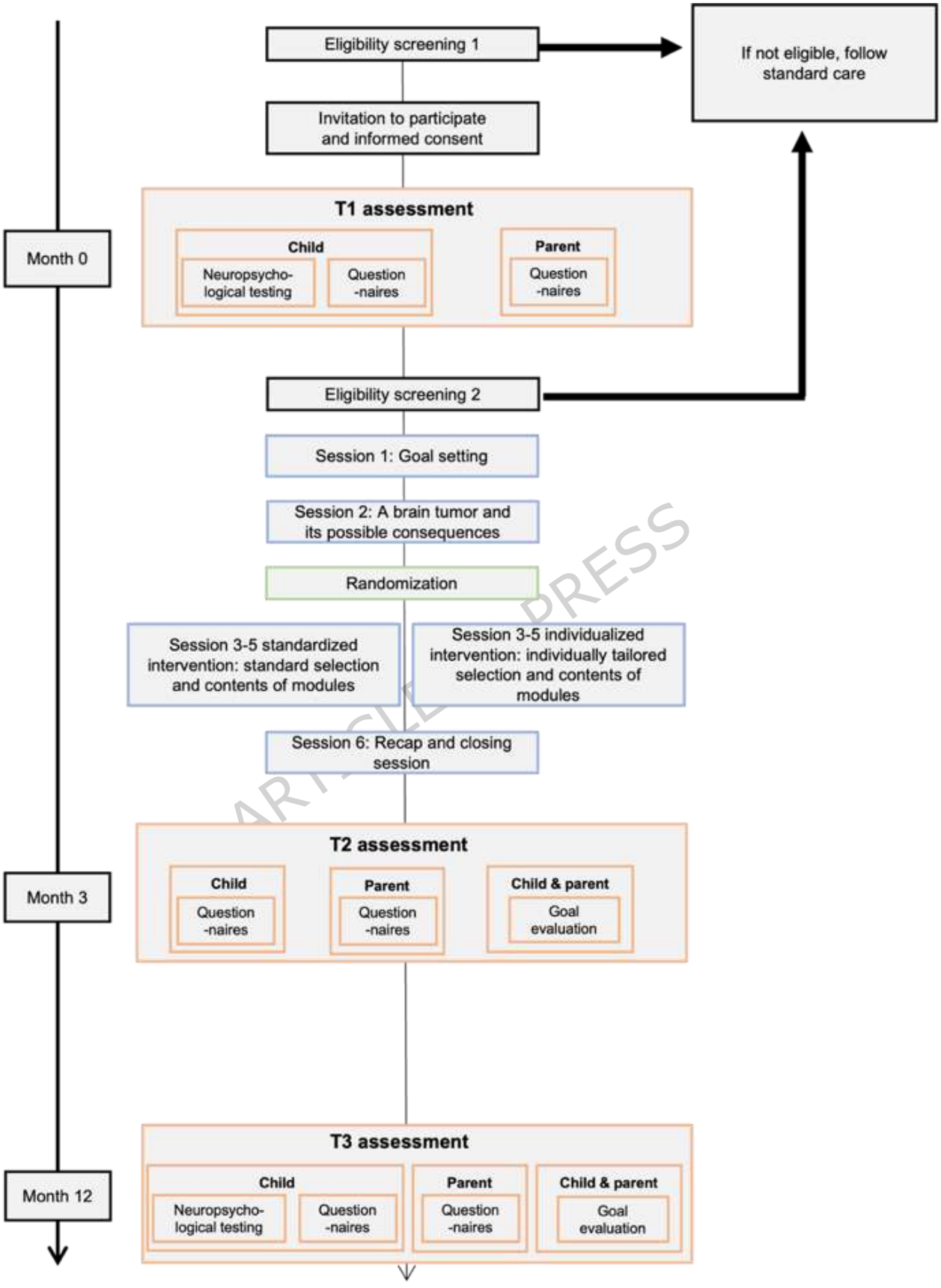
Trial design {8}

The present study is a single-center, parallel group, superiority RCT investigating the efficacy and process of a neuropsychological intervention for pediatric brain tumor patients experiencing cognitive problems.
The study compares a standardized version of the intervention to an individualized (tailored) version,

delivered over a period of three months (see figure 1, further details in sections {12} an {13}). Randomization to groups is based on a 1:1 ratio using stratification by age (8-12 or 13-17) and cognitive impairment (mild or severe, see {16b}).

Furthermore, an internal pilot phase is included during the first six months to assess recruitment, completion of intervention materials, and data collection, which may be used to adjust the implementation of the RCT (see {12} and {21b}).

Fig. 1



Study protocol flowchart

Stakeholder involvement

The study was developed collaboratively with childhood cancer survivor representatives, psychosocial professionals, and physicians (including pediatric oncologists and rehabilitation physicians), alongside researchers. These contributors provided input on content, delivery, and practical feasibility to ensure the study and intervention were clinically relevant, acceptable to families, and implementable in real-world settings.

Methods: Participants, interventions and outcomes

Study setting {9}

This single-center study will be conducted in The Princess Máxima Center for Pediatric Oncology in Utrecht, The Netherlands. The Princess Máxima Center is the national, centralized care setting for pediatric cancer patients.

Eligibility criteria {10}

Patients must meet all of the following criteria to be included:

- Age between 8-17 years
- Diagnosed with a primary brain tumor
- Completed treatment for a primary brain tumor (patients who are considered "wait and see" and have not received treatment are also eligible)
- Experiencing cognitive problems (≥1 standard deviation below normative mean or estimated Intelligence Quotient (IQ) on ≥2 scores, including Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V) / Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV) (44, 45), Intelligence and Development Scales - Second Edition (IDS-2)(46), Conners Continuous Performance Test – Third Edition (CPT3)(47), 15-Word Test (15-WT)(48) tests and/or self- or proxy-reported Pediatric Quality of Life Inventory – Cognitive Fatigue (PedsQL Cognitive Fatigue)(49) or Behavior Rating Inventory of Executive Function – Second Edition (BRIEF-2)(50) questionnaires (screening 2, see figures 1 and 2 and section {12})
- A parent/caregiver with whom they have regular contact to participate in the intervention

Patients will be excluded if they:

- Lack signed informed consent
- Cannot complete assessments and interventions due to language barriers (non-Dutch speakers)
- Are receiving palliative/end-of-life care
- Are currently receiving other neuropsychological treatment
- Have severe developmental or psychiatric disorders requiring alternative interventions (e.g., autism spectrum disorder, schizophrenia, major depressive disorder)
- Have significant sensory, motor, or developmental problems necessitating alternative neuropsychological assessments (e.g., blindness, deafness, developmental delay with Full-Scale Intelligence Quotient (FSIQ) <55)

Psychologists delivering the intervention must either (1) be registered as a health care psychologist or clinical (neuro)psychologist in the Dutch legal register for Professions in Individual Health Care (Beroepen in de Individuele Gezondheidszorg; BIG); or (2) master's level psychologist working under the supervision of a registered health care psychologist.

Who will take informed consent? {26a}

Informed consent will be obtained by trained and certified research study staff. For potential participants, parents/caregivers and patients (≥12 years) will receive oral and written patient information and informed consent forms. Thereafter, patients/families will be contacted after 1-2 weeks by telephone or during a scheduled hospital visit to further discuss the study and answer any questions they may have. If patients/families do not consent to the study, this will not impact their regular care.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

No biological specimens will be collected as part of this study. Participants will be asked to consent to the potential use of their collected data for future or follow-up scientific research within the domain of pediatric brain tumors. Collected data will be stored securely at the Princess Máxima Center for up to 15 years. Giving consent for future or follow-up research is optional; declining will not affect eligibility for or participation in the

main ERNIE study, nor will it influence the standard of care received.

Interventions

Explanation for the choice of comparators {6b}

The interventions are based on existing psychoeducation and strategy training materials(51, 52) (see also {11a}), and therefore the primary aim is not to validate the interventions themselves, but rather to assess the added value of individualization to these existing materials. Most evidence-based interventions in neuropsychology have been developed and tested in a standardized manner, yet few studies have directly compared standardized and individualized approaches. This comparison addresses a key research gap (see also {6a}).

A usual care control group was considered, but deemed unsuitable due to the heterogeneity of standard services for pediatric brain tumor survivors, ranging from intensive rehabilitation to no structured support. Similarly, a waitlist or no-treatment control group was deemed not possible due to ethical and practical reasons (i.e., the study is 12 months in length with the follow-up measurement and patients are experiencing cognitive complaints and treatment should be provided). Furthermore, passive controls such as waitlists may introduce methodological biases, including nocebo effects (where participants experience worse outcomes due to negative expectations) and exaggerated treatment effects (53, 54).

Therefore, the standardized versus individualized intervention arms provide a more interpretable and clinically relevant comparator, allowing for a rigorous assessment of the potential added value of individualized neuropsychological care.

Intervention description {11a}

Intervention overview

Patients and parents will participate in a structured neuropsychological intervention designed to address neuropsychological (i.e., cognitive and social-emotional) difficulties following pediatric brain tumor diagnosis and treatment. The intervention consists of six sessions over approximately three months, delivered either in-person at the Princess Máxima Center or online via a secure web portal, based on patient and family preference. An overview of differences between the individualized and standardized interventions are shown in Table 1; further details are described below.

Trained psychologists will serve as therapists (see {10}) and the PhD student will provide support as needed (e.g. administrative support, providing materials, scheduling of appointments). Interventions will be conducted with patients and one parent together, although components of sessions can be conducted separately when desired.

Table 1. Outline of interventions

	Individualized intervention	**Standardized intervention**
Who	Patient and one parent/caregiver; patient and parent/caregiver follow same program	
Where	In-person at hospital and/or online through secure server	
When	6 sessions within ~3 months	6 sessions within ~3 months
What	Modules on several neuropsychological domains	
How	Specific approach; individually tailored selection and contents of modules, based on individual neuropsychological profile and intervention goals	Generic approach; standard selection and contents of modules

Assessments (T1, T2, T3)

The study includes three assessments. Before starting the intervention, participants will complete a baseline (T1) neuropsychological assessment, including measures of cognitive, social-emotional, daily functioning, fatigue, and family domains. This is followed by a post-intervention assessment (T2) and a follow-up assessment (T3), approximately 3 and 12 months after baseline, respectively. Further details are described in section {8} and figure 1.

Defining goals (session 1 and 2)

In the first session, the patient, parent and therapist collaboratively identify up to three individualized goals related to neuropsychological difficulties in daily life (home, school, or community settings). The Canadian Occupational Performance Measure (COPM(55)) will be used to define goals. COPM is a semi-structured interview with established validity and reliability, and it asks questions regarding functional performance in home, school, or community environments (30-45 minutes). This qualitative information will then be

reformulated into a quantitative scale using Goal Attainment Scaling (GAS(56, 57)) based on established guidelines(31).

GAS scales will be reviewed by an independent GAS expert for quality assurance. At the start of session two, the therapist will review the refined GAS goals with the patient and parent to confirm that they agree with the goals before continuing with the intervention sessions.

Goals and interventions will focus on neuropsychological domains (see below). Academic, speech, or motor impairments will not be addressed by these interventions. If patients are (only) experiencing these problems, they will be referred for services through their treating physician, psychologist, or school.

Intervention modules (sessions 2-6)

After defining and setting goals in the first intervention session, participants in both intervention arms will continue with a psychoeducation session on the possible consequences of brain injury in session two. Participants will learn about how the brain may be impacted after brain tumor diagnosis or treatment, including a potential impact on thinking, feeling, or behavior. The psychoeducation part of session two is followed by an explanation of the metacognitive strategy that will be applied in each session.

Sessions three to five focus on specific neuropsychological domains, depending on the intervention arm. Modules are selected from the following list:

- Fatigue
- Attention and concentration
- Speed of information processing
- Learning and memory
- Planning, initiative and flexibility
- Sensory processing
- Emotions and behavior

These modules consist of psychoeducation about the specific domain, followed by tips and (meta)cognitive strategy training. The sixth and final session of the neuropsychological intervention will serve as a concluding

session, encompassing a summary of the content covered throughout the intervention, facilitating closure, and providing an opportunity for discussion and reflection.

Standardized intervention

In the standardized intervention, all participants receive the same set of modules. Following the psychoeducation session (session two), a pre-determined, standard set of three modules is delivered (see above for possible modules). One module is delivered per session. This set of modules is based on the most common neuropsychological symptoms after pediatric brain tumor(58-60). Moreover, patients and parents will choose tips and strategies to apply without explicit coaching from the therapist or information on their neuropsychological profile.

Individualized intervention

By contrast, the individualized intervention is tailored to each participant's unique neuropsychological profile and goals, as identified through assessments (neuropsychological tests and questionnaires) and interviews. For session three to five, therapists may select modules from the full module list. This tailored set of modules may therefore include both modules offered in the standardized intervention as well as additional modules, to best address the patient's needs. Sessions are flexible in structure: multiple modules may be covered in a single session, or a single module may be explored across multiple sessions, depending on the needs of the participant.

Furthermore, the therapists will explicitly target the specific psychoeducation (from session three onwards) to the individual neuropsychological profile and the patient/family's goals. For example, the therapist will explicitly link the offered psychoeducation information to the specific neuropsychological complaints or deficits that the patient experiences, and will discuss the specific situations in which the patient experiences these complaints or deficits.

Lastly, the therapist, patient, and parent will collaboratively choose tips and strategies to apply that are most fitting with the neuropsychological profile and goals.

Intervention techniques

The modules will start with psychoeducation about the specific domain, followed by tips and (meta)cognitive strategy training (as described above). Through tips and strategy training, both the patient and parent will

learn skills or strategies to support the various neuropsychological domains. For example, setting a bedtime routine for sleep, using a planner for organization, and using mnemonics for memory. The patient (together with their parent) will be asked to practice these strategies at home, school, and/or community environments, depending on their goals. In each session, the intervention team will review events in past weeks and how specific strategies have been implemented. Next, they will learn new information or strategies, practice strategies, and modify strategies as needed. The intervention will conclude with a summary of strategies used and guidance to continue using those strategies.

Intervention materials

The intervention materials will be based on established psychoeducation and intervention materials for children, but compiled specifically for this study. This includes psychoeducation and strategy training from the Brains Ahead!(51) and BrainLevel (52) programs, which were developed by researchers and rehabilitation specialists in the Netherlands.

Criteria for discontinuing or modifying allocated interventions {11b}

Discontinuation of the intervention may occur in the event of informed consent withdrawal, participant request, or upon clinical recommendation by their care provider (e.g., due to changes in medical status or recurrence of disease). The investigator can decide to withdraw a participant from the study for urgent medical or psychiatric reasons; these participants will be referred for alternative treatment through their treating physician or psychologist. In cases of disease recurrence or progression, participants can continue in the neuropsychological intervention (if they are willing/able and there is no interference to their medical treatment).

Strategies to improve adherence to interventions {11c}

To promote adherence, intervention sessions will be coordinated with regular care visits where possible. After the first session for goal development, intervention sessions can be completed through video calls if desired. Families will receive a binder in which they can add the intervention materials, which are either given on paper or emailed after each session. The therapist will review past session progress and plan actionable steps for the next session through homework assignments. Compliance with intervention sessions and adherence to the protocol are recorded as part of the tertiary research question.

Relevant concomitant care permitted or prohibited during the trial {11d}

Within regular care, our center has a neuropsychological monitoring program for patients with brain tumors (called Brain CARE program). The ERNIE study and the Brain CARE program have overlap in neuropsychological assessments and most of the questionnaires. Therefore, this lessens the time burden for participating in the ERNIE study for those within the Brain CARE program. Depending on the timing of the appointments, this data from regular care can be used for the ERNIE study.

To avoid confounding effects, children who are currently receiving other neuropsychological treatments will not be eligible to participate. In both groups, we will not interfere with other regular care in the hospital and/or community. For example, patients may be receiving physiotherapy close to their home and they will be allowed to continue these sessions during this study. These additional supports will be documented through parent questionnaires.

Provisions for post-trial care {30}

After completion of the study, participants may return to standard neuropsychological or psychosocial care available at the Princess Máxima Center or within the community. Any ongoing needs identified during the study will be communicated with the participants and treating psychologist (with permission).

Outcomes {12}

Assessments will occur at 3 time points: baseline (0 months; T1), post-intervention (3 months; T2), and follow-up (12 months; T3) (figures 1 and 2). See table 2 for an overview of assessments. All measures are available in Dutch, have age-standardized norms, and have adequate evidence for reliability/validity.
The neuropsychological assessments are performed by trained psychologists. Patients and parents complete questionnaires through the online KLIK PROM portal (www.hetklikt.nu). This secure environment is used for all assessments of patient-reported outcome measures (PROMs) in the Princess Máxima Center.

Study parameters/endpoints for primary and secondary objectives

As noted in Objectives {7}, the same study parameters are used for both the primary and secondary objectives and therefore are described together here. The difference is that the primary objective uses parameters from the post-intervention timepoint (T2); whereas the secondary objective uses parameters from all timepoints (T1/T2/T3).

The primary outcome will be Goal Attainment Scaling (GAS(56, 57)), which is assessed through parent and patient interview (Table 2). This method allows for scoring and tracking of an individual's goals, but in a standardized format. Therefore, each participant has their own outcome measure, but the scaling is the same across participants to allow for statistical comparisons. Scores are expressed as standardized T-scores with a mean (M) of 50 and standard deviation (SD) of 10, allowing comparison across participants, where higher scores indicate greater goal attainment relative to expectations.

GAS scoring will be completed following established guidelines(56). In addition to goal attainment, goal satisfaction will be measured. This will be assessed through parent/patient interview using the COPM (Table 2; and see section {11a}).

Neuropsychological tests and questionnaires will also be collected to assess cognitive, social-emotional, daily functioning, fatigue, and family domains (Table 2). Neuropsychological tests with the patient will assess estimated IQ, working memory, processing speed, sustained attention, executive functioning, memory, and social functioning (at T1/T3 timepoints). On these tests, children will be asked to define words, complete puzzles, repeat numbers in a specific sequence, copy figures within a time limit, draw plans and remember and repeat words. These measures will not be completed at post-intervention (T2) phase because neuropsychological tests cannot be repeated within a short period (and to reduce burden).

Scores are either continuous or categorical (yes/no) depending on the metric. For example, neuropsychological measures are continuous and are expressed as age standardized scores (e.g., IQ: M = 100, SD = 15), scaled scores (M = 10, SD = 3), T-scores (M = 50, SD = 10) or Z-scores (M = 0, SD = 1). These standardized formats are routinely used in psychological assessment to compare performance to age-based normative samples. For analyses, scores will be converted to a common metric (Z-scores) so that higher values consistently represent better outcomes.

Table 2. Study parameters/endpoints

Domain	Type of Measure	T1	T2	T3	Measure	Measurement units
Goal attainment	Interview (parent/patient)	X	X	X	Goal attainment scaling (GAS(56, 57))	Standardized T-score, M = 50, SD = 10; higher scores indicate greater goal attainment
Goal satisfaction	Interview (parent/patient)	X	X	X	Canadian Occupational Performance Measure (COPM(55))	Scale of 1-10, higher scores indicate higher importance, performance or satisfaction.
Daily functioning	Questionnaire (parent)	R	X	R	Adaptive behavior (ABAS-3[b] (61))	Scaled scores, M=10 and SD = 3 and standard scores, M=100 and SD=15. Higher scores indicate better functioning.
Fatigue	Questionnaire (parent/patient)	R	X	R	Fatigue (PedsQL - MFS(49))	Scale score of 0-100. Higher scores indicate more complaints.
Cognitive functioning	Questionnaire (parent)	R	X	R	Executive functioning in daily life (BRIEF-2(50))	T-scores, M=50, SD = 10. Higher scores indicate more complaints.
	Direct tests (patient)	R	-	R	Estimated IQ (EIQ) (WISC-V/WAIS-IV(44, 45) Vocabulary, Matrices)	Converted to Z-scores, M = 0, SD = 1. Higher scores indicate higher performance.
		R	-	R	Working memory (WISC-V/WAIS-IV(44, 45) Digit Span)	

		R	-	R	Processing speed (WISC-V/WAIS-IV(44, 45) Coding)	
		R	-	R	Sustained attention (CPT3(47) Task)	
		R	-	R	Executive functioning (IDS2(46) Road Walking)	
		R	-	R	Verbal memory (15-WT(48) List Learning)	
		R	-	R	Social functioning (IDS2(46) Socially Competent Behavior)	
Social-emotional functioning	Questionnaire (parent/patient)	X	X	X	Emotional problems (PROMIS[b] Anxiety and Depressive Symptoms Short Form 3.0)(62, 63)	T-scores, M=50, SD = 10. Higher scores indicate more complaints.
		X	X	X	Social functioning (PROMIS Peer Relationships short form 3.0)(62, 64)	T-scores, M=50, SD = 10. Higher scores indicate more complaints.
Parent/ family	Questionnaire (parent)	R	X	R	Parental stress (DT-P[c])(65)	Scale of 1-10, higher scores indicate higher distress.
Premorbid/ supports	Questionnaire (parent)	X	X	X	Socioeconomic status, birth, developmental, psychiatric, school history	Categorical, Low/High, Yes/No
Demographic/ clinical	Medical records	R	R	R	Demographic (age, sex)	Age in years. Sex: Female, Male, Other.
		R	R	R	Tumor (location, grade, histology)	Location: categorical. Grade: low, high or

						unknown; 1-4. Histology: categorical.
		R	R	R	Treatment (surgery, radiotherapy, chemotherapy)	Yes/No
		R	R	R	Complications (e.g., mutism, hydrocephalus, vision/hearing problems)	Yes/No

R: measure completed for regular care and/or Brain CARE

X: extra measure completed for study

- not obtained at time point

a. Adaptive Behavior Assessment System – Third Edition

b. Patient-Reported Outcomes Measurement Information System

c. Distress Thermometer for Parents

Study parameters/endpoints for the third objective

A process evaluation will be conducted for the third objective (Table 3). This will include an internal pilot phase embedded in the first 6 months of the study. The internal pilot allows for an assessment of recruitment, completion of the intervention according to intended protocol, and data collection in an early phase, and therefore, minor adjustments can be made to ensure greater success of the RCT. This internal pilot phase is further detailed in Interim analyses {21b}, where the predefined progression criteria are outlined. These criteria determine whether minor adjustments to the study design are required. There are no formal stopping rules linked to the internal pilot, since the intervention is behavioural, non-invasive, and considered low risk. The pilot is not intended to terminate the study but to optimize feasibility. Recruitment cessation would only be considered under exceptional circumstances (e.g., inability to enroll any participants despite adjustments). The internal pilot phase is ongoing and has not yet concluded

Also, an assessment of implementation, experiences, and facilitators/barriers will be conducted at the 3-month post-intervention phase (T2). The purpose of this assessment will be to evaluate quality of implementation, family and therapists experiences, and other facilitators and barriers that may be associated with implementing the intervention.

Table 3. Tertiary outcome measures

Purpose	Type of Measure	T1	T2	T3	Name of Measure
Internal pilot	Researcher records	X	X	-	Recruitment, completion of intervention materials, outcome data
Process evaluation	Questionnaire (parent/patient/therapist)	-	X	-	Experiences of families/therapists
	Researcher records	-	X	-	Implementation (completion of intervention materials/dose/reach/costs) and facilitators/barriers

X: extra measure completed for study

- not obtained at time point

Internal pilot

For the internal pilot phase, key components that will be evaluated include recruitment, completion of intervention materials, and data collection rates.

Implementation

Development and training of the intervention will be conducted. First, we will use treatment manuals that have already been established(51, 52) (see also section {11}) and any adaptations will have been completed during the development phase. Second, the therapists will complete a short training program, highlighting goal setting, core elements, and specific intervention contents.

Dose, reach, and costs of the interventions will also be described. These will be defined as follows: dose will be the number and length (in minutes) of sessions completed; reach will be the number, percentage, and demographics of patients who received the interventions (versus non-participants); and costs will be calculated for materials, travel, and staff investment for the interventions.

In addition, researchers will document facilitators and barriers, including attendance, frequency/location/length of sessions, which elements and modules were used in the interventions and any

issues encountered. The time to recruit sufficient participants, response rates, and attrition rates will also be documented.

Experiences of families/therapists

Patients and parents who participated in the research will complete a questionnaire about overall satisfaction and suggestions for improvement. For example, they can provide comments about their motivation, content, location, accessibility (e.g., online and/or travelling to hospital), and frequency of sessions. Additionally, the therapists will complete a questionnaire regarding their satisfaction, perceived (dis)advantages of the interventions, time investment, any issues encountered, and suggestions for improvement. This information will provide additional information about the facilitators and barriers of the interventions.

Other study parameters for all objectives

Demographic/clinical data will be identified from the medical record (Table 2). This will include demographic (age, sex), tumor (location, grade, size, histology), treatment (surgery, radiotherapy, chemotherapy, targeted therapies), and complications (cerebellar mutism syndrome, hydrocephalus, meningitis, seizure, stroke, visual or hearing problems, neurological deficits). Premorbid history will be collected at baseline (T1) through a parent questionnaire to obtain further information on pre-diagnosis problems

(i.e., birth, developmental, psychiatric, school history). Information on parental distress will be obtained through a parent questionnaire (DT-P(65)). These study parameters will be used for descriptive purposes or as covariates (see section {20} for statistical plan). Scores are either continuous or categorical (yes/no) depending on the metric.

Participant timeline {13}

The overview of enrollment, interventions and assessments is shown in the figure 1, as seen in section {8} and figure 2 below.

Fig. 2

		STUDY PERIOD			
	Enrolment	**Baseline**	**Allocation**	**Post-allocation**	
TIMEPOINT	$-t_1$	t_1	0	t_2	t_3
ENROLMENT:					
Eligibility screening 1	X				
Informed consent	X				
Eligibility screening 2		X			
Allocation			X		
INTERVENTIONS:					
Standardized intervention			←	→	
Individualized intervention			←	→	
ASSESSMENTS:					
Goal evaluation (COPM and GAS)		X		X	X
Neuropsycho-logical assessment		X			X
Online questionnaires		X		X	X

SPIRIT figure: Schedule of enrollment, interventions and assessments

Sample size {14}

For the primary research objective, sample sizes were calculated that would be required to find differences on the primary outcome (GAS) between groups at the post-intervention phase. The power analysis was conducted in G*Power3(66) using an analysis of covariance for the primary objective (f=0.25, alpha=0.05, power=0.80, 2 groups, 6 covariates). A medium effect size of f=0.25 was used as this would represent a clinically meaningful difference in psychology (or 0.5 SD). The power analysis suggested that 128 participants would be needed to obtain sufficient power in this study.

There are approximately 1050 patients (8-17 years old) who would be followed in regular care over the span of 15 years (e.g., estimated 70 patients/year diagnosed between 2012 and 2027 and could be eligible). It is expected that approximately 197 patients can be included based on: 75% survival rate; 50% of patients experiencing cognitive problems; and 50% of this group being interested in participating, based on current studies and incidence and survival rates in the Netherlands(67). We will recruit 144 patients to obtain our final sample size of 128 patients, accounting for 10% attrition. Therefore, we anticipate meeting sample size requirements for this study.

Recruitment {15}

Investigators will receive a list of potential participants on a dashboard developed by the Data Intelligence team at the Princess Máxima Center. This list includes all children in the electronic patient portal between the ages of 8 and 17, with a central nervous system (CNS) cancer diagnosis and with a billing code within neurology or pediatric oncology. For screening 1 (figure 1 and 2), potential participants will be invited to participate based on age, treatment phase, and language status; all of these details are known through regular care. Before inviting a child to participate, the treating physician and/or psychologist will be consulted to ensure that approaching the family is appropriate. This allows consideration of factors such as the child's medical condition, current treatment phase, and psychosocial situation.

In addition, the Vereniging Kinderkanker Nederland (VKKN) patient organization and the Princess Máxima Center will be requested to publish an announcement regarding the study on their respective websites and/or newsletters. Leaflets will also be distributed in the outpatient clinic of the Princess Máxima Center and/or by healthcare providers from the center. If interested in the intervention and study, parents may contact the researchers by telephone or email.

Recruitment is expected to last 24 months.

Assignment of interventions: allocation

Sequence generation {16a}

Randomization is performed using the online randomization tool of the Castor Electronic Data Capture (EDC) database. Participants will be allocated to one of two intervention groups (1:1 ratio, blocks of 4). Stratification will be based on age groups (8-12 vs. 13-17) and severity of cognitive impairment based on the neuropsychological tests and questionnaires (i.e., mild impairments 1-2 SDs below norms vs. severe impairments >2 SDs below norms on ≥2 scores).

Concealment mechanism {16b}

Randomization/allocation will occur after informed consent, baseline (T1) assessments, and goal setting (in intervention sessions 1 and 2) have been performed (see figure 1). Randomization/allocation sequence will be generated and concealed using a secure web-based randomization tool within the Castor EDC system, based on an independently generated sequence. This is managed by a researcher not involved in post-intervention assessments.

Implementation {16c}

Group assignments will be performed centrally using the randomization system (described above). The outcome is communicated to the therapist by a designated researcher, the study coordinator (PhD student) or another researcher not involved in carrying out the intervention or the post-intervention assessment. The therapist will then carry out the assigned arm of the intervention.

Assignment of interventions: Blinding

Who will be blinded {17a}

Post-intervention outcome assessors and patient and parent will be blinded to group allocation. Outcome assessors cannot access the randomization tool in Castor and will not be involved in the intervention. To prevent bias, data analysis will be performed on a dataset from which all direct identifiers, including the study ID, have been removed. Due to the nature of the intervention, therapist blinding is not feasible.

Procedure for unblinding if needed {17b}

Unblinding is not anticipated due to the nature of the intervention. If necessary, the study coordinator will facilitate disclosure of group allocation. The informed consent form includes a question asking participants whether they would like to be informed of their assigned treatment arm after study completion.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Details about the study instruments, along with relevant references, are provided in the 'Outcomes {12}' section. All personnel responsible for data collection and handling will receive appropriate training and meet guidelines of Good Clinical Practice (GCP).

Plans to promote participant retention and complete follow-up {18b}

Follow-up will be coordinated with routine care visits as much as possible to minimize burden. Reminders and flexible scheduling will support participant retention. Partial data from discontinued participants will be analyzed when available.

Data management {19}

A comprehensive data management plan has been developed in collaboration with data managers from the Trial and Data Center (TDC) within the Princess Máxima Center. Data will be primarily collected on paper using case report forms (CRFs) designed for each study visit, and subsequently entered into a secure, validated electronic data capture system (Castor EDC). An electronic case report form (eCRF) is maintained for each participant. The Castor database complies with all applicable legal and ethical standards and includes features such as audit trails, user access controls, and range checks for data validation. Where applicable, missing or ambiguous data will be queried and resolved in accordance with predefined data validation procedures.

Confidentiality {27}

All potential and enrolled participant data will be handled confidentially. Data will be stored under a digit code (which is not based on the patient's initials or birth date) of which the key is safeguarded by the researchers. Identifiable data will be stored separately and securely. Only researchers involved with this study will have access to the source data. The data will be kept for at least 15 years, stored on secure databases that are only accessible by the researchers. The handling of personal data complies with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (Uitvoeringswet AVG).

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable. No biological specimens will be collected in this study.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

All data for the primary and secondary objectives will be presented quantitatively. All statistical analyses will be two-tailed with an alpha of 0.05. Effect estimates will be reported with 95% confidence intervals. Analyses will be conducted using IBM SPSS (Statistical Package for the Social Sciences) Statistics (68) or R (69).

Primary objective

Immediate efficacy

Goal attainment scaling (GAS) immediately after intervention (~3 months after baseline) will be used as the primary outcome, based on goals that were defined for each participant before the intervention started. In this analysis, we will examine if there are differences between the individualized intervention group and the standardized intervention group in terms of goal attainment. GAS scores are continuous (M=50, SD=10) where higher scores indicate greater progression towards goals. Differences between groups at the post-intervention phase will be compared with analysis of covariance (ANCOVA); GAS scores at baseline are the same for all patients and thus, only a post-intervention comparison (at T2) is required for the primary

objective. Predictors in models will include the two intervention groups with covariates of age at diagnosis, sex, time since diagnosis, treatment exposures (using the Neurological Predictor Scale)(70), and family socioeconomic status(71). We will also examine goal satisfaction, cognitive, social-emotional, daily functioning, fatigue, and family domains using similar ANCOVA models. Scores are continuous, e.g. Z-scores (M=0, SD=1). These analyses will assess the immediate effect of the intervention, which is needed for our primary objective. Changes over time and maintenance of goals will be assessed below.

Secondary objectives

Maintenance

Linear mixed modelling will be used to examine differences between intervention groups, changes over time, and if various risk/protective factors are associated with outcome. Outcomes will include GAS scaling (for maintenance of goals over time), goal satisfaction, cognitive, social-emotional, daily functioning, fatigue, and family domains. Predictors in models will include group and the interaction between group and time. Covariates in models will include age at diagnosis, sex, time since diagnosis, treatment exposures (using the Neurological Predictor Scale)(70), and family socioeconomic status(71). Assumptions for linear models (e.g., normality/linearity of residuals) will be examined and corrections and/or alternative models will be used if assumptions are not met(72).

Clinical significance

Clinical significance will also be examined with descriptive statistics. Differences between groups will be expressed as effect sizes with Cohen's d. This is calculated by group differences at the follow-up phase divided by the pooled standard deviation. Effects sizes <0.5 are considered small, 0.5-0.8 are considered moderate, and >0.8 are considered large(73). Furthermore, a reliable change index (RCI) between pre-test (T1) and follow-up (T3) phase will also be calculated for measures that have standardized norms (i.e., cognitive, social-emotional, daily functioning, fatigue, and family domains). This adjusts for potential practice effects based on standard error and test-reliability metrics (when available)(74, 75). Clinically significant changes are based on an RCI value of 1.645 points(74).

Methods for additional analyses (e.g. subgroup analyses) {20b}

Tertiary objective

Implementation

Descriptive statistics for dose (number/length of sessions) and reach (number/percentage of patients who received intervention vs. not) will be examined at the post-intervention timepoint (T2). Also, descriptive statistics of costs for materials, travel for families, staff time investment (training, administrative support, therapist team), and facilitators/barriers (e.g., attendance, frequency/length of sessions, recruitment rates, attrition) will be calculated. Comments from therapists will be summarized qualitatively to examine other facilitators or barriers encountered during the intervention sessions.

Experiences of families/therapists

Descriptive statistics for patient/parent satisfaction will be calculated at the post-intervention timepoint (T2). Also, the comments from families and therapists regarding aspects such as motivation, content, location, accessibility, frequency of sessions, any issues encountered, and suggestions for improvement will be summarized qualitatively. Differences between the 2 intervention groups will be examined with parametric or non-parametric tests where possible (e.g., t-tests to examine differences in satisfaction ratings).

Potential related factors

An assessment of potential factors that can impact the implementation variables and experiences will be explored. For example, differences in dose, reach, and recruitment based on demographic factors (e.g., age, sex) will be examined. Parametric tests will be used for continuous outcomes if normally distributed (e.g., linear correlation for assessing relationship between age and intervention dose). Non-parametric tests will be used for categorical outcomes (e.g., Chi-square) or if continuous outcomes are non-normally distributed (e.g., Mann-Whitney test). This analysis will determine whether certain groups or characteristics are associated with greater dose, reach, or recruitment.

Methods to account for multiplicity

For analyses involving multiple comparisons, both uncorrected and corrected p-values will be reported. Corrections for multiplicity will be performed using the False Discovery Rate (FDR) method, which controls the expected proportion of false positives while maintaining statistical power. This approach will be applied

across relevant outcome measures where multiple testing occurs.

Descriptive statistics

Patient demographic and clinical information at baseline (T1) will be described using descriptive statistics: mean, standard deviation, and range for continuous variables; frequency and percentage for categorical variables. These variables are shown in Table 2. These characteristics will also be compared between the 2 groups at post-intervention (T2) and follow-up (T3) timepoints. T-tests or ANOVA will be used to compare normally distributed, quantitative variables. For non-normally distributed variables, non-parametric tests will be performed. Chi-square tests will be used to analyze categorical variables.

Raw data from the neuropsychological tests and questionnaires will be corrected for age/sex using published norms (Table 2). Descriptive statistics and one-sample t-tests will be used to compare obtained results to age expectations, which will determine whether the overall sample has different scores than would be expected for their age (at each time point). Also, at-risk performance will be defined as <1 SD from the standardized mean. Chi-square tests will be used to examine if the proportion of participants scoring in the at-risk range is different than expected (i.e., 16%). These results will describe mean performance and frequency of impairment in daily functioning, cognitive, social-emotional, fatigue, and family/parent domains (for each time point). Also, descriptive statistics will be calculated for the GAS goal attainment score[55,56] and goal satisfaction (for each time point).

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Analyses will be conducted according to participants' originally assigned intervention groups, as allocation will not change. This is regardless of protocol adherence. All randomized participants who complete baseline assessments (T1) will be included in the analyses; individuals who withdraw before T1 will be excluded, as no outcome data will be available. Participants who discontinue the intervention or who have missing data at one or more later time points will remain in their assigned group, and analyses will use all available observed data. We will not impute missing data. Protocol adherence will be reported through the tertiary objective of the intervention process (section {12}).

Linear mixed model analyses will accommodate missing data under the assumption of missing at

random. We will examine any baseline differences between participants with and without missing data; if there are any significant differences, this will help to guide which predictors will be included in the models to assess and address potential bias. If the assumption of missing at random is not tenable, we will examine whether missingness differs between the two intervention arms. If the extent or pattern of missing data is comparable across arms, the risk of bias is reduced.

Interim analyses {21b}

The first 6 months of the study will be the internal pilot phase. Key components that will be evaluated include recruitment, completion of the intervention according to intended protocol, and data collection (Table 3). Progression criteria will be based on an average of 6 participants recruited per month, minimum 70% completion of intervention materials, and minimum 90% of data collection for the primary outcome (GAS). Based on these pre-defined criteria, this phase will examine whether minor adjustments to the study design are required. For example, if recruitment rates are not progressing as expected, we will make minor changes to the recruitment process (e.g., broaden inclusion criteria). Only when changes are considered minor and not interfering with core elements of intervention, participants who are in the pilot phase will be included in the analyses. These criteria serve as progression criteria only; no early stopping rules are defined due to the minimal-risk behavioural nature of the intervention.

For the internal pilot evaluation, descriptive statistics will be used to summarize rates of recruitment, completion of intervention materials, and outcome measures. This will be examined for both intervention arms.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Public access to participant-level data is not planned, due to the sensitive nature of patient information. The statistical analysis plan and code will be made publicly accessible. Requests for further protocol details, data or materials should be directed to the corresponding author and Biobank and Data Access Committee (BDAC) of the Princess Máxima Center.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The day-to-day management of the study will be conducted by a study coordination team at the Princess Máxima Center, consisting of the principal investigator, study coordinator and research staff. This team will meet regularly to discuss trial-related matters. Trial oversight is ensured by a trial manager, who is independently appointed and not formally part of the study team. Oversight meetings with the study coordinator will focus on key metrics such as enrolment, protocol adherence and serious adverse events (SAEs).

Composition of the data monitoring committee, its role and reporting structure {21a}

The study will be monitored an independent Contract Research Organization (CRO). The monitoring will be executed according to the guidelines of the NFU (Nederlandse Federatie van Universitaire Medische Centra) for studies classified as ‘low risk, similar to regular care’ and according to a monitoring plan. Monitoring activities for this study will include oversight of enrolment progress, the informed consent process, source data review and verification, safety reporting, and the completeness of both the trial master file (TMF) and investigator site files (ISF).

Following each monitoring visit, the CRO will provide a written site monitoring report summarizing all findings, discrepancies, and action points. The clinical research associates (CRAs) conducting the monitoring are independent of the study team and have no competing interests, ensuring objective and unbiased oversight.

Adverse event reporting and harms {22}

The study involves non-invasive, low-risk interventions such as neuropsychological assessments and questionnaires. As such, adverse events (AEs) or serious adverse events (SAEs) related to study procedures are not anticipated. However, given the clinical condition of participants, AEs/SAEs may occur during the study period.

Any spontaneously reported or observed AEs will be documented in the medical record and reviewed by the principal investigator. SAEs related to study procedures and occurring within 24 hours of the

visit will be reported to the Sponsor, who will notify the ethics committee as per regulatory requirements.

Frequency and plans for auditing trial conduct {23}

In accordance with the monitoring plan (section {21a}), no audits are planned.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Amendments to the study protocol will be submitted to the relevant ethics committee and communicated to site staff, participants (if applicable), and trial registries. Minor administrative changes will be documented and filed.

Dissemination plans {31a}

Study results will be communicated through peer-reviewed journals, conference and internal presentations, and reports to stakeholders. No restrictions apply to the publication of this work. The results of the randomized controlled trial will be reported according to the most recent CONSORT guidelines, including use of the CONSORT flow diagram

Discussion

The ERNIE study represents an important step towards advancing neuropsychological treatment in pediatric brain tumor survivors. By evaluating an individualized, comprehensive, and family-centered intervention within a randomized controlled trial, this study addresses critical gaps from previous research in this population.

A notable strength of the ERNIE study is its inclusion of both efficacy and process measures, such as neuropsychological outcomes as well as feasibility, reach, and cost of the interventions. These measures are critical not only for understanding whether the intervention is effective, but also for successful implementation in routine care. Another key strength is the use of patient- and family-defined goals as primary outcomes, which increases ecological validity and aligns with practices in pediatric rehabilitation. Furthermore, the study is grounded in interdisciplinary collaboration. It brings together representatives of

childhood cancer survivors, psychosocial professionals, physicians (e.g. oncologists and rehabilitation physicians) and researchers to develop and deliver a clinically relevant and feasible intervention.

Despite these strengths, some limitations must be acknowledged. The single-center design and restriction to Dutch-speaking participants may limit the generalizability of findings, particularly in more diverse or decentralized healthcare systems. In addition, blinding of therapists is not feasible, which could introduce bias. However, blinded outcome assessors and the use of validated instruments enhance methodological quality. Lastly, the resource intensity of a new intervention is challenging, which may hinder therapist capacity and thus sample size. Insights from the study's process evaluation, including identified facilitators and barriers, can advance translation of the research findings into clinical practice.

Future research could address these limitations by adapting the intervention and outcome measures for use in multicenter, multilingual, and more diverse settings to enhance reach and inclusivity. In addition, alternative delivery models, such as fully digital, group-based, or stepped-care formats, could be explored to increase flexibility and efficiency. Integrating interventions into existing school or community-based support systems may further support broader adoption and long-term sustainability. A complementary area for future research involves the family context. The ERNIE intervention includes parents as active partners to enhance child outcomes, such as supporting generalization and skill use. Yet, family factors such as parental stress and overall family functioning, though not directly targeted in this study, may shape intervention outcomes and warrant attention in future work(76-78).

Looking forward, the ERNIE study has the potential to inform best practices not only within pediatric neuro-oncology but also more broadly in pediatric rehabilitation and personalized medicine. Ultimately, this line of research holds promise for improving neuropsychological functioning and broader quality of life for pediatric cancer survivors and their families.

Trial status

Current protocol version is v1.1 (10 July 2024). Recruitment commenced in November 2024 and recruitment completion is expected in November 2026. Given the 1-year follow-up assessment, data collection will be completed around November 2027.

Abbreviations

ABAS-3	**Adaptive Behavior Assessment System – Third Edition**
AN(C)OVA	**Analysis of (co)variance**
AVG	**General Data Protection Regulation (GDPR); in Dutch: Algemene Verordening Gegevensbescherming**
BDAC	**Biobank and Data Access Committee**
BIG	**Legal register for Professions in Individual Health Care, in Dutch: Beroepen in de Individuele Gezondheidszorg**
BRIEF-2	**Behavior Rating of Executive Function-2**
CNS	**Central Nervous System**
COPM	**Canadian Occupational Performance Measure**
CPT-3	**Continuous Performance Test-3**
CRA	**Clinical Research Associate**
CRO	**Contract Research Organization**
DT-P	**Distress Thermometer for Parents**
(e)CRF	**(electronic) Case Report Form**
EDC	**Electronic Data Capture**
(E)IQ	**(Estimated) Intelligence Quotient**
FSIQ	**Full-Scale Intelligence Quotient**
GAS	**Goal Attainment Scaling**
IDS-2	**Intelligence and Development Scales-2**
ISF	**Investigator Site File**
KLIK	**Kwaliteit van Leven in Kaart (Online Questionnaire Portal)**
KWF	**Dutch Cancer Society, in Dutch: Koningin Wilhelmina Fonds voor de Nederlandse Kankerbestrijding**
NFU	**Netherlands Federation of University Medical Centers; in Dutch: Nederlandse Federatie van Universitaire Medische Centra**
PedsQL	**Pediatric Quality of Life Inventory**
PROM(IS)	**Patient-Reported Outcomes Measure(ment Information System)**

RCI	**Reliable Change Index**
RCT	**Randomized Controlled Trial**
(S)AE	**(Serious) Adverse Event**
SPSS	**Statistical Package for the Social Sciences**
TDC	**Trial and Data Center**
TMF	**Trial Master File**
VKKN	**Dutch Childhood Cancer Organization, in Dutch: Vereniging Kinderkanker Nederland**
WAIS-IV	**Weschler Adult Intelligence Scale-IV**
WISC-V	**Weschler Intelligence Scale for Children-V**
15-WT	**15-Word Test; in Dutch: 15-Woordentest**

Declarations

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Authors' contributions {31b}

Roxanna Hofman (Conceptualization, Methodology, Writing—original draft, Writing—review & editing, Visualization), Rachèl Kemps (Conceptualization, Methodology, Writing—original draft, Writing—review & editing, Supervision), Jeanine Voorman (Conceptualization, Methodology, Writing—review & editing), Femke Aarsen (Conceptualization, Methodology, Writing—review & editing), and Marita Partanen

(Conceptualization, Methodology, Writing—original draft, Writing—review & editing, Supervision, Funding acquisition). All authors read and approved the final manuscript.

Funding {4}

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Availability of data and materials {29}

See also 31c.

Ethics approval and consent to participate {24}

This study was approved by the Medical Research Ethics Committee NedMec (reference: 24-131/G). Written informed consent to participate will be obtained from all patients (≥12 years) and/or parents/guardian (child <16 years).

Consent for publication {32}

Not applicable.

Competing interests {28}

The authors declare that they have no competing interests.

Authors' information (optional)

Not applicable.

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