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CHILDREN'S ONCOLOGY GROUP

ACCL10P1

Computerized Cognitive Training for Pediatric Brain Tumor Patients: A Pilot Study

A COG Groupwide Study

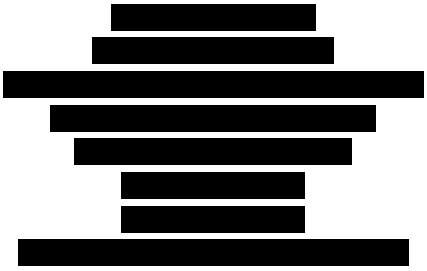

TABLE OF CONTENTS

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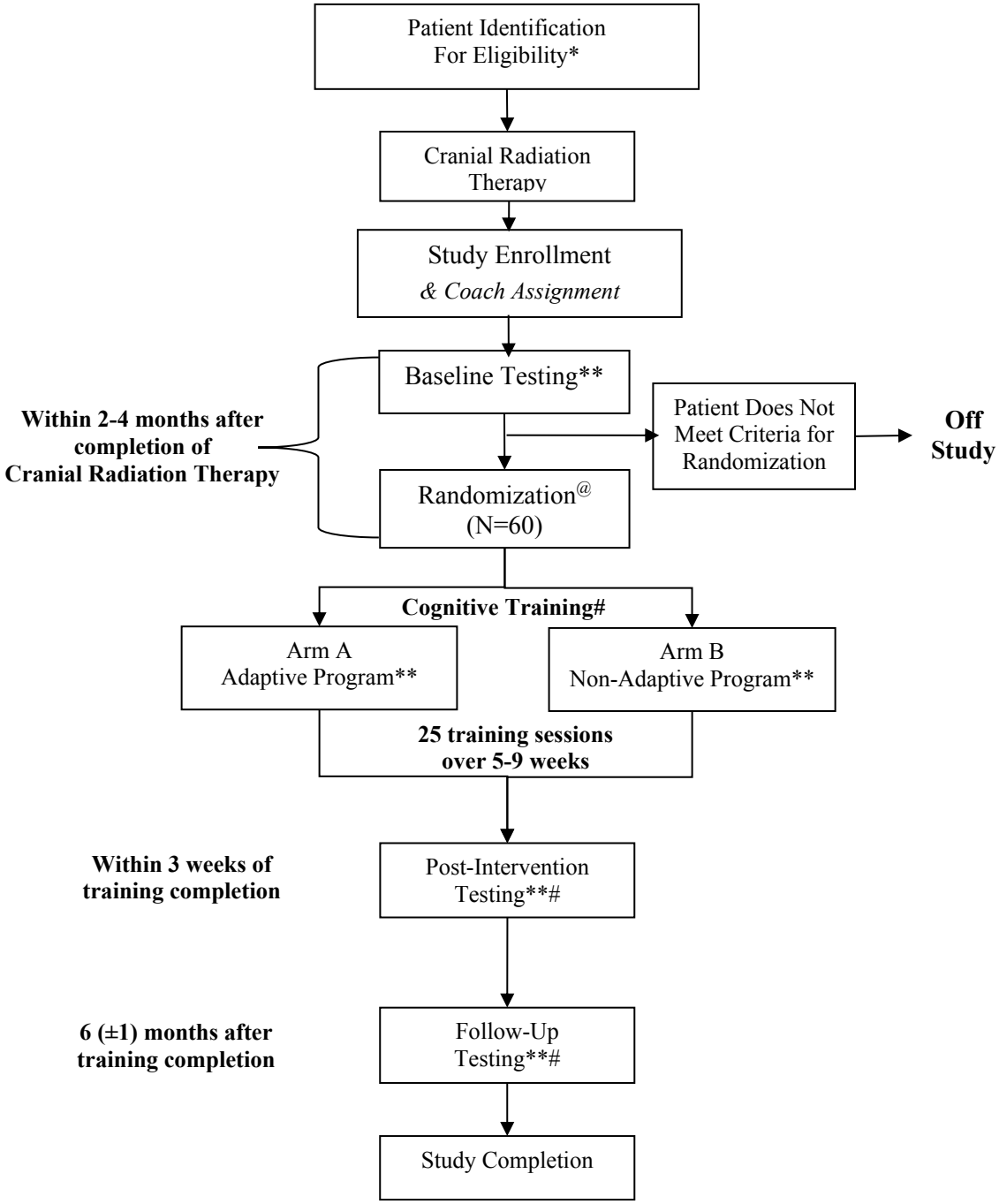
ABSTRACT

Pediatric patients with brain tumors receiving cranial radiation therapy (CRT) have an increased likelihood of experiencing significant neurocognitive decline over time, especially with regard to working memory (WM) and attention skills. These deficits, in turn, are associated with declines in intelligence quotient (IQ) and academic performance, which can impair quality of life (QOL) of survivors into adulthood. Thus, there is a critical need to develop methods to preserve neurocognitive functioning in those at risk. Computerized cognitive training (CT) is a convenient and cost-effective way of potentially preserving brain function in patients with brain tumors. To date, however, no studies have examined the feasibility or efficacy of this type of intervention in children receiving CRT. There are no known adverse effects of the intervention; rather, children find it an enjoyable and stimulating experience that can be completed at home. Computerized CT is a method that, if established as feasible and efficacious, has high potential for rapid translation to clinical practice.

EXPERIMENTAL DESIGN SCHEMA



* See Section 3.2 for Eligibility Criteria.
** See Section 4.5 and Appendix III for required and optional (but highly encouraged) study assessments. Timing required: Baseline Testing and Randomization within 2-4 months after completion of CRT.
# Cognitive Training must initiate within 2 weeks after Baseline Testing (see Section 3.1.4). Patients with progressive disease or relapse will be removed off protocol therapy.
@ Randomization is via Callback: see Section 3.1.6 for procedure summary and Section 4.2 for criteria.

1.0 SPECIFIC AIMS

1.1 Primary Objective

To assess the feasibility of a home-based, computerized cognitive training program for patients with pediatric brain tumors who are undergoing cranial radiation therapy (CRT), treated in COG institutions.

Hypothesis: The home-based computerized cognitive training (CT) program will be feasible and acceptable, as defined by 75% of randomized participants across sites achieving 80% treatment compliance, and parent- and child- reported technical ease-of-use and satisfaction.

1.2 Exploratory Objective

To estimate the effect size of this program on measures of attention and working memory in patients with brain tumors treated with CRT in order to design a definitive large-scale clinical trial.

Hypothesis: Participants will show increases in attention and working memory compared to participants in the active control group, as measured by both objective and subjective measures of attention and working memory following completion of the intervention. Moreover, participants will maintain increased attention and working memory scores at a 6-month follow-up assessment.

2.0 BACKGROUND AND RATIONALE

The majority of children with brain tumors who receive CRT will experience neurocognitive deficits. In particular, deficits in attention and working memory have emerged as among the most common neurocognitive sequelae of CRT. These difficulties make it harder for children to process and store new information, and contribute to declines in IQ and academic functioning over time. Later, these effects, and others, lead to limited vocational opportunities and reduced likelihood of independent living. As such, there is a critical need for interventions to mitigate deficits and/or restore cognitive functioning in this population.

Home-based computerized cognitive training (CT) is a novel approach that has shown robust efficacy in improving working memory in children with attention disorders and localized brain injury. Our research team is currently evaluating the feasibility and efficacy of such an intervention delivered to survivors of pediatric cancer with neurocognitive late effects. However, the potential for these interventions to *preserve* cognitive functioning in children receiving CRT has never been evaluated.

Using a randomized clinical trial design conducted in multiple, COG-affiliated institutions, the overarching goal of this proposal is to evaluate whether a home-based computerized CT intervention is feasible for use with pediatric brain tumor patients during the active phase of treatment. Potentially, preservation of working memory (WM) skills in children during the period following radiation exposure may allow for long-term preservation of brain function. Consequently, changes that that are thought to stem from weak WM, such as declining intellectual and academic functioning, may also be averted. The results of this study will serve as pilot data on the basis of which a larger, randomized clinical trial will be planned.

2.1 Brain Tumors in Children and Adolescents – Acute and Long-Term Effects of Treatment

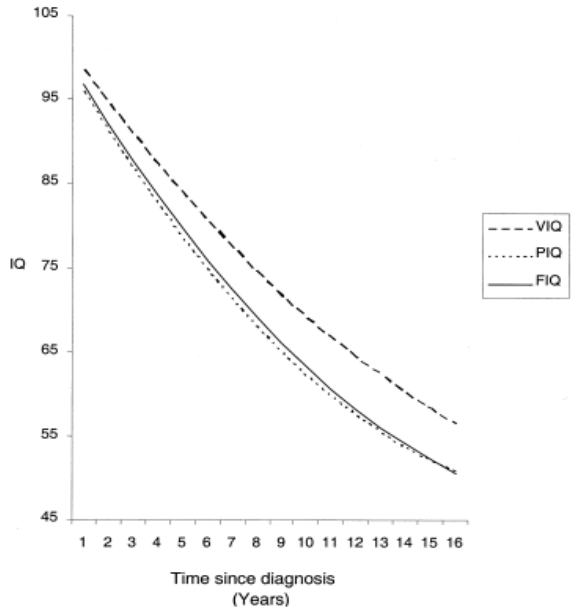


Figure 1: Estimated declines in IQ in pediatric brain tumor survivors following CRT [2]

Brain tumors are often treated with some combination of neurosurgery, chemotherapy and CRT. While advances in treatment have increased the likelihood of cure, survival is often characterized by significant impairments in neurocognitive functioning, including academic failure, deficits in social functioning, and vocational difficulty.[3,4] Identified risk factors include age under 6 to 8 years at diagnosis, female sex, tumor location, shunted hydrocephalus, presence of seizures, post-operative sequelae such as stroke, infection or cerebellar mutism, and importantly, use of CRT.[5] To mitigate these impairments, researchers have adjusted treatment protocols to eliminate or delay CRT, and to reduce radiation doses and fields. These measures, along with improved neurosurgical techniques, have reduced treatment-related cognitive declines while maintaining or improving survival rates.[6] Despite these advances, however, recent studies have found that 40 to 100% of brain tumor survivors evidence some cognitive deficit resulting from disease and/or treatment effects.[7,8] Decreases in IQ of more than one standard deviation are common, particularly for children treated at younger ages.[2] Declines in nonverbal and full-scale scores tend to be more precipitous than changes in verbal IQ (see Figure 1).

Notably, investigators have posited that attention and WM deficits underlie the changes in intelligence and academic performance frequently seen in survivors of brain tumors.[9-12] In healthy children, Fry and Hale[13] found that almost half of developmental increases in IQ could be attributed to age-related improvements in WM and processing speed. Similar findings have been documented in pediatric cancer survivors. Schatz and colleagues, for example, found that 45 percent of the variance in IQ was attributable to these processes[14]. In addition, Reddick and colleagues found that 70 percent of survivors' functional impairments at school and other settings were accounted for by their attention problems[11].

Because WM capacity increases 2- to 3- fold from ages 4 to 16,[15] disruption to the development of these processes can significantly curtail a wide range of a child's abilities over time. This may take the form of declines in IQ, as described above, or difficulty with executive functioning and academic performance. For example, children with reading difficulties frequently have deficits in WM which appear to contribute to problems with phonological memory.[16,17] Math skills are also strongly linked to WM capacity in typically-developing children, accounting for between 20% - 57% of the variance in math performance.[16,18,19] *Thus, improving or preserving WM in these patients may help to offset declines in IQ, executive functioning, and academic performance over time.*

2.2 Existing Efforts to Prevent or Improve Neurocognitive Late Effects

Given the severity of neurocognitive late effects experienced by many survivors of pediatric brain tumors, investigators over the last decade have focused on methods of

preventing or ameliorating late effects. Improvements in surgical techniques, conformal radiation therapy, and radiation dose reductions have been partially successful in reducing toxicity;[6,20] however, neurocognitive sequelae remain prevalent.[21] Beyond changes in primary therapy, based on evidence of attention and WM deficits, researchers also have started to investigate the efficacy of interventions targeting these impairments. These efforts have historically focused on *compensation* for acquired deficits rather than *restoration* of functioning. Indeed, the current standard-of-care for survivors with cognitive and academic late-effects emphasizes school-based accommodations such as preferential seating and extended time for coursework and exams.[22]

More recent interventions including pharmacotherapy and cognitive remediation have been tested in pediatric cancer survivors. The psychostimulant methylphenidate has improved performance on attention and learning tasks in both adult brain tumor patients[23] and survivors of childhood cancer,[24-26] though most cognitive and academic scores remained unchanged in children. Cognitive remediation[27,28] and problem-solving[29] for pediatric cancer survivors with impairment also have been explored. The most rigorously-evaluated program focused on the acquisition of strategies to improve cognitive, attentional, and academic performance; it consisted of two-hour, therapist-directed sessions every week for six months. While this program has shown improvement in academic performance of some survivors,[28] effect sizes for many indices of academic and adaptive functioning were small. Moreover, only 60% completed the program; it may be that the frequency and duration of clinic visits were not feasible for some subjects.[30] *Short-term, focused interventions that can be delivered outside of a clinic setting may enhance feasibility for this population.*

Compared with the growing empirical basis for intervening during the survivorship period, there are almost no studies that have attempted to intervene during the treatment phase, before neurocognitive declines occur. Yet, preliminary data from research on traumatic brain injuries[31] and 22q11 deletion syndrome[32] indicate that there may be a therapeutic window of opportunity following primary brain injury in which to attenuate secondary or delayed morbidity. Under this assumption, one recent, as yet unpublished, study used an intense (40-50 hrs) program focused on improving math concepts, including problem solving, with a small sample of children newly diagnosed with leukemia.[33] Compared to children who did not receive the intervention, those who did improved their math achievement by greater than one standard deviation. Importantly, they also evidenced improvements in their nonverbal WM scores, which were not targeted by the intervention. In contrast, nonverbal WM scores in the control group declined over the intervention and follow-up period. Although preliminary, these data suggest the possibility that early intervention can prevent neurocognitive decline in children who are receiving treatment for childhood cancer. As with cognitive remediation efforts in the survivorship period, however, such an intense program may be impractical for, or unavailable to, a sizable portion of patients and their families.

In sum, although rehabilitative strategies exist, none has been shown to be robustly effective in restoring functioning once late effects have developed. The optimal strategy to maximize cognitive functioning is to *prevent* these deficits from occurring. *Therefore, there is a critical need for programs targeting the preservation of neurocognitive functioning in pediatric patients with brain tumors being treated with CRT. Ideally, such an intervention should be effective, short-term and applicable to a wide-range of potential participants, who will not be limited by time, distance or cost. The current application addresses this need.*

2.3 Cognitive Training Programs

CT programs have been used for decades to reduce or stabilize neurocognitive deficits in populations of individuals with accidental or disease-related brain injury. These activities can include paper-and-pencil tasks, memory games, and one-on-one instruction with a cognitive "coach," usually a neuropsychologist, occupational therapist, educator, or similar professional. Many *computerized* CT programs targeting attention and WM problems, primarily in children and adolescents with attention deficit hyperactivity disorder (ADHD), have recently been developed. Most consist of a series of tasks of increasing complexity, and there is emerging support for their efficacy.[34-39]

2.3.1 Cogmed

Recently, Klingberg and colleagues developed a computerized CT program targeted at reducing deficits in WM.[35,36] The program, called *Cogmed RM*, consists of game-like exercises targeting visuo-spatial WM skills. Feedback about participants' performance is given visually and verbally to increase interest and compliance. The program is *adaptive*, such that difficulty of the training tasks increases with the skill of the participant on a trial-by-trial basis. The program is designed primarily for home use, with minimal training and support required. Its use has increased WM functioning in a wide range of samples, including healthy adults, stroke patients, children with specific WM deficits, and children with ADHD.[35,36,38-43] WM skill has improved by both objective and subjective report,[35,39] there have been associated brain changes captured by functional imaging,[40] and, importantly, improvements in academic functioning.[38] Effect sizes for most outcome measures were medium to large, and broadly consistent with those obtained from many medication trials for patients with ADHD.

2.3.2 Preliminary Data

Dr. Hardy has thus far performed two separate, small-sample trials of computerized CT with survivors of childhood cancer who have received CNS-impacting treatment (i.e., acute lymphoblastic leukemia (ALL) and brain tumors). The first trial, funded by Duke's Comprehensive Cancer Center, evaluated the efficacy of a computerized CT program known as Captain's Log with nine survivors of pediatric cancer.[1] The program was associated with good feasibility and acceptability, and outcomes reflected significant improvements in WM and parent-rated inattention symptoms over a 3-month trial (see Figure 2). However, the study was limited by the lack of a control group and very small sample size.

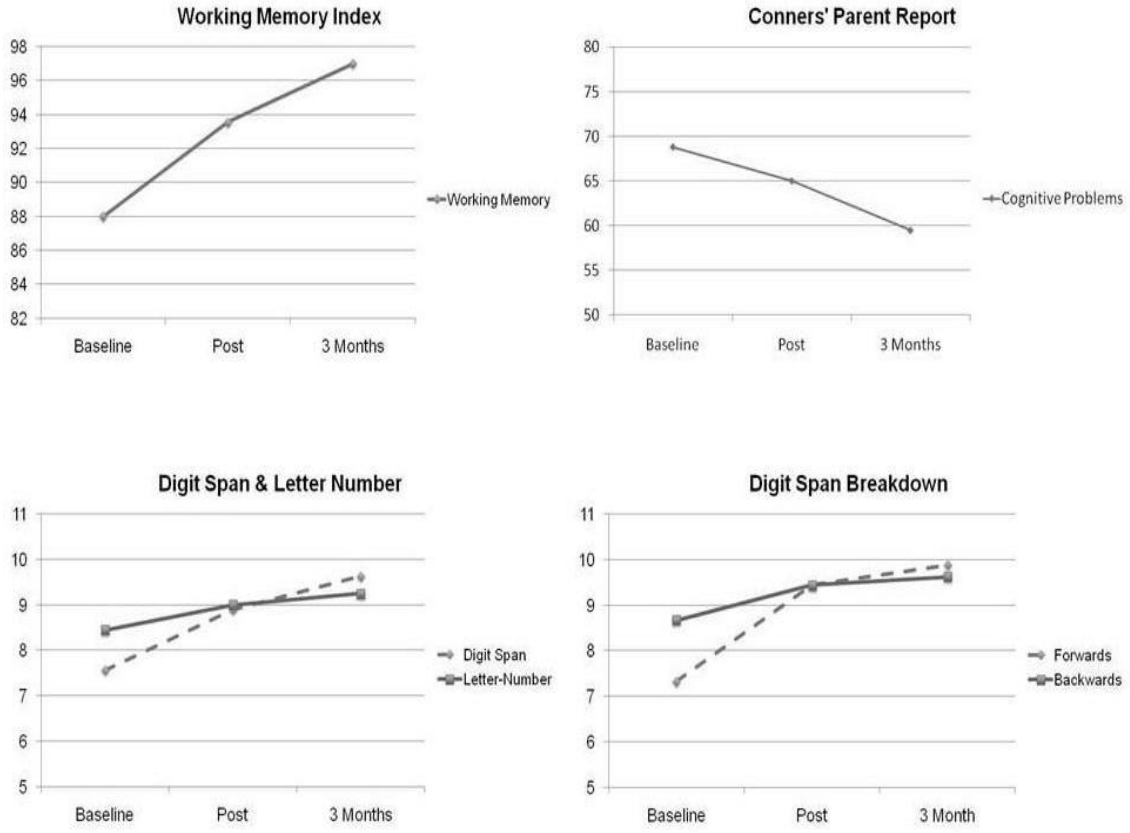


Figure 2: Changes in parent-rated attention problems over the course of a computerized cognitive intervention for survivors of ALL and brain tumors [1]

The second trial, *Targeting Inattention in Childhood Cancer Survivors* (TRICCS; NCI R03-CA132570), addressed several of the limitations of the first, using the *Cogmed RM* program (described above). Cogmed was selected for the second trial given its focus on improving WM skills and on the number of published studies indicating its efficacy with ADHD and other samples. The trial included both an intervention group that completed an adaptive version of the program and an active control group. Compliance rates for the trial (n = 20) were high (Mean = 98.1% of sessions completed, SD = 6.02). Feasibility and acceptability indicate high levels of participant and parental satisfaction with the intervention. Indeed, 94.4% of parents reported that they were somewhat or very satisfied with their child's participation in the intervention, and 68.7% of children indicated that they either often or always enjoyed their training sessions. Further, data from the *Cogmed* Training Index, a program-specific score that is used to gauge children's progress with WM skills targeted by the *Cogmed* tasks, indicated that the participants achieved a mean training index improvement of 31 (SD = 11, range = 15 – 54), very similar to that of a sample of 550 children with ADHD who have completed the program with a mean index improvement of 26.2.[44] Finally, survivors completing the adaptive version evidenced increases in attention (d = .52) and WM (d = .46; as measured by the Wide Range Assessment of Memory and Learning – Second Edition[45]) and decreases in parent-rated attention problems (d = .50; as measured by the Conners-3 Parent Rating Scale[46]) as compared to survivors completing the non-adaptive version (Fig. 3).[47]

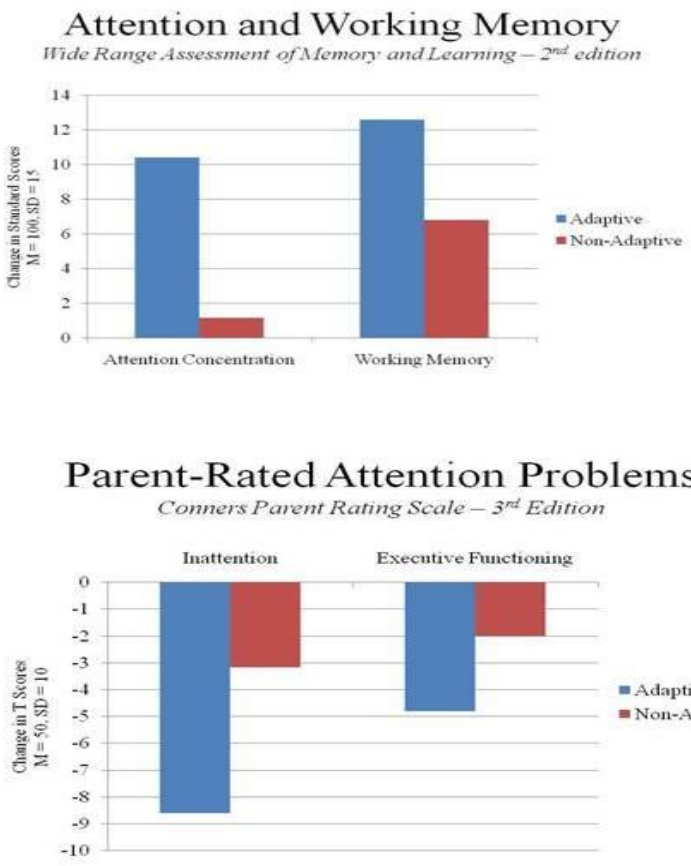


Figure 3: Pre-post change scores on outcome measures for pediatric ALL and brain tumor survivors completing adaptive vs. non-adaptive versions of *Cogmed*.

2.4 Summary

The current standard of care is to address survivors' neurocognitive difficulties *after* they appear, either via pharmacological intervention or cognitive remediation, resulting in modest improvements at best. Thus, there is a critical need for novel and efficacious treatment approaches targeted towards mitigating CRT-associated difficulties in this population. Computerized CT has no known adverse effects, will not interact with pharmacological interventions, is cost-effective, and can be easily administered in the home setting with parental oversight. If such a program is shown to be feasible and efficacious in a sample of pediatric patients at high risk for neurocognitive deficits, the intervention could be rapidly translated to clinical practice.

3.0 ENROLLMENT PROCEDURES AND ELIGIBILITY CRITERIA

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in eRDES. If you have problems with enrollment, refer to online help in the Applications area of the COG Website.

3.1.4 Timing

Patients must be enrolled in the study via eRDES **prior** to baseline testing. After baseline testing, patients meeting criteria for randomization (per Section 4.2) will be randomized prior to starting cognitive training sessions. **Baseline testing followed by randomization must both occur within 2-4 months after completion of CRT**. Cognitive training sessions must be initiated within 2 weeks after completion of baseline testing.

3.1.5 Inclusion of Women and Minorities

Both males and females of all races and ethnic groups are eligible for this study.

3.1.6 Randomization

After baseline testing and within 2-4 months of completing CRT, patients meeting criteria for randomization (see Section 4.2) will be assigned to either **Arm A** (adaptive testing) or **Arm B** (non-adaptive testing). Randomization will be stratified by age (< 8 vs. ≥ 8 years), treatment intensity (whole brain vs. focal radiation) and Coach (A vs. B). Note: the patient's coach assignment can be found on the Eligibility form receipt in eRDES (the field is auto-populated by the system **after** the form has been validated and saved). *Coach A or B assignment at enrollment should not be confused with the assignment to treatment Arm A or B at randomization.*

Treatment randomization is accomplished by completing the Callback in eRDES (refer to instruction on the Case Report Forms for details). The Callback must be completed prior to initiation of study treatment.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

INCLUSION CRITERIA

3.2.1 Age

The patient must be aged 6 to 16 years at study enrollment, inclusive.

3.2.2 Diagnosis and Treatment

Patient must be newly diagnosed or relapsed/progressed with a brain tumor that has not previously been treated with CRT.

***Note**: COG therapeutic study participation is not required for ACCL10P1 enrollment.*

3.2.3 Timing

Patient enrollment must occur within 4 calendar months following completion of CRT.

***Reminder:** after patient enrollment, baseline testing followed by randomization must occur within 2-4 months after completion of CRT (see Section 3.1.4).*

3.2.4 Training Support

3.2.4.1 The patient must have an identified caregiver who is willing and able to oversee the training practice during the intervention period (i.e., for 5-9 weeks starting approximately 3 months after completion of CRT).

3.2.4.2 The patient must have access to a telephone and phone number where they can be reached.

3.2.5 Language Skills

The patient and caregiver must have reading, speaking and listening comprehension of English.

EXCLUSION CRITERIA

3.2.6 Diagnosis and Treatment

3.2.6.1 Patients with pontine glioma are not eligible.

3.2.6.2 Patients with an estimated survival of less than one year are not eligible.

3.2.6.3 Patients with a history of traumatic brain injury prior to tumor diagnosis are not eligible.

3.2.7 Performance Level

3.2.7.1 Patients with a motor, visual, or auditory handicap that prevents computer use (e.g., unresolved posterior fossa syndrome) are not eligible to participate in this trial.

3.2.7.2 Patients with Full-Scale IQ < 70 per previous testing OR existing diagnosis of/educational classification as a student with an Intellectual Disability are not eligible.

REGULATORY

3.2.8 All patients and/or their parents or legal guardians must sign a written informed consent (patient assent is also recommended when applicable according to each institution's policy).

3.2.9 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PLAN

4.1 Overview of Treatment Plan

Our goal is to establish feasibility and preliminary efficacy of this intervention in a small sample of 60 randomized participants. Patients 6-16 years old newly diagnosed with a brain tumor requiring CRT will be identified for participation in this study by the institutional oncologist, nurses, psychologist, or other member of the healthcare team at each participating site. This age range was selected because it includes children who are old enough to be able to complete the intervention, and young enough to be at substantial risk for CRT-related late effects.[2,5,7,8,48]

Within 2-4 months of completing CRT, enrolled participants will complete baseline measures (see Section 4.7 and Appendix III). Those who meet criteria for randomization per Section 4.2 will be randomized to the intervention arm or an active control group. Almost all participants are expected to be receiving chemotherapy during this period. Randomization will be stratified by known risk factors including age (< 8 vs. ≥ 8),[5] treatment intensity (whole brain vs. focal radiation) and also by Coach (A versus B).[2,48] Reminder: at enrollment participants will be randomized to receive *Cogmed* coaching from one of two coaches (Coach A or Coach B) according to a block randomization schedule. The patient's coach assignment record can be found on the Eligibility form receipt in eRDES (a field auto-populated by the system after the form has been validated and saved).

The design will be a single-blind, dose-controlled trial in which half of the participants will be randomized to the adaptive intervention condition and half will complete training on a non-adaptive comparison computer program. At each assessment (baseline, post-treatment, and follow-up), the person performing any cognitive testing (i.e., computerized assessment and/or the optional psychologist battery) will be blinded to randomization. Given the role of cognitive-behavioral coaching in the CT program, it will not be possible for coaches to be blinded to participants' randomization status, but coaches will not perform any of the pre- or post-training assessments. In our previous work, we had no difficulty maintaining this blind between coaches and examiners. Parents and participants will be blinded to randomization, at least initially. Because they will have been informed that the two study conditions are distinguished by their difficulty level, some parents and/or children may be able to guess their randomization status. Reminder: if patient starts or changes dosage of psychostimulant medications during the study period, patient will be removed off study.

Cogmed (see Appendix II) is a home-based, computerized, interactive, audio-visual CT program. Designed to be completed over 25 training sessions spanning 5-9 weeks, *Cogmed* consists of twelve engaging exercises that target skills involving visuo-spatial and verbal WM (separate versions of the program are available for preschool- and school-aged children). This CT program is particularly appropriate for the pediatric brain tumor population because of its ease-of-use, ability to be completed at home, and established efficacy in other patient

populations.[35,38,41,42] Primary outcomes will include measures of attention and WM. Of note, participants assigned to the non-adaptive condition will complete a modified version of the computerized CT consisting of tasks that never increase in difficulty. If patients do not complete the training within 9 weeks, they will be removed off protocol therapy (see Section 5.1).

Participants will be asked to return to the clinic within three weeks of completing the intervention program for brief follow-up testing; ideally this appointment would be scheduled in conjunction with one of their regular clinic visits. Six months following completion of the intervention patients will return to complete another brief assessment to evaluate stability of any changes over time. At that time, following completion of all testing procedures, families will be informed of whether they received the adaptive or non-adaptive intervention (i.e., participants will be unblinded) and families enrolled in the non-adaptive arm of the study will be given the opportunity to complete the adaptive training at no cost and with the support of a Cogmed-certified coach.

4.2 Criteria for Randomization

Patients must fulfill all criteria listed below to proceed to randomization, otherwise, patient will be off study.

4.2.1 Timing

The maximum period between the end of radiation and randomization is 4 months.

4.2.2 Criteria

4.2.2.1 Patients with evidence of IQ < 70 (from psychologist administered baseline testing or other cognitive testing) OR existing diagnosis of/educational classification as a student with an Intellectual Disability, will not be eligible.

4.2.2.2 Patients diagnosed with any mental health disorder (e.g., depression, anxiety, oppositional defiant disorder) that, in the treating physician or psychologist's opinion, would preclude or take treatment precedence over participation in CT will not be eligible.

Reminder: if a patient starts or changes dosage of a psychostimulant medications, the patient will be taken off study – See Section 5.2.

4.3 Procedures

Three study visits will be required for participation in the study (see Section 4.7). First is the screening/baseline assessment, which will be conducted for all participants following study enrollment. The baseline testing must be performed within 4 months after the completion of CRT. The two remaining study visits are the post-intervention assessment and the follow-up assessment, which will be needed only for participants who meet criteria for randomization and who are randomized. Screening/baseline assessment may include administration of an abbreviated intellectual test battery, a WM battery, and a computerized attention measure (see Appendix III). Parents will complete questionnaire measures regarding their child's adaptive, behavioral, emotional, and attentional functioning. Clinical interviewing will be conducted to clarify any potential problems identified on the questionnaires; final decisions about psychosocial eligibility of children will be made by the evaluating psychologist at each site based on all available data. Participants and their parents will each receive a $15 gift card (or comparably valued prize/compensation) for participation in the screening/baseline assessment. It is anticipated that some children who complete the screening/baseline assessment will not meet randomization criteria based on evidence of

intellectual disability or psychiatric functioning. In the trial of *Cogmed* with survivors, less than 10% of children screened were excluded from participation for these reasons.

Participants meeting criteria for randomization will be trained in the use of the *Cogmed* programs in the clinic by study personnel (see below and Appendix II). In order to avoid biasing the sample towards socioeconomically advantaged individuals, participants without dedicated access to an adequate home computer will be provided with a laptop computer or tablet device for the duration of the intervention, regardless of whether they are assigned to the adaptive or non-adaptive arms. Moreover, families without available internet access will be provided with wireless internet cards for the duration of the intervention. The intervention will consist of three to five, 15- to 45-minute sessions (younger children practice for less time) per week for 5 to 9 weeks (total = 25 sessions). If patients do not complete the training within 9 weeks, they will be removed off protocol therapy but will remain on study and will receive the post-intervention and follow-up assessment. Similarly, patients who do not complete the 25 sessions for any reason will receive the post-intervention and follow-up assessment unless they meet Off Study Criteria (see Section 5.0 below). Thus, using an intent-to-treat approach, every effort will be made to obtain post-intervention and follow-up data on every child who is randomized, unless they meet Off Study Criteria.

To assist participants as they complete the intervention, a treatment "coach" will be available to parents and children by phone throughout the intervention period. Weekly phone contact with the coaches will be scheduled so that compliance and feasibility data may be collected and so that any problems (e.g., training issues, adverse events, technical problems) can be addressed efficiently. Of note, *Cogmed* routinely provides technical assistance to individuals using the programs at no additional cost. Additionally, to promote compliance and maintain children's interest in the program, participants will earn $10 gift cards (or comparably valued prizes/compensation) after completion of approximately each third of the training (total = $30). This incentive schedule is similar to the one used in the trial of this program in survivors of childhood cancer, and was associated with a compliance rate of 85%.

4.4 Computerized Cognitive Training Treatment

Cogmed RM and Cogmed JM (see Appendix II) are computer programs that are installed from a CD-ROM and compatible with most Windows-based computers. They are commercially available to qualified practitioners through *Cogmed*; Dr. Hardy has already received training and certification as a practitioner and has experience treating children on a previous NCI study (R03-CA132570). The program consists of twelve visually engaging and interesting exercises that target skills involving visuo-spatial and verbal WM. Difficulty of the tasks is automatically adjusted on a trial-by-trial basis throughout each training session to match a child's current WM such that as the child becomes more proficient, the exercises become more difficult. *Cogmed RM* is designed for children aged 8 to 18 and *Cogmed JM* is the preschool version of the computer program (ages 4 to 7).

Throughout training, the child's assigned intervention coach has online access to detailed information about his or her training sessions. Specifically, coaches can see when and how long children trained, and the outcome (pass or fail) of each of the 120 trials children complete during a single training session. Using this information, coaches can modify the training sequence or make suggestions to the child and/or parent about how progress can be maximized (e.g., by taking a short break after three failed trials to prevent frustration). Strategies to promote treatment success and compliance are based on cognitive-behavioral principles (e.g., positive reinforcement, self-encouragement, problem-solving). Families will have phone meetings at least once per week with an intervention coach to ensure

compliance, track progress, provide feedback and answer any questions that may have arisen during treatment.

4.5 Neuropsychological and Behavioral Measures

4.5.1 Study Instruments

The instruments used are listed in Table 1 below, and described in Appendix III. If your institution does not have access to all test instruments specified in Appendix III, it may be possible to borrow the test materials. Loaning of test kits will be dependent upon availability. **Please note that only English test kits and materials are available for loan.** At least 3 weeks prior to the date of assessment, contact [redacted] with your request for materials.

4.5.2 Baseline Testing, with and without Optional Psychologist Portion

The full list of study assessments to be completed at baseline are presented below in Table 1.

For sites participating in the psychologist portion (optional): a brief neuropsychological/behavioral assessment will be conducted at baseline to establish that children are cognitively and psychologically eligible for participation, and in order to document individual and family variables that later may be found to relate to feasibility. Specifically, children will complete neuropsychological measures and a psychiatric interview will be conducted by a study psychologist at each site to determine whether the child meets criteria for any DSM-5 mental health disorder that, in the psychologist's opinion, would contraindicate participation in the intervention. For example, a child with significant performance anxiety may be excluded if the evaluating psychologist feels that study participation was likely to increase the child's anxiety during training. Thus, the intent would be to avoid enrolling children for whom cognitive training may exacerbate existing, clinically significant mood or behavioral symptoms. The baseline assessment will require 60-90 minutes.

Note that, if a site is not participating in the optional psychologist-administered battery, a member of the child's medical or psychosocial support team may provide approval for the child to participate in the study, based on available information about the child's current or prior mental health. Dr. Hardy may be contacted prior to participant enrollment with any questions about what parameters should be considered before approving a child for participation.

4.5.3 Post-Intervention and 6-month Follow-up Assessments

CogState, a brief, computerized assessment of memory functioning will be administered following the intervention (at approximately 5 months post-CRT) and again 6 months following the completion of the intervention. The computerized testing can be administered by any individual who completes online training for CogState or who has already completed online training for any of the other COG trials for which CogState has been used (i.e., AAML1331, AALL1131, ACCL0922). Parents/caregivers will also asked to complete the BRIEF and the Feasibility Interview at these timepoints. Testing will require approximately 20-30 minutes at each timepoint. The child will also complete the Feasibility Interview

at the post-intervention assessment, and the parent will complete the Computer Use questionnaire and ABAS-3 at the 6-month follow-up.

Optional Testing: It is highly recommended that the psychologist-administered measures also be administered, if possible, following the intervention (at approximately 5 months post-CRT) and again 6 months following the completion of the intervention. Measures were selected to be compatible with COG ALTE07C1, when possible, in order to be consistent with the Behavioral Science Committee's resolution to streamline assessments, promote higher compliance with neurocognitive study aims, reduce costs, and increase the ability to compare findings across COG-supported studies. The psychologist-administered post-intervention assessments will require about 30 minutes each. At each institution, a psychologist or neuropsychologist will oversee this optional testing.

4.6 Feasibility Interview

For a previous trial with survivors of childhood cancer (R03-CA132570), a 13-item survey (see Appendix VA and VB) for parents and children was developed and utilized to assess technical feasibility, adherence, satisfaction, and ease-of-use. The Feasibility Interview will be completed by the parent by phone following Session 12. Additionally, both child and parent will complete a second interview during the post-intervention assessment. See Table 1 below.

4.7 Testing Schedule

Table 1 presents the assessments to be completed by study timepoint. See Appendix III for a description of the study instruments. The assessments should be administered in the order listed in Table 1.

Table 1: Testing Schedule

Testing Session	Child	Parent
Baseline	- CogState ***Optional (psychologist-administered) measures***: - WISC-V (Block Design, Vocabulary, Digit Span, Coding, Symbol Search, and Spatial Span subtests) - CMS (Dot Location and Faces subtests) - CVLT-C - Instructional WM	- Socioeconomic Status Measure - Computer Use Questionnaire - COG Language Questionnaire - BASC-3 - BRIEF - ABAS-3 - BIS
Following CT Session 12		- Feasibility Interview
Post-Intervention	- Feasibility Interview - CogState ***Optional (psychologist-administered) measures***: - WISC-V (Digit Span, Coding, Symbol Search, and Spatial Span subtests) - CMS (Dot Location and Faces subtests) - Instructional WM	- Feasibility Interview - BRIEF
6-Month Follow-Up	- CogState ***Optional (psychologist-administered) measures***: - WISC-V (Digit Span, Coding, Symbol Search, and Spatial Span subtests) - CMS (Dot Location and Faces subtests) - CVLT-C - Instructional WM	- Computer Use Questionnaire - BRIEF - ABAS-3

4.8 Feedback to Participants

The study psychologist at each site will inform the health care providers of participants who receive scores in the bottom 7% (i.e., 1.5 SD below the mean) relative to the standardization sample on the WISC-V estimated IQ, WISC-V Working Memory Index, WISC-V Processing Speed Index, or the BRIEF Metacognitive or Behavioral Regulation Indices, given that extreme scores on these measures may reflect significant difficulties that can interfere with learning. When children receive scores at or more extreme than 1.5 SD from the mean, their health care team will be informed of the results in the form of a letter listing the scores of concern. In this way, the health care team can follow up with families to determine if further assessment is warranted based on whether or not families are observing difficulties in their child's functioning at home or in school, and make a referral as they would normally do when families report concerns of this kind.

This feedback requirement will not apply to sites that are not completing the optional psychologist-administered portion of the testing visits.

5.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

5.1 Criteria for Removal from Protocol Therapy

a) Refusal of further protocol treatment by patient/parent/guardian.
b) Completion of planned study treatment.
c) Physician determines it is in patient's best interest.
d) Patient does not complete the computerized cognitive training within 9 weeks.
e) Development of seizures or change in functional status that will prevent patient from completing further treatment or assessments.
f) Progressive disease or relapse

5.2 Off Study Criteria

a) Death
b) Lost to follow-up (prior to 6-month follow-up testing)
c) Completion of all study assessments.
d) Withdrawal of consent for any further data submission.
e) Patient did not meet criteria to proceed to randomization.
f) Patient is started on psychostimulant medications or change in dose of psychostimulant medication.
g) Patient refuses randomization

6.0 STATISTICAL CONSIDERATIONS

6.1 Statistical Design

This primary goal of the study is to establish feasibility of a home-based computerized cognitive training program *Cogmed*, on patients 6 to 16 years of age with pediatric brain tumors and undergoing CRT. Within approximately 2-4 months of completing CRT, patients meeting criteria for randomization will be randomized 1:1 to Arm A the intervention arm (adaptive program) or Arm B the active control arm (non-adaptive program). Randomization will be stratified by known risk factors including age (< 8 years vs. ≥ 8 years), treatment intensity (whole brain vs. focal RT) and also by Coach (A versus B).[2,48] Randomized patients are expected to complete 25 training sessions over 5 to 9 weeks, and then complete a post-

intervention testing and a 6-month follow-up testing. The treating psychologist and/or the individual performing computerized cognitive testing must be blinded for testing.

6.2 Patient Accrual and Expected Duration of Trial

The study accrual target is 60 randomized patients evaluable for the primary endpoint of intervention compliance. It is anticipated that some children who complete the baseline assessment will not meet the eligibility criteria for randomization based on evidence of intellectual disability or psychiatric functioning. In the trial of *Cogmed* with survivors, less than 10% of children screened were excluded from participation for these reasons.

Randomized patients who are removed off protocol therapy for medical reasons (relapse/progression, death, physician's determination in the patient's best interest, development of seizures or other change in functional status, or starting or changing the dose of psychostimulants) would be deemed inevaluable for the primary compliance endpoint. Therefore, using an estimate of 15% for screen failures and inevaluable patients, we project that we may need to enroll up to 71 participants.

With enrollment open to all institutions within COG, we anticipate that our goal of accruing 60 evaluable patients from those eligible is feasible within two years after Amendment #1 is activated. There are very few on-therapy cognitive intervention trials from which to base an estimate of feasibility, though at St. Jude Children's Research Hospital, recruitment to SJMB03, which has a reading-based intervention program embedded in the study, was strong. Specifically, 64% of children enrolled on the protocol have been randomized to either the treatment or standard-of-care arm of that protocol. The primary reasons that children were not randomized, in order of frequency, included 1) age outside the inclusion criteria, 2) poor medical status (including posterior fossa syndrome), 3) non-English speaking, and 4) parents did not consent to randomization (Shawna Palmer, study PI, personal communication on Oct. 29, 2010). We anticipate that parents of children receiving cranial radiation therapy will be aware of the potential risks of neurocognitive late effects, and that at least one quarter of these parents will be willing to have their children participate in a cognitive intervention trial, particularly since it is home-based. The project has the strong support of the Behavioral Sciences Committee, and we have identified key personnel at each site who can help to inform colleagues about the study and motivate referrals of eligible patients.

6.3 Statistical Analysis Methods

6.3.1 Endpoints

Primary endpoint is intervention compliance defined as at least 80% of sessions completed (i.e., completing at least 20 sessions within 9 weeks of starting training). The target is to have at least 75% of the participants compliant with intervention.

Secondary endpoints on subjective and objective measures of attention and WM include parent-rated executive function and WM using the Metacognition subscales from the BRIEF, the measure of executive function using the Groton Maze Learning task of the CogState battery and measure of WM by the one-back task from CogState. In addition, for participants who have participated in the optional psychologist-administered battery, we will analyze the measure of WM using Digit Span from Wechsler Intelligence Scales, measures of verbal and visual memory using Dot Location from Children's Memory Scale Spatial Span from Wechsler Scale.

Secondary endpoints on feasibility are the item responses to the 13-item Feasibility Interview assessing technical feasibility, adherence, satisfaction and ease of use.

6.3.2 Power Considerations

Because there is no evidence that a home-based, computerized CT program will be feasible for this population and in multiple COG institutions, our primary aims are to evaluate the program's ease of use and participant compliance, which we will define as 80% of sessions completed within 9 weeks of starting treatment. The goal is to have at least 75% of participants being compliant (i.e., completing 20 or more of the 25 sessions). Randomized patients who are removed off protocol therapy for medical reasons (relapse/progression, death, physician's determination in the patient's best interest, development of seizures or other change in functional status, or starting or changing the dose of psychostimulants) would be deemed inevaluable for the primary compliance endpoint. With 60 evaluable participants, if the true compliance rate in the study participants is 59%, the power to detect such decrease from the target 75% compliance rate is 0.82. Power consideration is based on a Z-test for binomial proportion with continuity correction at 1-sided level of 0.05.

6.3.3 Analysis Plan

Compliance rate (the portion of patients who complete at least 80% of the sessions within 9 weeks) will be calculated for the overall study population and each arm separately. Z-test for binomial proportion with continuity correction will be used to examine if the overall compliance rate is lower than the target of 75%. Confidence intervals of the estimated compliance rate will be constructed for the overall study population and for each arm separately. We will use Fisher's exact test to examine if there is any significant difference in the compliance rate between the 2 arms. Compliance data on the number of sessions completed for all patients and for patients on each arm will also be described by summary statistics such as mean or median, and compared between the 2 arms by two-sample t-test or Wilcoxon rank sum test. We will use descriptive and summary statistics to report parent and child ratings of the intervention's technical feasibility, ease-of-use, and satisfaction across the three time-points that this information is collected. In addition, we will use descriptive and summary statistics to detail the total number of patients enrolled, determine rates and reasons for non-eligibility and patient refusal for randomization, characterize socioeconomic status of the parents and computer usage for the patients and evaluate the number and type of adverse incidents reported through the questionnaires (if any). We will use a series of t-tests (for continuous variables) and Chi-square tests or Fisher's exact tests (for non-continuous variables) to examine potential differences between eligible patients who accept or decline to be randomized to the treatment phase, between participants who are compliant (i.e., 80% of sessions completed) and noncompliant, and for other medical, psychosocial, and contextual factors.

The analysis of preliminary efficacy will be conducted on an intent-to-treat basis. We will use descriptive/summary statistics to summarize the objective and the subjective measures of attention and WM in each arm and the differences between the 2 arms on the post-intervention/6-month assessment or on the difference between the post-intervention/6-month assessment and the baseline assessment. Linear regression models using the post-intervention/6-month assessment as outcome will also be used to estimate the effect size of intervention with adjustment for potential confounders including the baseline assessment. Linear

mixed model analyses which include measures at all time-points will also be considered to examine and estimate the effect size of the intervention with adjustment for within-patient dependence of the measures over time. We will also explore in various regression models which medical, psychosocial, and environmental factors are related to feasibility, acceptability, and short-term efficacy of the intervention. In particular, age of the participants and socioeconomic status measures which are potentially important predictors will be examined in these models.

6.4 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Racial Categories	DOMESTIC PLANNED ENROLLMENT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	4	5	0	0	9
White	16	27	3	5	51
More Than One Race	0	0	0	0	0
Total	21	32	3	5	61

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	3	6	0	0	9
More Than One Race	0	0	0	0	0
Total	3	7	0	0	10

7.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection*". A submission schedule is included.

7.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. CDUS reporting is not a responsibility of institutions participating in this trial.

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APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at: https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Requirements for ACCL10P1 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- IROC Credentialing Status Inquiry (CSI) Form
  NOTE: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab
→ Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

APPENDIX II: COGMED RM AND COGMED JM

Cogmed RM and Cogmed JM are computer programs installable from a CD-ROM and compatible with any Windows-based computer or tablet device. They are commercially available to qualified practitioners through *Cogmed*; Dr. Hardy has already received training and certification as a practitioner and has experience treating children on the NCI R03-CA132570 study. The program consists of twelve visually engaging and interesting exercises that target skills involving visuo-spatial and verbal WM. Difficulty of the tasks is automatically adjusted on a trial-by-trail basis throughout each training session to match a child's current memory span, such that as the child becomes more proficient, the exercises become more difficult. *Cogmed RM* is designed for children aged 8 to 16. Exercises have space and robot themes with names such as "Decoder," "Space Whack," and "Visual Data Link." For example, "Asteroids," a visuo-spatial WM exercise, consists of a number of asteroids floating through space. The asteroids light up in a random order, after which the child is asked to click on the asteroids in the order in which they just were highlighted. When done correctly, the highlighted asteroids explode. In "Stabilizer," a verbal memory exercise, children hear a series of letters while lights illuminate with each letter. Then, when the letter appears on the screen, the child must select the correct light that was originally paired with that letter. *Cogmed RM* also contains a game, "Robo Racing," that children can play at the end of each session as a reward for completing their session. Children are encouraged to perform well during their training session to earn more "energy" that can later be used during the reward game. *Cogmed JM* is the preschool version of the computer program, designed for children aged 4 to 7 years (see Figure 1 for an example exercise).

Figure 1 Cogmed JM activity – "Ferris Wheel"
Adapted from www.cogmed.com

In each version of the intervention, children complete 25 training sessions. Children are asked to complete between 3 and 5 sessions per week, so the total treatment time to complete 25 sessions may range from 5 to 9 weeks. For children completing *Cogmed RM*, sessions typically last between 25 and 45 minutes, depending on the child's working memory span. For younger children completing *Cogmed JM*, sessions are designed to be shorter in accordance with young children's cognitive stamina; thus, younger children's training sessions typically last about 15 minutes.

Throughout training, the child's intervention coach has online access to detailed information about his or her training sessions. Specifically, coaches can see when and how long children trained, and the outcome (pass or fail) of each of the trials children complete during a single training session. Using this information, coaches can modify the training sequence or make suggestions to the child and/or parent about how progress can be maximized (e.g., by taking a short break after three failed trials to prevent frustration). Families will have phone meetings at least once per week with an intervention coach to ensure compliance, track progress, provide feedback and answer any questions that may have arisen during treatment. Coaches will also have an assessment script for these calls, for re-evaluating medical, psychological, and environmental factors that may potentially be related to feasibility and efficacy of the intervention.

Treatment compliance: The *Cogmed* programs automatically track the number and length of children's sessions, along with their progress through program levels. This is accomplished through the Internet, every time the child logs into the program. For those families without home-internet access, they will be asked to connect the program after every 3rd session from a library or commercial establishment with free wireless internet access. To date, participants on our survivor trial (R03-CA132570) have had no difficulty uploading data over the course of the intervention, and thus we anticipate no difficulty in the proposed project. To promote compliance and maintain children's interest in the program, participants will earn a $15 gift card (or comparably valued prize/compensation) for participating in the baseline testing. In addition, participants will earn $10 gift cards (or comparably valued prizes/compensation) after session numbers 9, 18, and 25. The participant and their parent will each receive $15 (gift cards/prizes) for completing the post-intervention and follow-up testing.

APPENDIX III: STUDY ASSESSMENT INSTRUMENTS

Note: Study measures were chosen to overlap with those used in ALTE07C1, with the addition of the computerized CogState battery, which was chosen given its ability to be administered repeatedly over short intervals with negligible practice effects. The measure assigned initially by age will be used during the study even if the patient could move up to the next age level.

IQ*	Attention/ Working Memory	Verbal Memory	General	Parent Report
WISC-V** (Block Design Vocabulary)	CogState	CVLT-C**	Feasibility Interview	Feasibility Interview
	CMS** (Dot Location and Faces)			BASC-3*
	WISC-V** (Digit Span, Coding, Symbol Search, and Spatial Span subtests)			BRIEF
	Instructional WM**			ABAS-3
				BIS
				Socioeconomic Status Measure*
				Computer Use Questionnaire
				COG Language Preference Questionnaire

* Baseline only
** Optional psychologist-administered measure

Patient-Completed Measures

Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V)[49-51]. The WISC-V measures intellectual functioning in children aged 6-16 (WISC-). For this project, the Vocabulary and Block Design subtests will be used at baseline only to estimate IQ. Additionally, working memory (Digit Span, Spatial Span), Coding and Symbol Search subtests will be administered at all time points for sites that have a psychologist to administer these measures.

Children's Memory Scale (CMS)[52]. The CMS is a test to assess verbal and visual memory in individuals 5-16 years of age. Dot Location and faces will be administered at all timepoints for sites that have a psychologist to administer these measures.

California Verbal Learning Test – Children's Version (CVLT-C)[53,54]. The CVLT-C involves verbally presenting a list learning task over the course of 5 trials. The test measures multiple aspects of how verbal learning occurs, or fails to occur, as well as the amount of verbal material learned. The CVLT-C is designed for individuals 5-16 years of age. The CVLT-C will be administered at baseline and 6-month follow-up for sites that have a psychologist to administer these measures.

CogState is a computerized testing software package that offers a range of semi-automated assessment modules for individuals aged 6-90 (www.cogstate.com). The software can be installed on most computer systems and can be proctored by a research assistant with minimal training. Data are automatically uploaded, scored, and stored. Test batteries can be fully customized, and include tasks tapping visual motor, processing speed, visual attention, visual and verbal learning and memory, and working memory. A battery suitable for evaluating the core neurocognitive processes affected by cancer treatment would take between 12-18 minutes. Reliability is .77 with no practice effects when testing intervals are greater than one month[55]. Age-based standard scores (mean = 100, SD 10) are computed for each task based on a normative sample of several hundred individuals. CogState tasks have been used successfully in trials of populations relevant to pediatric cancer patients[56]. Specifically, it has been used with attention deficit hyperactivity disorder participants, for which CogState tasks discriminate between those with and without the diagnosis, and those on and off medication[57], as well as typically-developing children[58]. In addition, CogState has been used in samples of patients with concussions[59], HIV/AIDS[60], pediatric cerebral malaria[61], and adult cancer patients[62]. CogState is also currently being used in a multi-site trial funded by NCI to examine neurocognitive symptoms in long-term survivors of pediatric cancer. CogState will be administered at all time points.

Instructional Working Memory Task (Instructional WM). The Instructional WM is a brief task administered to children to evaluate functional application of WM skills. Children are asked to use task props (e.g., pencils, folders, etc.) to follow an increasingly complex set of instructions. For example, a child might be asked to "Pick up the blue ruler and put it in the red folder". Scores are calculated based on a combination of accuracy in following the instructions weighted by how many actions the child is asked to perform with a single command. The instructional WM will be administered at all time points for sites that have a psychologist to administer these measures.

***Feasibility Interview*:** In our previous trial with survivors of childhood cancer (R03-CA132570), we developed a 13-item survey for parents and children assessing technical feasibility, adherence, satisfaction, and ease-of-use. The Feasibility Interview will be completed by the parent by phone after session 12. Additionally both child and parent will complete a second feasibility interview during the post-intervention assessment.

Parent-Completed Measures

COG Language Preferences Questionnaire. The child's language preference will be determined before testing begins using the parent-completed COG Language Preference Questionnaire. In order for the child to be enrolled, it must be determined that the neuropsychological testing procedures can be completed in English. If a parent is unable to complete the parent-report measures in English, the child will still be allowed to enroll but parent-report data will not be obtained. The COG Language Preference Questionnaire can be accessed on the COG website at:
https://www.cogmembers.org/Prot/ALTE07C1/ALTE07C1COGlanguageprefquestionnaire.pdf.

Behavior Assessment System for Children, 3rd edition (BASC-3)[63]. The BASC-3 describes the behaviors, thoughts, and emotions of children and adolescents. The parent rating scale will be utilized for individuals older than 2 years and less than 18 years of age. The questionnaire yields composite and scale scores in the domains of externalizing, internalizing, school, and other problems as well as adaptive skills and behavioral symptoms. The BASC-3 will be administered only at baseline.

Behavior Rating Inventory of Executive Functioning (BRIEF)[64,65] is a parent-completed measure of behavioral executive functioning. For this study, items from the Metacognition subscales will be used. The BRIEF will be administered at all time points as an additional outcome measure.

Adaptive Behavior Assessment System, 3rd edition (ABAS-3)[66]. The ABAS-3 will be used for the assessment of adaptive skills in individuals older than 2 years and less than 18 years of age. Separate scale scores are available for 10 areas of adaptive skills. The ABAS-3 will be administered at baseline and 6 months following the completion of training.

Brief Impairment Scale (BIS)[67]. The BIS is a parent-completed, 23-item questionnaire evaluating social and functional impairment yielding scale scores for Interpersonal, School, and Self (personal) functioning. The BIS will be administered at baseline only.

Feasibility Interview**:** In our previous trial with survivors of childhood cancer (R03-CA132570), we developed a 13-item survey for parents and children assessing technical feasibility, adherence, satisfaction, and ease-of-use. The Feasibility Interview will be completed by the parent by phone. Additionally the child will complete a feasibility interview during the post-intervention assessment.

Socioeconomic Status Measure: The Socioeconomic Status measure is a brief measure consisting of questions related to parents' marital status, education, and work. This measure will be completed by parents at baseline only.

Computer Use Questionnaire: The Computer Use questionnaire assesses the frequency and nature of the child's computer use at home and at school. It will be completed by parents at baseline and at 6-month follow-up.

APPENDIX IV: SOCIOECONOMIC STATUS MEASURE

Obtain at Baseline.

Subject:_____ Subject ID: _____

Date:_____

We would like to ask you a few questions about yourself and your family. The questions ask about educational background and current work. Please answer all of the questions as completely as possible.

1. Are you (please check all that apply):
   - ☐ Single: (Please specify further)
     - ☐ Never married
     - ☐ Separated
     - ☐ Divorced
     - ☐ Widowed
   - ☐ Married: (Please specify further)
     - ☐ To the other parent of my child with brain tumor
     - ☐ To someone else
   - ☐ Living with a significant other/partner: (Please specify further)
     - ☐ With the other parent of my child with brain tumor
     - ☐ With someone else
   - ☐ Not living with, but have a partner: (Please specify further)
     - ☐ The other parent of my child with brain tumor
     - ☐ Someone else
   - ☐ In a civil union

2. If you are not living with the other parent of your child, how often does that parent see your child?
   - ☐ Not applicable, I live with the other parent
   - ☐ Less than once per month
   - ☐ A few times per month
   - ☐ About once per week
   - ☐ A few times per week
   - ☐ Almost every day

3. What was the highest grade or level of school that the main caregiver has completed?
   - ☐ Grade school (grades 1-8)
   - ☐ High school, but didn't graduate
   - ☐ High school, completed
   - ☐ Training after high school, other than college
   - ☐ Some college
   - ☐ College graduate
   - ☐ Post graduate level
   - ☐ Unknown

5a. What kind of work are you doing? (What is your occupation?)

(For example: homemaker, retail sales, machinist, etc.)

5b. What are your most important activities or duties?

(For example: selling merchandise, filing, supervising, etc.)

5c. What kind of business or industry is this?

(For example: retail shoe store, automobile manufacturing, state labor department, etc.)

PLEASE SKIP #6 and 7a, b, c if you are living alone.

6. What was the highest grade or level of school your spouse/significant other has completed?

- ☐ Grade school (grades 1-8)
- ☐ High school, but didn't graduate
- ☐ High school, completed
- ☐ Training after high school, other than college
- ☐ Some college
- ☐ College graduate
- ☐ Post graduate level
- ☐ Unknown

7a. What kind of work is your spouse (significant other) doing? (What is his/her occupation?)

(For example: homemaker, retail sales, machinist, etc.)

7b. What are his/her most important activities or duties?

(For example: selling merchandise, filing, supervising, etc.)

7c. What kind of business or industry is this?

(For example: retail shoe store, automobile manufacturing, etc.)

APPENDIX VA: PARENT FEASIBILITY AND ACCEPTABILITY INTERVIEW

Obtain Following CT Session 12 and After Training Completion

Subject: _____ Subject ID: _____

Date: _____ Session: 12 25

Respondent: _____

Technical feasibility:

1. Did the computer program work every time you tried it? Yes No

   a. If no, please describe problems: _____

   _____

   _____

2. Did you have any problems with the computer itself? Yes No

   a. If yes, please describe problems: _____

   _____

   _____

Adherence:

1. How often did your child resist/protest/complain about completing exercises on the computer this month?

   Never Rarely Sometimes Often Always

2. How did you typically respond to your child when s/he resisted doing exercises?

_____

_____

3. Do you think your child would have completed the exercises even without the opportunity to earn a gift card? Why or why not?

_____

_____

_____

a. Which of the following might make your child more likely to complete all the exercises?
_____ More money on the gift cards.
_____ More frequent rewards.
_____ Fewer required sessions.
_____ Shorter sessions.

Satisfaction / Ease of use:

1. Using the following scale, how easy or difficult was it for your child to use the computer to do the exercises in the following areas?

very easy somewhat easy neither easy/hard somewhat hard very hard

a. turning on/logging in: _____

b. starting the program: _____

c. using the mouse: _____

2. Using the following scale, how easy or difficult was it for your child to do the exercises?

very easy somewhat easy neither easy/hard somewhat hard very hard

3. Using the following scale, how often were you present with your child while s/he was doing the exercises?

Never Rarely Sometimes Often Always

4. Using the following scale, how often did your child experience physical pain or discomfort while using the computer program?

Never Rarely Sometimes Often Always

If any response other than "never": Please describe the physical pain or discomfort your child experienced: _____
_____
_____

5. Using the following scale, how often did your child experience frustration while using the computer program?

Never Rarely Sometimes Often Always

6. Using the following scale, how often did your child feel bored during the computer exercises?

   Never Rarely Sometimes Often Always

7. Using the following scale, how often did your child enjoy completing the exercises?

   Never Rarely Sometimes Often Always

8. Using the following scale, how satisfied were you with your child's participation in the study this month?

Very dissatisfied Somewhat dissatisfied Neither Somewhat satisfied Very Satisfied

Other comments or concerns: _____

_____

_____

For post-intervention administration only (please transcribe responses electronically):

1. What suggestions do you have about how we could make participating in this intervention easier for children and families?

2. What were the biggest difficulties you experienced in helping your child complete the training?

3. In what ways were the study team (your coach, the psychologist, the research assistant) most helpful to you during the study and intervention?

4. Was there anything you found unhelpful as you and your child participated?

APPENDIX VB: CHILD FEASIBILITY AND ACCEPTABILITY INTERVIEW

Obtain After Training Completion

Subject: _____ Subject ID: _____

Date: _____

1. Using the following scale, how often did you feel frustrated while using the computer program?
   - ☐ Never
   - ☐ Rarely
   - ☐ Sometimes
   - ☐ Often
   - ☐ Always

2. Using the following scale, how often did you feel bored during the computer exercises?
   - ☐ Never
   - ☐ Rarely
   - ☐ Sometimes
   - ☐ Often
   - ☐ Always

3. Using the following scale, how often did you enjoy the computer exercises?
   - ☐ Never
   - ☐ Rarely
   - ☐ Sometimes
   - ☐ Often
   - ☐ Always

Comments:
_____
_____

APPENDIX VI: COMPUTER USE QUESTIONNAIRE

Obtain at Baseline and 6 months following the completion of training.

1. How often does your child use a computer at school?
    a. Every day or nearly every day
    b. 2-3 times per week
    c. Once per week
    d. Occasionally, but less than once per week
    e. Very rarely
    f. Don't know

2. How often does your child use a computer at home?
    a. Every day or nearly every day
    b. 2-3 times per week
    c. Once per week
    d. Occasionally, but less than once per week
    e. Very rarely
    f. No home computer

3. If your child uses a computer at home, which of the following activities does your child use the computer for (circle all that apply)?
    a. Homework
    b. Video games
    c. Educational activities other than homework
    d. Email or social networking
    e. Watching video content
    f. Browsing for news, entertainment, or informational content

4. How many hours does your child spend on the computer each week at home?
    a. Less than 1
    b. 1-3
    c. 4-7
    d. 8-14
    e. More than 14 hours per week

APPENDIX VII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ACCL10P1
(for children from 7 through 12 years of age)

Study of Computerized Cognitive Training for Children with Brain Tumors

1. We have been talking with you about your planned cancer treatment that includes radiation therapy to your head. Radiation therapy to your head is a cancer treatment that can affect your thinking, learning and remembering. These kinds of effects can make it harder for you to learn in school.

2. We are asking you to take part in a research study because you are scheduled to get radiation therapy to your head to treat your cancer. A research study is when doctors work together to try out new ways to help people who are sick. This study will look to see if a treatment called cognitive training will get rid of effects on your thinking, learning and remembering you might have from the radiation therapy.

3. Children who are part of this study will complete 25 cognitive training sessions for your thinking and remembering. The training sessions are different kinds of computer games. You will complete the sessions at home using a computer or tablet. The sessions will happen over 5 to 9 weeks. You will assigned to either the adaptive or non-adaptive cognitive training program. You will not be told which of these 2 programs you are assigned.

4. Before you start the training sessions you will have some tests for your thinking, learning and remembering. Soon after you finish the training sessions you may have some more tests of your thinking, learning and remembering. And about 6 months after you have finished the training sessions, you may have some more tests of your thinking, learning and remembering. Then you will have finished being in this study.

5. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is less effects on your thinking and remembering from the cranial radiation therapy, but we don’t know for sure if there is any benefit of being part of this study.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risk to you from being in this study is that you may find the training sessions or the testing to be boring or tiring. The study may also remind you about other problems you are having.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. Make sure to ask your doctors any questions that you have.

INFORMATION SHEET REGARDING RESEARCH STUDY ACCL10P1
(for teens from 13 through 17 years of age)

Computerized Cognitive Training for Pediatric Brain Tumor Patients: A Pilot Study

1. We have been talking with you about your planned cancer treatment that includes cranial radiation therapy. Cranial radiation therapy is a cancer treatment that can affect your ability to think, learn and remember. These kinds of effects can make it harder for you to learn in school.

2. We are asking you to take part in a research study because you are scheduled to get cranial radiation therapy to treat your cancer. A research study is when doctors work together to try out new ways to help people who are sick. This study will look to see if a treatment called cognitive training will get rid of effects on your thinking, learning and remembering you might have from the cranial radiation therapy.

3. Children and teens who are part of this study will complete 25 cognitive training sessions. The training sessions are different kinds of computer games. You will complete the sessions at home using a computer or tablet. The sessions will happen over 5 to 9 weeks. You will assigned to either the adaptive or non-adaptive cognitive training program. You will not be told which of these 2 programs you are assigned.

4. Before you start the training sessions you will have some tests for your thinking, learning and remembering. Soon after you finish the training sessions you may have some more tests of your thinking, learning and remembering. About 6 months after you have finished the training sessions, you may have some more tests of your thinking, learning and remembering. Then you will have finished being in this study.

5. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is less effects on your thinking, learning and remembering from the cranial radiation therapy, but we don’t know for sure if there is any benefit of being part of this study.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risk to you from being in this study is that you may find the training sessions or the testing to be boring or tiring. The study may also remind you about other problems you are having.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. Make sure to ask your doctors any questions that you have.