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Running Head: Executive Function Intervention for Children with CHD

Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: Protocol for a Randomized Controlled Trial of Working Memory Training

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Abstract

Introduction: Executive function (EF) impairments are among the most prevalent neurodevelopmental morbidities in youth with congenital heart disease (CHD). To date, no studies have been undertaken to investigate the efficacy of cognitive interventions aimed at improving EF outcomes in children with CHD.

Methods and analysis: This is a single center, single-blinded, two-arm randomized controlled trial to test the efficacy of Cogmed Working Memory Training (Cogmed) *versus* standard of care in children with CHD after open-heart surgery in infancy. Participants will consist of 100 children with CHD aged 7-12 years who underwent open-heart surgery before the age of 12 months. Participants will be randomly allocated to either an intervention group including training on the home-based Cogmed intervention for a duration of approximately 5 weeks or a control group who receive the standard of care for children with CHD. We seek to evaluate the efficacy of Cogmed at post-treatment and 3-months after completion of the intervention. Baseline, post-treatment, and 3-month follow-up assessments will include specific measures of EF, cognitive and social functioning, and ADHD symptoms. The primary outcome of this study will be the change in standardized mean score on the List Sorting Working Memory test from the NIH Toolbox for the Assessment of Neurological and Behavioral Function. Secondary outcomes will include measures of social skills, inhibitory control, cognitive flexibility, and behavioral EF as well as ADHD symptoms as measured by the Behavior Rating Inventory of Executive Function, Second Edition and the Conners 3rd Edition. The efficacy of the intervention will be evaluated by comparing within-subject differences (baseline to post-treatment, baseline to 3-month follow-up) between the two groups using an intention-to-treat analysis.

Ethics and dissemination: This study has received full Institutional Review Board (IRB) approval from Boston's Children's Hospital IRB (P00022440) and has also been reviewed and approved by the Human Protection Agency from the US Department of Defense.

Trial Registration Number: NCT03023644

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Strengths and limitations of this study

- To our knowledge, this is the first randomized controlled trial (RCT) investigating the efficacy of an executive function intervention in improving outcomes for children with congenital heart disease (CHD).
- The home-based Cogmed Working Memory Training (Cogmed) is among the most widely-used evidence-based programs targeting core executive function skills and will directly address the most frequent neurodevelopmental impairment for children with critical CHD that strongly impacts their ability to succeed in academic and social environments.
- This intervention will be individually adapted to each child's own executive function level, which ensures an optimal level of performance throughout the sessions.
- As a home-based intervention, Cogmed reduces the need for hospital-based treatment visits, potentially reducing the burden for families of children with chronic health conditions such as critical CHD.
- This RCT will include computerized individual measures of neurodevelopment and parent- and teacher-rating scales of behavioral and social outcomes as well as collection of patient-specific factors to investigate their potential relationship with response to treatment.

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INTRODUCTION

Congenital heart lesions are among the most common birth defects,[1-2] with approximately 1% of infants born with congenital heart disease (CHD). Of these, more than one-third will present with critical CHD requiring cardiac surgery in infancy.[3] Advances in prenatal diagnosis as well as medical and surgical care have reduced mortality rates for all forms of CHD. However, evidence of central nervous system damage, including delayed brain maturation *in utero* and abnormal brain metabolism and microstructure associated with hypoxic-ischemic injury, has been reported by a wealth of studies of critical CHD.[4-7] A dramatic increase in the population of survivors of infant heart surgery has been accompanied by the increased recognition of their long-term postoperative morbidities. Neurodevelopmental disabilities, particularly executive function (EF) impairments, are currently the most prevalent long-term morbidity in the population with CHD.[4] EF refers to a set of higher-order neurocognitive abilities that serve to coordinate and organize actions towards a goal, allowing the individual to adapt to new or complex situations.[8] Impairments in EF manifest as behavioral dysregulation and attention problems, impaired working memory (i.e., the ability to keep information in mind and manipulate it over a short period of time), and problems with organization and planning abilities. EF is more strongly associated with school readiness than is IQ, predicts both mathematics and reading competence throughout the school years[8-10] and is strongly associated with social cognition (i.e., decoding other people's mental and emotional states and responding to rapid-paced social interactions).[9]

Executive dysfunction can profoundly impact all dimensions of a child's development[11-14] and is a core feature of attention deficit hyperactivity disorder (ADHD)[15] and autism spectrum symptoms.[16-17] If untreated, deficits in EF may also predispose individuals to later addiction,[18]

eating disorders and obesity,[19] and risk-taking behaviors.[20] These adverse sequelae may carry profound implications for the educational achievement, future employment, and quality of life of individuals with CHD.[4] To date, no trials have been undertaken to test treatments aimed at improving executive dysfunction and attention deficits in the CHD population.

EF in critical CHD

Impairments in EF are at the heart of the neurodevelopmental phenotype associated with critical CHD after open-heart surgery.[21-34] EF deficits in children with CHD were first reported in school-aged children with dextro-transposition of the great arteries (d-TGA).[25] Standardized neuropsychological testing showed that patients with d-TGA had substantial difficulty planning and alternating between tasks, which suggested impairments in cognitive flexibility and working memory as well as deficits in planning and sustained attention. On the Behavior Rating Inventory of Executive Function (BRIEF), parents and teachers of adolescents with CHD reported significant difficulties, particularly with regard to working memory.[22] Compared to normative values, parents' ratings were worse by ~0.5 SD and those of teachers by ~1 SD, suggesting not only statistically significant but clinically meaningful impairments. More recent findings also reported specific EF impairments in preschool and school-aged children with d-TGA.[21,23-24] In particular, children had important difficulties in behavioral regulation and cognitive control of attention, and they had worse performances on verbal and visual working memory tasks. Consistent findings have been reported by studies including children with other types of critical CHD such as tetralogy of Fallot[28] or single ventricle physiology requiring the Fontan operation.[29] Finally, EF impairments have been associated with worse psychosocial

health status and worse quality of life in youth with critical CHD,[31] highighting the potential impact of long-term executive dysfunction on mental health in CHD.[32]

Working memory intervention for children with CHD

The American Heart Association (AHA) recommends routine neurodevelopmental screening of all CHD survivors.[4] A burgeoning literature documents the prevalence and importance of impaired EF and ADHD in CHD survivors,[21-40] and brain imaging studies have provided key information on the underlying disturbances in brain structure and microstructure in patients with CHD.[5-7] Yet to date, no trials have been undertaken to test interventions targeting EF and attention deficits in the CHD population.[34]

Cogmed Working Memory Training (Cogmed) is the most widely used computerized evidence-based intervention that targets EF, specifically providing intensive structured training of working memory.[41-54] It has been shown to improve executive performance in several clinical and non-clinical pediatric populations, including children with ADHD,[41-42;46-47] low working memory and low achievement,[43-44] and children who were born preterm or extremely low-birth weight.[53-54] Unlike other hospital- or laboratory-based interventions, Cogmed can be implemented as a home-based intervention for children. Studies using Cogmed have shown that subjects demonstrate the ability to transfer skills to non-trained tests of working memory as well as to tasks that involve similar processes, including attention, inhibition, and non-verbal reasoning.[51-53] The positive effect of training has been observed on parental ratings of inattention, including the DSM-IV Parent Rating Scale, ADHD-RS-IV, BRIEF, and Conners' Parent Rating Scale. Sustained improvements in behavior as measured by rating scales have also been observed in ADHD,[48] brain injury,[49-50] and non-clinical groups.[51-52]

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In summary, several randomized controlled trials evaluating the use of Cogmed in healthy children[44; 51-52] and in children with various conditions[41-42;47;53-54] have demonstrated that this neurocognitive intervention produces significant generalized and sustained enhancement on measures of EF, and also on everyday life learning and behavioral skills. It is proposed that training working memory using Cogmed is a promising intervention for school-aged children with critical CHD because: (1) it addresses the most frequent neurodevelopmental morbidities that strongly impact the ability to succeed in academic and social environments; (2) it allows for intensive and structured practice of targeted skills, with possible transfer to other neurodevelopmental domains; (3) it is individually adapted to each child's own EF levels, which ensures an optimal level of performance throughout the sessions; (4) it is closely monitored, and various parameters of the child's performance are systematically recorded (e.g., correct answers, speed at which tasks are completed); (5) it is child-friendly and rewarding, which facilitates children's compliance; and, finally, but importantly (6) as a home-based intervention, it reduces the need for hospital/clinic-based visits and multiple costs of individual therapy, potentially reducing the burden for families of children with chronic health conditions such as critical CHD.

In this project, we will conduct a randomized controlled trial (RCT) to provide the first proof-of-concept that Cogmed intervention improves neurodevelopmental outcomes in children with CHD, and that the improvements persist to 3 months. We will enroll children with CHD who underwent infant open-heart surgery as this population corresponds to the highest risk category for developmental disorders and disabilities as stated in the AHA guidelines (Class I; Level of Evidence A).[4] We propose to determine post-treatment and longer-term effects on both laboratory-based tests and ecological measures of children's EF, ADHD, and social difficulties

in everyday life. Our study will also provide insight into factors that are associated with response to treatment, identifying children who may be most likely to benefit from the intervention.

Aims and hypotheses

Specific Aim 1: To evaluate the immediate efficacy of home-based Cogmed intervention for neurodevelopmental outcomes in children with CHD. We hypothesize that children who receive the Cogmed intervention, compared with controls receiving standard of care, will display greater improvement from baseline to post-treatment assessment in EF and social development, and greater reduction in symptoms of ADHD.

Our primary outcome measure will be the change in standardized mean score on the working memory test from the National Institutes of Health Toolbox for the Assessment of Neurological and Behavioral Function (NIH Toolbox)[55] from baseline to post-treatment. Secondary outcomes include changes in standardized mean scores on tests of cognitive flexibility, attention, inhibitory control, and speed of processing from the NIH Toolbox; the Global Executive Composite from the Behavior Rating Inventory of Executive Function, 2nd Edition (BRIEF-2)[56], the Global Index and the ADHD Index from the Conners 3rd Edition (Conners-3)[57], and the Social Responsiveness Scale, 2nd Edition (SRS-2).[58]

Specific Aim 2: To assess the longer-term effects of the Cogmed intervention at 3-month follow-up. We predict that significant gains in neurodevelopmental and behavioral outcomes will persist 3 months after cessation of intervention for children who received Cogmed as compared to controls.

The primary and secondary outcomes will be the same as those in Specific Aim 1, except that the change in scores will be from baseline to 3-month follow-up (i.e., approximately 3 months after the last Cogmed session).

Specific Aim 3: To explore cognitive, medical, and sociodemographic factors associated with changes in neurodevelopmental and behavioral scores for children who received Cogmed intervention.

METHODS AND ANALYSIS

Study design

This is a single center, single-blinded, two-arm RCT to test the efficacy of Cogmed intervention *versus* standard of care in children with CHD after neonatal and/or infant open-heart surgery (n=50 in each group). All eligible subjects will undergo a baseline neurodevelopmental assessment and then will be randomly assigned to either the standard home-based Cogmed intervention or to a control group receiving the standard of care for children with CHD. All participants will undergo a post-treatment and a 3-month follow-up assessment. All investigators collecting outcome data will be blinded to patients' group assignment (Cogmed intervention *versus* standard of care) and to medical and surgical histories. For children assigned to the Cogmed group, post-treatment assessments will be performed one to two weeks after the end of the intervention (i.e., approximately 7-8 weeks after baseline assessment) and follow-up will be performed 3 months after the end of the intervention (i.e., approximately 5 months after baseline assessment). For children in the control group, post-treatment and 3-month follow-up assessments will be performed approximately 7-8 weeks and 5 months after baseline assessment, respectively.

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Participants and recruitment

Participants will be included if they meet the following criteria: (1) diagnosis of CHD requiring open-heart surgery before one year of age; (2) age between 7 and 12 years at baseline assessment; (3) ≥6 months post cardiac surgery; (4) had received cardiovascular care at Boston Children's Hospital; (5) English or Spanish speaking; (6) informed consent from parent/guardian as well as assent of the child. Exclusion criteria will be: (1) diagnosed chromosomal anomalies and/or genetic syndromes; (2) severe physical and/or sensory impairments (hearing, visual, or psychomotor) that would prevent the use of the computerized program; (3) confirmed diagnosis of an autism spectrum disorder and/or severe developmental or intellectual disorder that would prevent successful completion of the planned study testing; (4) placement in a separate classroom receiving individual support; (5) scheduled to undergo major cardiac interventions in the 6 months following enrollment; (6) received, receiving, or scheduled to receive Cogmed or any other computerized behavioral training program targeting EF or ADHD. We will not exclude children with a pre-existing neurological history (e.g., epilepsy, stroke) or with a history of a concurrent diagnosis of ADHD (treated or untreated). Rather, we will account for these factors in the data analysis.

Eligible children living in the United States will be recruited through patient databases of Boston Children's Hospital Cardiology Clinic and affiliated New England medical centers. Families will be invited to participate in the study via a mail packet and follow-up phone call. Flyers and study brochures will be displayed in Boston Children's Hospital Cardiology Clinic and affiliated medical centers as well as in some local advocacy parent organizations. Participants will be assessed for eligibility and enrolled by a study coordinator and a research

nurse. Informed consent and assent from the child will be obtained by a study coordinator or a research neuropsychologist before the baseline assessment at the hospital.

Randomization and stratification

All eligible subjects will undergo a baseline neurodevelopmental assessment (Figure 1) and then will be randomly assigned to either the standard home-based Cogmed intervention group or to a control group (standard of care). Subjects will be assigned in the order in which they are enrolled into the study. Randomization will be done by computerized permuted blocks design with blocks of varying sizes. Once a subject has been assigned to a group, he/she will remain in the same trial arm for the duration of the study. The randomization scheme will involve two stratification factors: type of CHD (univentricular or biventricular) and baseline level of EF (a score <85 or ≥85 on the working memory test from the NIH Toolbox). Figure 1 shows the flowchart of the trial design.

Intervention group: Home-based Cogmed Working Memory Training

Children randomly assigned to receive the Cogmed intervention will complete the standard home-based format of the program, Cogmed RM, for children aged 7 years and older. The training program contains 12 different neurocognitive tasks. All tasks are adaptive, i.e., task complexity levels are automatically adjusted to match each child's working memory capacity. Tasks become more difficult as a function of performance on a session-by-session basis. Each training session lasts approximately 40-50 minutes, with one session to be completed per day 5 days each week for 5 weeks, for a total of 25 sessions. The program yields individual session-by-session and task-by-task training results, including the children's responses, time spent on each

task, and evolution curves. Cogmed is not FDA-regulated. Based on our specific aims, Cogmed is considered a Non-Significant Risk Device.

Study tablets (i.e., iPads) will be provided to families randomized to the Cogmed group in order to standardize the method of delivery. Families will receive a link for downloading a web-based software program to the tablet. The program will be installed on the tablet by a study coordinator who will explain how the training program works and how to log into the system and complete training. The training session and installation of the program will be completed after baseline assessment and randomization. Parents and children will be actively involved, and during the installation session, children will complete several practice trials under the supervision of the study coordinator. The 25 sessions will be completed by the child, supervised by a parent. For the first 5 sessions, the child trains on the same set of games; on the 6th session and every 5th session thereafter, a new task is introduced and replaces one of the initial tasks. At the end of each session, the child can play an age-appropriate tablet game as a reward. After each session, a parent will upload the results to a secure website. Families will be contacted weekly to check program function and discuss concerns. Compliance is automatically registered and is defined as completing at least 20 sessions, the criterion by which children will be categorized as compliant or non-compliant to treatment.[41-42]

To implement this intervention, each investigator and study coordinator involved in coaching will be certified as a "Cogmed Coach." The Cogmed Coaches will monitor children's performance every week during the intervention to permit continuous evaluation of treatment compliance and fidelity. A designated Cogmed Coach will be available during the trial to respond to any questions or help with any difficulties during the training. Parents will be asked to complete a training evaluation scale following completion of Cogmed; this scale is an integrated

component of Cogmed that gathers information regarding the child's motivation and attention during the training as well as parents' feedback. As soon as a child finishes the intervention, a blinded post-treatment assessment will be scheduled to occur within the following weeks.

Control group: Standard of care

Children randomly assigned to the control group will receive the standard of care recommended for patients with critical CHD. This includes cardiac surveillance and, if needed, neurodevelopmental counseling and screening at Boston Children's Hospital Cardiac Neurodevelopmental Program. Once enrolled in the study, a child in the control group will not receive Cogmed intervention or any other cognitive intervention that targets executive functions or ADHD symptoms until after the 3-month follow-up assessment is completed, i.e., 5-6 months after initial enrollment. Like children assigned to the intervention group, children in the control group can continue treatments that are already in place for other neurodevelopmental disabilities (e.g., speech therapy, occupational services). For children in the control group, post-treatment and 3-month follow-up assessments will be performed 6 to 7 weeks and 4 to 5 months after baseline assessment, respectively. After the study is completed, children in the control group will be offered the possibility of completing the Cogmed intervention at no cost.

Primary outcome measure

The NIH Toolbox[55] is a set of computerized assessments designed to measure outcomes in longitudinal or intervention trials. This battery is particularly appropriate for our study because it is presented in a computerized child-friendly version, paralleling that of the Cogmed intervention. The *List Sorting Working Memory Test* from the NIH Toolbox is the primary outcome of the trial. This standardized measure assesses the ability to process information across a series of modalities (visual-spatial and verbal), to hold this information in a short-term buffer,

and to actively manipulate it mentally. It is considered an excellent composite indicator of children's EF skills, as it requires the simultaneous implementation of control of attention and working memory abilities on tasks of increasing complexity. Mean scores are automatically computed and are compared to a standardization sample of US children of the same age. They are normally distributed (mean=100, SD=15) in the standardization sample. The construct validity of the NIH Toolbox working memory tasks is 0.58 for convergent validity and 0.30 for divergent validity. This test has a test-retest reliability of 0.89 (95% confidence interval: 0.85 to 0.92).

Secondary outcome measures

NIH Toolbox Cognition Battery.[55] We will include tests that measure cognitive flexibility, attention and inhibitory control, episodic memory, language, and processing speed. Mean scores on the following tests will be our secondary outcomes: (1) *Flanker Inhibitory Control and Attention Test*, which measures a child's ability to control automatic response tendencies that may interfere with achieving a goal; (2) *Dimensional Change Card Sort Test*, which assesses a child's capacity to switch among multiple aspects of a task; (3) *Picture Sequence Memory Test*, which measures a child's ability to remember the sequence of pictures shown on the screen; (4) *Picture Vocabulary Test* and *Oral Reading Recognition*, which assess receptive vocabulary and reading decoding skills; and (5) *Pattern Comparison Processing Speed Test*, which assesses the amount of time it takes a child to process a set amount of information. All scores are standardized and normally distributed (mean=100, SD=15) in the standardization sample. The test-retest reliability of these tests varies between 0.82 and 0.96.

Behavior Rating Inventory of Executive Function, Second Edition.[56] The BRIEF-2 is a standardized questionnaire measuring children's every-day life executive functioning. It includes

nine scales: Inhibit, Self-Monitor, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Task-Monitor, and Organization of Materials. Parent and teacher versions of the BRIEF-2 will be included. We will analyze the General Executive Composite T score (mean=50, SD=10 for the standardization sample) for each version (Parent and Teacher), which incorporate results from all clinical scales. The composite indices of the BRIEF-2 have high internal consistency (0.94 to 0.98 in the normative sample) and high test-retest reliability (0.84 to 0.88 for parents over a 2-week interval; 0.90 to 0.92 for teachers over a 3.5-week interval).

Conners, 3rd Edition.[57] The Conners-3 is a questionnaire which assesses ADHD-related behaviors in children 3 to 17 years old. We will analyze mean T scores (mean=50, SD=10 for the standardization sample) for the ADHD Inattentive and ADHD Hyperactive-Impulsive DSM-5 Symptom Scales as well as the ADHD Index for each version (Parent and Teacher). For children 6-11 years old, the Cronbach's alpha coefficients for scores on the scales range from 0.87 to 0.95 for both parent and teacher ratings, indicating satisfactory internal consistency. Test-retest reliability for the scales ranges from 0.67 to 0.72 for parents and 0.47 to 0.80 for teachers.

Social Responsiveness Scale, Second Edition.[58] The SRS-2 questionnaire evaluates autism spectrum symptoms, including those relating to social awareness, social cognition, communication, social motivation, and autistic traits, in individuals older than 2.5 years. We will analyze T scores (mean=50, SD=10 for the standardization sample) from both versions (Parent and Teacher). Ratings show good internal consistency and interrater reliability.

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Table 1. Schedule of neurodevelopmental assessment data collection

	Assessment	Informant	Baseline	Post-treatment*	Follow-up**
Primary Outcome	NIH Toolbox List Sorting Working Memory Test	Child	**X**	**X**	**X**
Secondary Outcomes	NIH Toolbox Cognition Battery	Child	**X**	**X**	**X**
	Behavior Rating Inventory of Executive Function, Second Edition	Parent	**X**	**X**	**X**
		Teacher	**X**	**X**	**X**
	Conners, Third Edition	Parent	**X**	**X**	**X**
		Teacher	**X**	**X**	**X**
	Social Responsiveness Scale, Second Edition	Parent	**X**	**X**	**X**
		Teacher	**X**	**X**	**X**

*Post-treatment (one to two weeks after cessation of intervention and/or 6 to 7 weeks after baseline).

**3-month follow-up (3 months after completion of the intervention and/or 4 to 5 months after baseline).

Covariate measures

We will investigate cognitive, medical, and sociodemographic patient-specific factors as predictors of response to the intervention, at both post-treatment and 3-month follow-up assessments. The following variables will be investigated: baseline IQ scores on the Wechsler Intelligence Scale for Children, Fifth Edition[59], and perinatal medical history such as birth weight, gestational age, type of CHD, history of neurological abnormalities, number of open-heart surgeries, intensive care unit length of stay, and total number of hospitalizations.

Sample size and power considerations

Our specific aims are to determine whether there are significant differences between the intervention and control groups in the changes in scores on the List Sorting Working Memory Test between measurements at baseline and post-treatment (Specific Aim 1) and between baseline and 3-month follow-up (Specific Aim 2). Although this test has a good test-retest

reliability of ρ=0.87, to be conservative, we will assume a value of ρ=0.70 between measurements at baseline and post-treatment and between baseline and 3-month follow-up on the same subject. Given a sample size of 100 subjects, ρ=0.70 for within-subject correlations, and a two-sided Type I error rate of 5%, we have 81.4% power to detect a mean difference of 0.5 SD between treatment groups, with a conservative 20% attrition rate (hence, analyzing a minimum of 80 subjects) in our primary outcome measure. This corresponds to a mean difference of 7.5 units, given an expected SD of 15 for the List Sorting Working Memory Test of the NIH Toolbox.

Among children who receive the Cogmed intervention, we also seek to assess associations of cognitive, sociodemographic, and medical factors with changes in the scores for our primary outcome measure (Specific Aim 3). Given a sample size of 50 children randomized to receive Cogmed intervention and a two-sided Type I error rate of 5%, we have 79.9% power to detect a correlation of 0.43 (or $R^2 = 0.43^2 = 0.185$ from a linear regression) between a patient-specific factor and our primary outcome variable even with a conservative 20% attrition rate (analyzing a minimum of 40 subjects).

Data analysis plan

For Specific Aims 1 and 2, the efficacy of the intervention will be evaluated by comparing within-subject differences (baseline to post-treatment, baseline to 3-month follow-up, and, in secondary analyses, post-treatment to 3-month follow-up) across treatment groups using an intention-to-treat analysis.

Descriptive statistics will be calculated, including means, standard deviations, medians, and interquartile ranges for continuous variables and frequency counts and percentages for

categorical variables. The primary outcome measure, the List Sorting Working Memory Test of the NIH Toolbox, and most other study outcomes are continuous variables. T tests and linear regression will be used to assess differences between the intervention and control groups for continuous outcomes (i.e., differences in means, 95% CI). Proportions and logistic regression will be used to examine group differences in binary outcomes (i.e., chi square tests, odds ratios, 95% CI). We expect that randomization will produce balance between treatment groups in terms of demographic and baseline factors, but we will use regression methods to adjust for any factors that may be unbalanced. All analyses will be accompanied by graphical exploration of the data and screening for outlying and influential observations. Data transformations and nonparametric methods (e.g., Wilcoxon rank sum tests) will be used as appropriate when parametric assumptions are violated. Primary analyses of treatment group differences will focus on complete cases. In secondary analyses, we will assume no change over time for subjects who do not return for their post-treatment assessment (i.e., last value carried forward approach), but we will also carry out other sensitivity analyses to assess the strength of our findings based on other missing data assumptions.

For Specific Aim 3, we will explore the associations between patient factors and within-subject differences (baseline to post-treatment, baseline to 3-month follow-up) using correlation and linear regression methods, including consideration of possible confounding or effect modification. Because we will be conducting multiple analyses with several predictors and primary and secondary outcomes in an exploratory fashion, we will interpret results cautiously, based not only on significance levels ($p<0.05$, two-tailed) but also on the magnitude of differences, correlations, or regression effects. As appropriate, we will also consider the use of other statistical methods, such as generalized additive models, partial and sparse partial least

squares, and family-wise error rates, in our approach. Analyses will be conducted primarily using SAS, Stata, SPSS, and R.

ETHICS AND DISSEMINATION

This study has received full Institutional Review Board (IRB) approval from Boston's Children's Hospital IRB (P00022440) and has also been reviewed and approved by the Human Protection Agency from the United States Department of Defense. Protocol modifications and amendments will be submitted to the ethical committees for approval. This trial has been registered with the American Clinical Trials Registry (NCT03023644). Prior to entering into the trial, all parents or legal guardians and children will give written informed consent or assent to participate. The study results will be disseminated through publications in scientific journals, presentations at scientific conferences, and directly to the families who participated in the study.

Discussion

This article has presented the background and design for a RCT investigating the efficacy of a 5-week working memory intervention for children with CHD who underwent open-heart surgery in infancy. This is the first study to investigate the effects of a neurocognitive intervention targeting EF in school-aged children with CHD. We will evaluate children's cognitive and social outcomes including autism spectrum and ADHD symptoms. Furthermore, the results from this trial will provide information on potential patient-specific factors associated with response to the intervention.

Executive dysfunction may have cascading adverse effects on a myriad of domains ranging from specific neurocognitive abilities to school achievement, social adaptation, and, ultimately, quality of life. Timely prevention and treatment of these issues is a priority in the care

of patients with CHD. If proven effective, this type of neurocognitive intervention could be implemented in a clinical outpatient practice for patients at increased neurodevelopmental risk.

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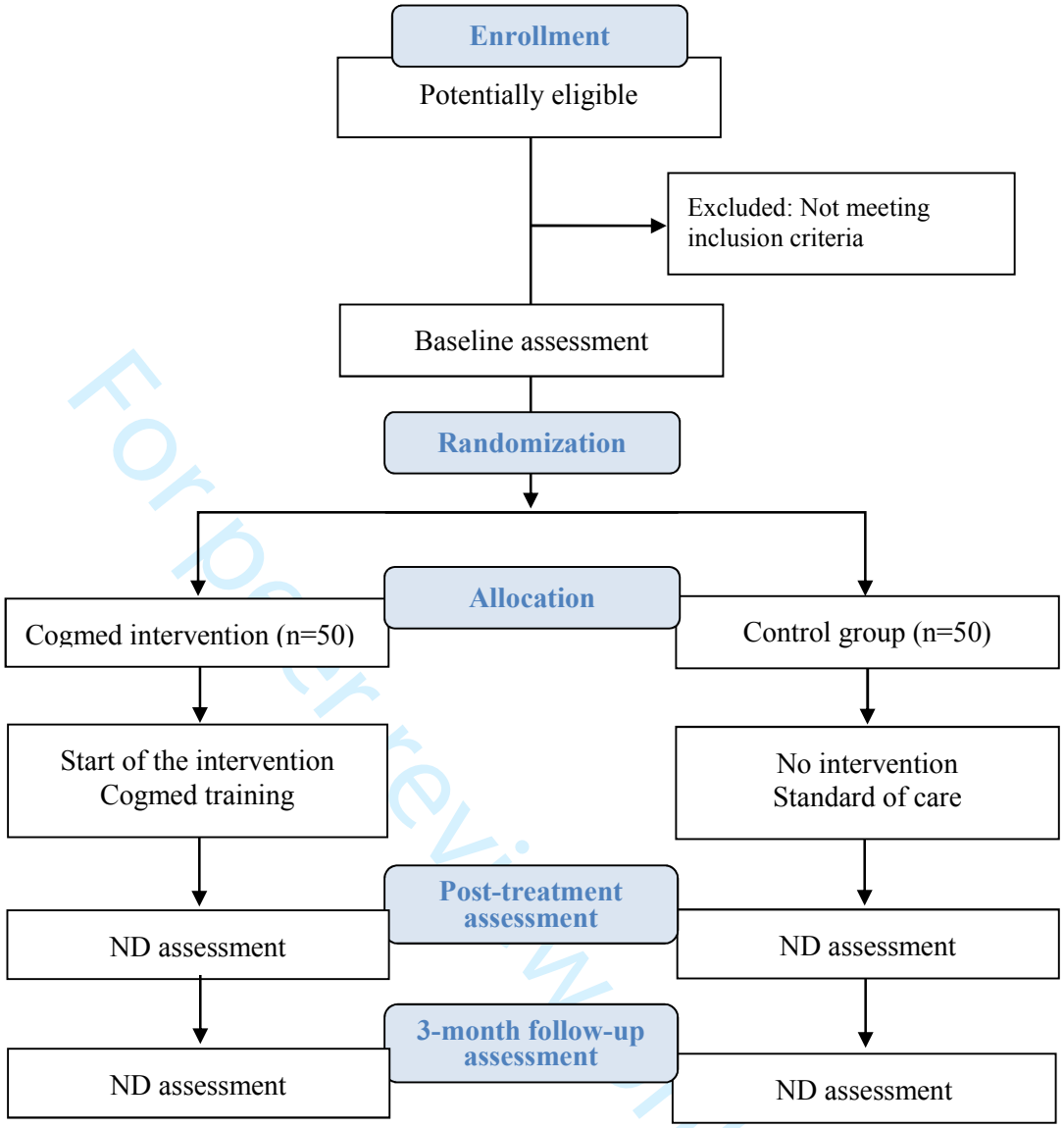
Figure 1. Flowchart of trial design (ND=neurodevelopmental)



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Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: Protocol for a Randomized Controlled Trial of Working Memory Training

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Running Head: Executive Function Intervention for Children with CHD

Abstract

Introduction: Executive function (EF) impairments are among the most prevalent neurodevelopmental morbidities in youth with congenital heart disease (CHD). To date, no studies have been undertaken to investigate the efficacy of cognitive interventions aimed at improving EF outcomes in children with CHD.

Methods and analysis: This is a single center, single-blinded, two-arm randomized controlled trial to test the efficacy of Cogmed Working Memory Training (Cogmed) *versus* standard of care in children with CHD after open-heart surgery in infancy. Participants will consist of 100 children with CHD aged 7-12 years who underwent open-heart surgery before the age of 12 months. Participants are randomly allocated to either an intervention group including training on the home-based Cogmed intervention for a duration of approximately 5 weeks or a control group who receive the standard of care for children with CHD. We seek to evaluate the efficacy of Cogmed at post-treatment and 3-months after completion of the intervention. Baseline, post-treatment, and 3-month follow-up assessments will include specific measures of EF, cognitive and social functioning, and ADHD symptoms. The primary outcome of this study is the change in standardized mean score on the List Sorting Working Memory test from the NIH Toolbox for the Assessment of Neurological and Behavioral Function. Secondary outcomes include measures of social skills, inhibitory control, cognitive flexibility, and behavioral EF as well as ADHD symptoms as measured by the Behavior Rating Inventory of Executive Function, Second Edition and the Conners 3rd Edition. The efficacy of the intervention will be evaluated by comparing within-subject differences (baseline to post-treatment, baseline to 3-month follow-up) between the two groups using an intention-to-treat analysis.

Ethics and dissemination: This study has received full Institutional Review Board (IRB) approval from Boston's Children's Hospital IRB (P00022440) and has also been reviewed and approved by the Human Protection Agency from the US Department of Defense. The results will be published in peer-review journals and presented at scientific conferences.

Trial Registration Number: NCT03023644

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Strengths and limitations of this study

- To our knowledge, this is the first randomized controlled trial (RCT) investigating the efficacy of an executive function intervention in improving outcomes for children with congenital heart disease (CHD).
- The home-based Cogmed Working Memory Training (Cogmed) is among the most widely-used evidence-based programs targeting core executive function skills and will directly address the most frequent neurodevelopmental impairment for children with critical CHD that strongly impacts their ability to succeed in academic and social environments.
- This intervention is individually adapted to each child's own executive function level, which ensures an optimal level of performance throughout the sessions.
- As a home-based intervention, Cogmed reduces the need for hospital-based treatment visits, potentially reducing the burden for families of children with chronic health conditions such as critical CHD.
- This RCT includes computerized individual measures of neurodevelopment and parent- and teacher-rating scales of behavioral and social outcomes as well as collection of patient-specific factors to investigate their potential relationship with response to treatment.
- This is a phase II RCT to provide the first proof of concept that a cognitive intervention can improve outcomes in children with CHD. As such, it is single blinded (participants know their treatment group) and has a relatively short duration of follow-up (3 months).

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INTRODUCTION

Congenital heart lesions are among the most common birth defects,[1-2] with approximately 1% of infants born with congenital heart disease (CHD). Of these, more than one-third will present with critical CHD, most broadly defined as forms of CHD requiring surgical or catheter interventions or resulting in death in the first year of life.[1,3] Advances in prenatal diagnosis as well as medical and surgical care have reduced mortality rates for all forms of CHD. However, evidence of central nervous system damage, including delayed brain maturation *in utero* and abnormal brain metabolism and microstructure associated with hypoxic-ischemic injury, has been reported by a wealth of studies of critical CHD.[4-7] A dramatic increase in the population of survivors of infant heart surgery has been accompanied by the increased recognition of their long-term postoperative morbidities. Neurodevelopmental disabilities, particularly executive function (EF) impairments, are currently the most prevalent long-term morbidity in the population with CHD.[4] EF refers to a set of higher-order neurocognitive abilities that serve to coordinate and organize actions towards a goal, allowing the individual to adapt to new or complex situations.[8] Impairments in EF manifest as behavioral dysregulation and attention problems, impaired working memory (i.e., the ability to keep information in mind and manipulate it over a short period of time), and problems with organization and planning abilities. EF is more strongly associated with school readiness than is IQ, predicts both mathematics and reading competence throughout the school years[8-10] and is strongly associated with social cognition (i.e., decoding other people's mental and emotional states and responding to rapid-paced social interactions).[9]

Executive dysfunction can profoundly impact all dimensions of a child's development[11-14] and is a core feature of attention deficit hyperactivity disorder (ADHD)[15] and autism spectrum

symptoms.[16-17] If untreated, deficits in EF may also predispose individuals to later addiction,[18] eating disorders and obesity,[19] and risk-taking behaviors.[20] These adverse sequelae may carry profound implications for the educational achievement, future employment, and quality of life of individuals with CHD.[4]

EF in critical CHD

Impairments in EF are at the heart of the neurodevelopmental phenotype associated with critical CHD after open-heart surgery.[21-34] EF deficits in children with CHD were first reported in school-aged children with dextro-transposition of the great arteries (d-TGA).[25] Standardized neuropsychological testing showed that patients with d-TGA had substantial difficulty planning and alternating between tasks, which suggested impairments in cognitive flexibility and working memory as well as deficits in planning and sustained attention. On the Behavior Rating Inventory of Executive Function (BRIEF), parents and teachers of adolescents with CHD reported significant difficulties, particularly with regard to working memory.[22] Compared to normative values, parents' ratings were worse by ~0.5 SD and those of teachers by ~1 SD, suggesting not only statistically significant but clinically meaningful impairments. More recent findings also reported specific EF impairments in preschool and school-aged children with d-TGA.[21,23-24] In particular, children had important difficulties in behavioral regulation and cognitive control of attention, and they had worse performances on verbal and visual working memory tasks. Consistent findings have been reported by studies including children with other types of critical CHD such as tetralogy of Fallot[28] or single ventricle physiology requiring the Fontan operation.[29] Finally, EF impairments have been associated with worse psychosocial

health status and worse quality of life in youth with critical CHD,[31] highighting the potential impact of long-term executive dysfunction on mental health in CHD.[32]

Working memory intervention for children with CHD

The American Heart Association (AHA) recommends routine neurodevelopmental screening of all CHD survivors.[4] A burgeoning literature documents the prevalence and importance of impaired EF and ADHD in CHD survivors,[21-40] and brain imaging studies have provided key information on the underlying disturbances in brain structure and microstructure in patients with CHD.[5-7] Yet to date, no trials have been undertaken to test interventions targeting EF and attention deficits in the CHD population.[34]

Cogmed Working Memory Training (Cogmed) is the most widely used computerized evidence-based intervention that targets EF, specifically providing intensive structured training of working memory.[41-54] It has been shown to improve executive performance in several clinical and non-clinical pediatric populations, including children with ADHD,[41-42;46-47] low working memory and low achievement,[43-44] and children who were born preterm or extremely low-birth weight.[53-54] Unlike other hospital- or laboratory-based interventions, Cogmed can be implemented as a home-based intervention for children. Studies using Cogmed have shown that subjects demonstrate the ability to transfer skills to non-trained tests of working memory as well as to tasks that involve similar processes, including attention, inhibition, and non-verbal reasoning.[51-53] The positive effect of training has been observed on parental ratings of inattention, including the DSM-IV Parent Rating Scale, ADHD-RS-IV, BRIEF, and Conners' Parent Rating Scale. Sustained improvements in behavior as measured by rating scales have also been observed in ADHD,[48] brain injury,[49-50] and non-clinical groups.[51-52]

In summary, several randomized controlled trials evaluating the use of Cogmed in healthy children[44; 51-52] and in children with various conditions[41-42;47;53-54] have demonstrated that this neurocognitive intervention produces significant generalized and sustained enhancement on measures of EF, and also on everyday life learning and behavioral skills. It is proposed that training working memory using Cogmed is a promising intervention for school-aged children with critical CHD because: (1) it addresses the most frequent neurodevelopmental morbidities that strongly impact the ability to succeed in academic and social environments; (2) it allows for intensive and structured practice of targeted skills, with possible transfer to other neurodevelopmental domains; (3) it is individually adapted to each child's own EF levels, which ensures an optimal level of performance throughout the sessions; (4) it is closely monitored, and various parameters of the child's performance are systematically recorded (e.g., correct answers, speed at which tasks are completed); (5) it is child-friendly and rewarding, which facilitates children's compliance; and, finally, but importantly (6) as a home-based intervention, it reduces the need for hospital/clinic-based visits and multiple costs of individual therapy, potentially reducing the burden for families of children with chronic health conditions such as critical CHD.

In this project, we conduct a randomized controlled trial (RCT) to provide the first proof-of-concept that Cogmed intervention improves neurodevelopmental outcomes in children with CHD, and that the improvements persist to 3 months. We will enroll children with CHD who underwent infant open-heart surgery as this population corresponds to the highest risk category for developmental disorders and disabilities as stated in the AHA guidelines (Class I; Level of Evidence A).[4] We propose to determine immediate and 3-month post-treatment effects on both laboratory-based tests and ecological measures of children's EF, ADHD, and social difficulties

in everyday life. Our study will also provide insight into factors that are associated with response to treatment, identifying children who may be most likely to benefit from the intervention.

Aims and hypotheses

Specific Aim 1: To evaluate the immediate efficacy of home-based Cogmed intervention for neurodevelopmental outcomes in children with CHD. We hypothesize that children who receive the Cogmed intervention, compared with controls receiving standard of care, will display greater improvement from baseline to post-treatment assessment in EF and social development, and greater reduction in symptoms of ADHD.

Our primary outcome measure will be the change in standardized mean score on the working memory test from the National Institutes of Health Toolbox for the Assessment of Neurological and Behavioral Function (NIH Toolbox)[55] from baseline to post-treatment. Secondary outcomes include changes in standardized mean scores on tests of cognitive flexibility, attention, inhibitory control, and speed of processing from the NIH Toolbox; the Global Executive Composite from the Behavior Rating Inventory of Executive Function, 2nd Edition (BRIEF-2)[56], the Global Index and the ADHD Index from the Conners 3rd Edition (Conners-3)[57], and the Social Responsiveness Scale, 2nd Edition (SRS-2).[58]

Specific Aim 2: To assess the effects of the Cogmed intervention at 3-month follow-up. We predict that significant gains in neurodevelopmental and behavioral outcomes will persist 3 months after cessation of intervention for children who received Cogmed as compared to controls.

The primary and secondary outcomes will be the same as those in Specific Aim 1, except that the change in scores will be from baseline to 3-month follow-up (i.e., approximately 3 months after the last Cogmed session).

Specific Aim 3: To explore cognitive, medical, and sociodemographic factors associated with changes in neurodevelopmental and behavioral scores for children who received Cogmed intervention.

METHODS AND ANALYSIS

Study design

This is a single center, single-blinded, two-arm RCT to test the efficacy of Cogmed intervention *versus* standard of care in children with CHD after neonatal and/or infant open-heart surgery (n=50 in each group). All eligible subjects undergo a baseline neurodevelopmental assessment and then are randomly assigned to either the standard home-based Cogmed intervention or to a control group receiving the standard of care for children with CHD. All participants will undergo a post-treatment and a 3-month follow-up assessment. All investigators collecting outcome data are blinded to patients' group assignment (Cogmed intervention *versus* standard of care) and to medical and surgical histories. For children assigned to the Cogmed group, post-treatment assessments are performed one to two weeks after the end of the intervention (i.e., approximately 7-8 weeks after baseline assessment) and follow-up will be performed 3 months after the end of the intervention (i.e., approximately 5 months after baseline assessment). For children in the control group, post-treatment and 3-month follow-up assessments are performed approximately 7-8 weeks and 5 months after baseline assessment, respectively.

Participants and recruitment

Participants are included if they meet the following criteria: (1) diagnosis of CHD requiring at least one open-heart surgery before one year of age; (2) age between 7 and 12 years at baseline assessment; (3) ≥6 months post cardiac surgery; (4) had received cardiovascular care at Boston Children's Hospital; (5) English or Spanish speaking; (6) informed consent from parent/guardian as well as assent of the child. Exclusion criteria will be: (1) diagnosed chromosomal anomalies and/or genetic syndromes; (2) severe physical and/or sensory impairments (hearing, visual, or psychomotor) that would prevent the use of the computerized program; (3) confirmed diagnosis of an autism spectrum disorder and/or severe developmental or intellectual disorder that would prevent successful completion of the planned study testing; (4) placement in a separate classroom for severe sensory, motor, language or other developmental disability receiving individual support; (5) scheduled to undergo major cardiac interventions in the 6 months following enrollment; (6) received, receiving, or scheduled to receive Cogmed or any other computerized behavioral training program targeting EF or ADHD. We will not exclude children who underwent multiple heart or other surgeries, children with a pre-existing neurological history (e.g., epilepsy, stroke) or with a history of a concurrent diagnosis of ADHD (treated or untreated). Rather, we will account for these factors in the data analysis.

Eligible children living in the United States are recruited through patient databases of Boston Children's Hospital Cardiology Clinic and affiliated New England medical centers. Families are invited to participate in the study via a mail packet and follow-up phone call. Flyers and study brochures are displayed in Boston Children's Hospital Cardiology Clinic and affiliated medical centers as well as in some local advocacy parent organizations. Participants are assessed for eligibility and enrolled by a study coordinator and a research nurse. Informed consent and

assent from the child are obtained by a study coordinator or a research neuropsychologist before the baseline assessment at the hospital.

Patient and Public Involvement

Patients, patient/family advocacy groups, or the public were not involved in the design, recruitment and conduct of this study. Participants were informed of the burden of the intervention and the option to stop at any time point. All eligible patients completing our study will receive an individual report of the baseline assessment as well as a general report on study results for the group with CHD when data analyses are finalized.

Randomization and stratification

All eligible subjects undergo a baseline neurodevelopmental assessment (Figure 1) and then are randomly assigned to either the standard home-based Cogmed intervention group or to a control group (standard of care). Allocations are assigned using a computerized system only seen by the research assistant or study coordinator after confirming all eligibility criteria and consent. Subjects will be assigned in the order in which they are enrolled into the study. Randomization is done by computerized permuted blocks design with blocks of varying sizes. Once a subject has been assigned to a group, he/she will remain in the same trial arm for the duration of the study. The randomization scheme involves two stratification factors: type of CHD (univentricular or biventricular) and baseline level of EF (a score <85 or ≥85 on the working memory test from the NIH Toolbox). Figure 1 shows the flowchart of the trial design.

Intervention group: Home-based Cogmed Working Memory Training

Children randomly assigned to receive the Cogmed intervention will complete the standard home-based format of the program, Cogmed RM, for children aged 7 years and older.

The training program contains 12 different neurocognitive tasks. All tasks are adaptive, i.e., task complexity levels are automatically adjusted to match each child's working memory capacity. Tasks become more difficult as a function of performance on a session-by-session basis. Each training session lasts approximately 40-50 minutes, with one session to be completed per day 5 days each week for 5 weeks, for a total of 25 sessions. The program yields individual session-by-session and task-by-task training results, including the children's responses, time spent on each task, and evolution curves. Cogmed is not FDA-regulated. Based on our specific aims, Cogmed is considered a Non-Significant Risk Device.

Study tablets (i.e., iPads) are provided to families randomized to the Cogmed group in order to standardize the method of delivery. Families receive a link for downloading a web-based software program to the tablet. The program is installed on the tablet by a study coordinator who explains how the training program works and how to log into the system and complete training. The training session and installation of the program are completed after baseline assessment and randomization. Parents and children will be actively involved, and during the installation session, children will complete several practice trials under the supervision of the study coordinator. The 25 sessions will be completed by the child, supervised by a parent. For the first 5 sessions, the child trains on the same set of games; on the 6th session and every 5th session thereafter, a new task is introduced and replaces one of the initial tasks. At the end of each session, the child can play an age-appropriate tablet game as a reward. After each session, a parent will upload the results to a secure website. Families are contacted weekly to check program function and discuss concerns. Compliance is automatically registered and is defined as completing at least 20 sessions, the criterion by which children are categorized as compliant or non-compliant to treatment.[41-42]

To implement this intervention, each investigator and study coordinator involved in coaching is certified as a "Cogmed Coach." The Cogmed Coaches will monitor children's performance every week during the intervention to permit continuous evaluation of treatment compliance and fidelity. A designated Cogmed Coach will be available during the trial to respond to any questions or help with any difficulties during the training. Parents will be asked to complete a training evaluation scale following completion of Cogmed; this scale is an integrated component of Cogmed that gathers information regarding the child's motivation and attention during the training as well as parents' feedback. As soon as a child finishes the intervention, a blinded post-treatment assessment will be scheduled to occur within the following weeks.

Control group: Standard of care

Children randomly assigned to the control group will receive the standard of care recommended for patients with critical CHD. This includes cardiac surveillance and, if needed, neurodevelopmental counseling and screening at Boston Children's Hospital Cardiac Neurodevelopmental Program. Once enrolled in the study, a child in the control group will not receive Cogmed intervention or any other cognitive intervention that targets executive functions or ADHD symptoms until after the 3-month follow-up assessment is completed, i.e., 5-6 months after initial enrollment. Like children assigned to the intervention group, children in the control group can continue treatments that are already in place for other neurodevelopmental disabilities (e.g., speech therapy, occupational services). For children in the control group, post-treatment and 3-month follow-up assessments will be performed 6 to 7 weeks and 4 to 5 months after baseline assessment, respectively. After the study is completed, children in the control group will be offered the possibility of completing the Cogmed intervention at no cost.

Primary outcome measure

The NIH Toolbox[55] is a set of computerized assessments designed to measure outcomes in longitudinal or intervention trials. This battery is particularly appropriate for our study because it is presented in a computerized child-friendly version, paralleling that of the Cogmed intervention. The *List Sorting Working Memory Test* from the NIH Toolbox is the primary outcome of the trial. This standardized measure assesses the ability to process information across a series of modalities (visual-spatial and verbal), to hold this information in a short-term buffer, and to actively manipulate it mentally. It is considered an excellent composite indicator of children's EF skills, as it requires the simultaneous implementation of control of attention and working memory abilities on tasks of increasing complexity. Mean scores are automatically computed and are compared to a standardization sample of US children of the same age. They are normally distributed (mean=100, SD=15) in the standardization sample. The construct validity of the NIH Toolbox working memory tasks is 0.58 for convergent validity and 0.30 for divergent validity. This test has a test-retest reliability of 0.89 (95% confidence interval: 0.85 to 0.92).

Secondary outcome measures

NIH Toolbox Cognition Battery.[55] We include tests that measure cognitive flexibility, attention and inhibitory control, episodic memory, language, and processing speed. Mean scores on the following tests will be our secondary outcomes: (1) *Flanker Inhibitory Control and Attention Test*, which measures a child's ability to control automatic response tendencies that may interfere with achieving a goal; (2) *Dimensional Change Card Sort Test*, which assesses a child's capacity to switch among multiple aspects of a task; (3) *Picture Sequence Memory Test*, which measures a child's ability to remember the sequence of pictures shown on the screen; (4) *Picture Vocabulary Test* and *Oral Reading Recognition*, which assess receptive vocabulary and reading decoding

skills; and (5) *Pattern Comparison Processing Speed Test*, which assesses the amount of time it takes a child to process a set amount of information. All scores are standardized and normally distributed (mean=100, SD=15) in the standardization sample. The test-retest reliability of these tests varies between 0.82 and 0.96.

Behavior Rating Inventory of Executive Function, Second Edition.[56] The BRIEF-2 is a standardized questionnaire measuring children's every-day life executive functioning. It includes nine scales: Inhibit, Self-Monitor, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Task-Monitor, and Organization of Materials. Parent and teacher versions of the BRIEF-2 will be included. We will analyze the General Executive Composite T score (mean=50, SD=10 for the standardization sample) for each version (Parent and Teacher), which incorporate results from all clinical scales. The composite indices of the BRIEF-2 have high internal consistency (0.94 to 0.98 in the normative sample) and high test-retest reliability (0.84 to 0.88 for parents over a 2-week interval; 0.90 to 0.92 for teachers over a 3.5-week interval).

Conners, 3rd Edition.[57] The Conners-3 is a questionnaire which assesses ADHD-related behaviors in children 3 to 17 years old. We will analyze mean T scores (mean=50, SD=10 for the standardization sample) for the ADHD Inattentive and ADHD Hyperactive-Impulsive DSM-5 Symptom Scales as well as the ADHD Index for each version (Parent and Teacher). For children 6-11 years old, the Cronbach's alpha coefficients for scores on the scales range from 0.87 to 0.95 for both parent and teacher ratings, indicating satisfactory internal consistency. Test-retest reliability for the scales ranges from 0.67 to 0.72 for parents and 0.47 to 0.80 for teachers.

Social Responsiveness Scale, Second Edition.[58] The SRS-2 questionnaire evaluates autism spectrum symptoms, including those relating to social awareness, social cognition, communication, social motivation, and autistic traits, in individuals older than 2.5 years. We will

analyze T scores (mean=50, SD=10 for the standardization sample) from both versions (Parent and Teacher). Ratings show good internal consistency and interrater reliability.

The schedule of neurodevelopmental assessment data collection is presented in Table 1.

Table 1. Schedule of neurodevelopmental assessment data collection

	Assessment	Informant	Baseline	Post-treatment*	Follow-up**
Primary Outcome	NIH Toolbox List Sorting Working Memory Test	Child	**X**	**X**	**X**
Secondary Outcomes	NIH Toolbox Cognition Battery	Child	**X**	**X**	**X**
	Behavior Rating Inventory of Executive Function, Second Edition	Parent	**X**	**X**	**X**
		Teacher	**X**	**X**	**X**
	Conners, Third Edition	Parent	**X**	**X**	**X**
		Teacher	**X**	**X**	**X**
	Social Responsiveness Scale, Second Edition	Parent	**X**	**X**	**X**
		Teacher	**X**	**X**	**X**

*Post-treatment (one to two weeks after cessation of intervention and/or 6 to 7 weeks after baseline).

**3-month follow-up (3 months after completion of the intervention and/or 4 to 5 months after baseline).

Covariate measures

We will investigate cognitive, medical, and sociodemographic patient-specific factors as predictors of response to the intervention, at both post-treatment and 3-month follow-up assessments. The following variables will be investigated: baseline IQ scores on the Wechsler Intelligence Scale for Children, Fifth Edition[59], and perinatal medical history such as birth weight, gestational age, type of CHD, history of neurological abnormalities, number of open-heart surgeries, intensive care unit length of stay, and total number of hospitalizations.

Data Management and Safety Monitoring

Overall integration of the statistics, data management and administrative functions of this trial occur in the Department of Cardiology's Research Support and Statistics Core (RSSC) led by Drs. Jane Newburger and David Wypij. The RSSC will provide the infrastructure necessary to facilitate the conduct of this clinical trial including biostatistical analysis, computerized data

entry, data base programming and development, data management, quality control, assistance with manuscript preparation and administrative functions. The RSSC will provide a centralized resource for maintaining database. Study documents are being stored in individual subject folders, each folder containing a tracking page. All study materials are stored in a locked file cabinet accessible only to authorized study staff. All study data is recorded on Case Report Forms and entered into a REDCap (Research Electronic Data Capture) database.

A Data and Safety Monitoring Board (DSMB) is comprised of expert members in one of the specific areas at issue in the study: Cardiology, Neuropsychology and Biostatistics. Members will be independent of the study investigators and their Departments at Boston Children's Hospital as well as from the sponsors of this study. The function of the DSMB will be to advise the funding sources, Boston Children's Hospital and the study investigators on (1) final study designs and protocols prior to the beginning of data collection, (2) problems with protocol implementation, (3) frequency of occurrence of adverse events and their relation to study protocols, (4) withdrawals and losses to follow-up, (5) data interpretation and ethical issues, and (6) recommendations arising from the study. The DSMB Chair will receive reports of all serious events throughout the conduct of the study. This trial has been considered as a Non-Significant Risk device study and reviewed accordingly by the Boston Children's Hospital Institutional Review Board and the Human Research Protection Office (HRPO), US Department of Defense.

A complete description of this trial's data management plan, Safety Monitoring Board and Risk/Benefits Assessment is presented in Appendix 1.

Sample size and power considerations

Our specific aims are to determine whether there are significant differences between the intervention and control groups in the changes in scores on the List Sorting Working Memory

Test between measurements at baseline and post-treatment (Specific Aim 1) and between baseline and 3-month follow-up (Specific Aim 2). Although this test has a good test-retest reliability of ρ=0.87, to be conservative, we will assume a value of ρ=0.70 between measurements at baseline and post-treatment and between baseline and 3-month follow-up on the same subject. Given a sample size of 100 subjects, ρ=0.70 for within-subject correlations, and a two-sided Type I error rate of 5%, we have 81.4% power to detect a mean difference of 0.5 SD between treatment groups, with a conservative 20% attrition rate (hence, analyzing a minimum of 80 subjects) in our primary outcome measure. This corresponds to a mean difference of 7.5 units, given an expected SD of 15 for the List Sorting Working Memory Test of the NIH Toolbox.

Among children who receive the Cogmed intervention, we also seek to assess associations of cognitive, sociodemographic, and medical factors with changes in the scores for our primary outcome measure (Specific Aim 3). Given a sample size of 50 children randomized to receive Cogmed intervention and a two-sided Type I error rate of 5%, we have 79.9% power to detect a correlation of 0.43 (or $R^2 = 0.43^2 = 0.185$ from a linear regression) between a patient-specific factor and our primary outcome variable even with a conservative 20% attrition rate (analyzing a minimum of 40 subjects).

Data analysis plan

For Specific Aims 1 and 2, the efficacy of the intervention will be evaluated by comparing within-subject differences (baseline to post-treatment, baseline to 3-month follow-up, and, in secondary analyses, post-treatment to 3-month follow-up) across treatment groups using an intention-to-treat analysis.

Descriptive statistics will be calculated, including means, standard deviations, medians, and interquartile ranges for continuous variables and frequency counts and percentages for categorical variables. The primary outcome measure, the List Sorting Working Memory Test of the NIH Toolbox, and most other study outcomes are continuous variables. T tests and linear regression will be used to assess differences between the intervention and control groups for continuous outcomes (i.e., differences in means, 95% CI). Proportions and logistic regression will be used to examine group differences in binary outcomes (i.e., chi square tests, odds ratios, 95% CI). We expect that randomization will produce balance between treatment groups in terms of demographic and baseline factors, but we will use regression methods to adjust for any factors that may be unbalanced. All analyses will be accompanied by graphical exploration of the data and screening for outlying and influential observations. Data transformations and nonparametric methods (e.g., Wilcoxon rank sum tests) will be used as appropriate when parametric assumptions are violated. Primary analyses of treatment group differences will focus on complete cases. In secondary analyses, we will assume no change over time for subjects who do not return for their post-treatment assessment (i.e., last value carried forward approach), but we will also carry out other sensitivity analyses to assess the strength of our findings based on other missing data assumptions.

For Specific Aim 3, we will explore the associations between patient factors and within-subject differences (baseline to post-treatment, baseline to 3-month follow-up) using correlation and linear regression methods, including consideration of possible confounding or effect modification. Specific attention will be given to certain patient-specific risk factors including timing of first heart surgery (neonatal *versus* non-neonatal), number of surgeries and neurological complications. Because we will be conducting multiple analyses with several

predictors and primary and secondary outcomes in an exploratory fashion, we will interpret results cautiously, based not only on significance levels ($p<0.05$, two-tailed) but also on the magnitude of differences, correlations, or regression effects. As appropriate, we will also consider the use of other statistical methods, such as generalized additive models, partial and sparse partial least squares, and family-wise error rates, in our approach. Analyses will be conducted primarily using SAS, Stata, SPSS, and R.

ETHICS AND DISSEMINATION

This study has received full Institutional Review Board (IRB) approval from Boston's Children's Hospital IRB (P00022440) and has also been reviewed and approved by the Human Protection Agency from the United States Department of Defense. Protocol modifications and amendments will be submitted to the ethical committees for approval. Amendments to the study protocol will be added to publications reporting the study outcomes. This trial has been registered with the American Clinical Trials Registry (NCT03023644). Prior to entering into the trial, all parents or legal guardians and children will give written informed consent or assent to participate. Appendix 2 presents the study consent form. All information will follow IRB and Human Protection guidelines for confidentiality and data protection. The study results will be disseminated through publications in scientific journals, presentations at scientific conferences, and directly to the families who participated in the study. All co-investigators will be co-authors of the study outcomes publications without the use of professional writers. Data will be granted upon request.

Trial Progress

The trial is currently in the active recruitment phase (first baseline assessment March, 2017). This is Protocol V.4, 10 July 2018. Substantial protocol amendments will be communicated to

investigators via email and to other parties as required. All changes are submitted to Boston Children's Hospital's IRB, to the Sponsor of this trial (US Department of Defense) and updated in clinicaltrials.gov.

Discussion

This article has presented the background and design for a RCT investigating the efficacy of a 5-week working memory intervention for children with CHD who underwent open-heart surgery in infancy. This is the first study to investigate the effects of a neurocognitive intervention targeting EF in school-aged children with CHD. We will evaluate children's cognitive and social outcomes including autism spectrum and ADHD symptoms. Furthermore, the results from this trial will provide information on potential patient-specific factors associated with response to the intervention.

Executive dysfunction may have cascading adverse effects on a myriad of domains ranging from specific neurocognitive abilities to school achievement, social adaptation, and, ultimately, quality of life. Timely prevention and treatment of these issues is a priority in the care of patients with CHD. If proven effective, this type of neurocognitive intervention could be implemented in a clinical outpatient practice for patients at increased neurodevelopmental risk.

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Contributors JC, DCB, and JWN are the primary investigators and together with DW designed and established this research study. JC and JWN were responsible for ethics applications and reporting. JC, DCB, CH, and AL are responsible for data collection and implementation of the intervention. JC will take lead roles on preparation for publication of the clinical outcomes of the study. JWN, DCB, DW, CS, CH, and AL will contribute to the preparation of publications within their respective fields of expertise. DW and CS will take on a lead role of the statistical analysis for the study. JC drafted the final version of this manuscript. All authors critically reviewed and approved the final version. All data from this study will be submitted to peer-review journals and for presentation at national and international scientific conferences.

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Competing interests No competing interests are reported. Authors do not have any commercial or scientific affiliation with Pearson, Inc., distributor of Cogmed Working Memory Training.

Ethics approval Full ethical approval for this study has been obtained by the Boston Children's Hospital's Institutional Review Board (IRB) (IRB number P00022440) and has also been reviewed and approved by the Human Protection Agency from the United States Department of Defense. All parent/guardians and children will give written informed consent or assent to participate prior to entering into the trial.

Running Head: Executive Function Intervention for Children with CHD

Figure 1. Flowchart of trial design (ND=neurodevelopmental)

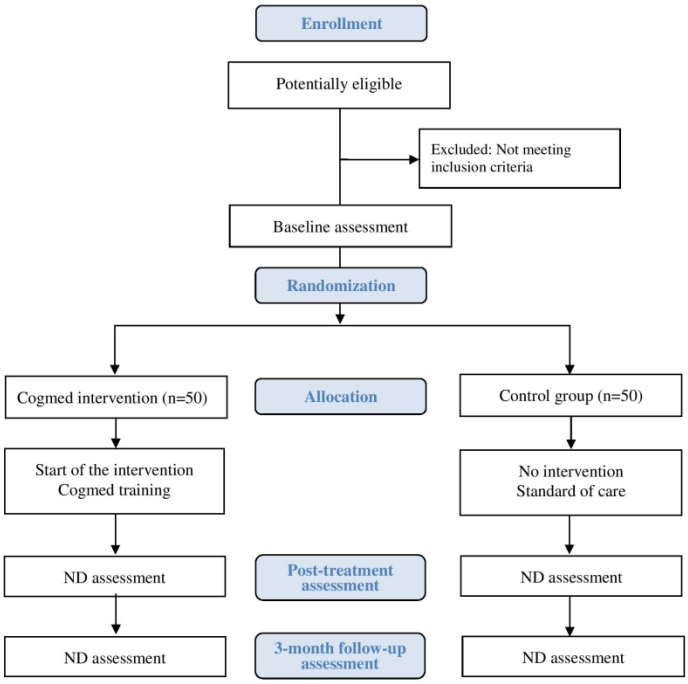

Figure 1. Study flow-chart

215x279mm (300 x 300 DPI)

Appendix 1

Calderon J, Bellinger DC, Hartigan C, Lord A, Stopp C, Wypij D, Newburger JW. Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: Protocol for a Randomized Controlled Trial of Working Memory Training.

1) Data Management and Quality Control

2) Data and Safety Monitoring Board

3) Risk/Benefits Assessment and Risk Management

1) Data management and quality control

Overall integration of the statistics, data management, and administrative functions of this trial will occur in the Department of Cardiology's Research Support and Statistics Core (RSSC). The RSSC will be led by Drs. Jane Newburger and David Wypij. Key support personnel in the RSSC will be a Master's level statistician/statistical programmer (Christian Stopp) and Study Coordinator (Carolyn Dunbar-Masterson).

The purposes of the Research Support and Statistics Core are as follows:

1. To support final protocol development during the Planning Phases of the clinical trial, including refinement of study design, eligibility criteria, baseline and outcome measures, power and sample size calculations, randomization methods, statistical analysis plans (including early stopping rules), and ethical considerations.
2. To assist in overall study coordination of patient follow-up, training of study personnel, quality control and quality assurance, development of Case Report Forms and Manuals of Operations, database development, data entry, database checks and updates, and maintenance of blinding and firewalls.
3. To perform statistical analyses and study monitoring (including adverse event monitoring and Data and Safety Monitoring Board reports).
4. To plan and perform final data analyses, support publication and abstract preparation, and create final data sets for archival purposes.
5. To plan and analyze ancillary studies, such as mechanistic studies or analyses of the association of clinical variables with the outcomes of the intervention.
6. To provide administrative support as needed for research excellence in the trial.

The Research Support and Statistics Core will provide the infrastructure necessary to facilitate the conduct of the proposed clinical trial. Its functions include biostatistical analysis, forms design, data base programming and development, clinical data management, quality control, clinical research study coordination, assistance with manuscript preparation, and administrative functions. It provides a centralized core of key program project staff. In addition to including facilities needed to conduct clinical research studies at Boston Children's Hospital, it provides a centralized resource for maintaining databases and facilitating quality-control procedures for all patient–related data. Individuals in the RSSC will provide computerized data entry and quality control of data. The policies, procedures, and resources already in existence in the Statistical and Data Coordinating Center of the Department of Cardiology at Boston Children's Hospital provide the infrastructure to facilitate these efforts. Computing resources and biostatistical collaboration will be provided for the design, conduct, analysis, and reporting of the trial. Computing resources will also be supported by the RSSC.

Study documents will be stored in individual subject folders; each folder will contain a tracking page that enables study staff and investigators to record annotations and comments regarding the clinical data. All study materials will be stored in a locked file cabinet that is accessible only to authorized study staff. For data analyses, all de-identified Cogmed records will be downloaded and stored with the corresponding subject identification number for each subject. The majority of neurodevelopmental tests have a computerized format that automatically calculates children's score as a function of their performance. Subject confidentiality will be maintained by recording subject data with use of a unique subject identifier. Identifiable data, such

as contact information and medical record numbers, will be recorded and stored separately from the clinical study data.

Case Report Forms will be developed jointly by the clinical, biostatistical, and data coordination team members working on this clinical trial. Forms design features include the selection of valid, reliable measurements that are less burdensome, development and testing of reliability measures, pre-testing of forms, formatting of forms to ensure clarity (standard conventions for coding close-ended questions, minimal use of open-ended questions), and smooth flow in question patterns to reduce missing data. A detailed Manual of Operations will be developed to ensure efficient, consistent, and accurate data collection and ease of communication. The Manual of Operations will allow updating, as needed, using dated footers. The Case Report Forms and Manual of Operations for this trial will be based on those successfully used in previous studies by the investigative team.

All study data will be recorded and maintained on Case Report Forms and entered into a REDCap (Research Electronic Data Capture) database. REDCap is a secure, fully customizable, web-based application designed to support data capture for clinical research studies. REDCap provides user-friendly Case Report Forms, audit trails, calculated fields, queries, and the ability to set up a calendar to schedule and track critical study events, such as participant visits. Auto-validation, branching/skip logic, and other features provide real-time data entry validation to prevent logic errors, range checks to reduce out-of-range values, context-specific help actions, and conditional logic to ensure accurate data collection. Designated users from the research study team can be assigned different levels of access. REDCap is designed to comply with HIPAA regulations,

and allows data export to common analysis packages such as SAS, Stata, R, or Excel. Daily database backup routines are executed to ensure data safety, security, and reliability.

2) Data and Safety Monitoring Board

A Data and Safety Monitoring Board will be comprised of five members, each of whom is eminent in one of the specific areas at issue in the study: Pediatric Cardiology, Psychiatry and Neurodevelopment, and Biostatistics. Members of the DSMB must be independent of the study investigators and their departments at Boston Children's Hospital. The function of the DSMB will be to advise the funding sources, Boston Children's Hospital, and study investigators on: (1) final study designs and protocols prior to the beginning of data collection, (2) problems with protocol implementation, (3) frequency of occurrence of adverse events and their relation to study protocols, (4) withdrawals and losses to follow-up, (5) data interpretation and ethical issues, and (6) recommendations arising from the study. The DSMB Chair will receive reports of all serious events throughout the conduct of the study. The exact schedule and procedures for monitoring or stopping a study will be established by the DSMB during the first year of the study.

Research Support and Statistics Core staff will assemble and maintain the required data on enrollment, adverse events and data quality for regular reporting to the DSMB, on a schedule to be dictated by the DSMB, and to prepare and present such reports. The methods of analysis for the clinical project and the criteria for early stopping will be developed by Dr. Wypij, with input and approval from the DSMB in general and the DSMB statistician in particular. Statistical analyses

pertinent to early-stopping decisions will be conducted by Dr. Wypij and presented for evaluation to the DSMB on the agreed-upon schedule.

3) Risks/Benefits Assessment

This trial has been considered as a Non-Significant Risk device study and reviewed accordingly by the Boston Children's Hospital Institutional Review Board and the Human Research Protection Office (HRPO), US Department of Defense.

Foreseeable risks:

This RCT does not involve any drugs or invasive procedures, and the injury associated with participation is highly unlikely. Therefore, the trial is likely to entail minimal risk to participants. The NSR determination for this study will not impact the risk/benefit ratio. Participating will require considerable time, particularly in the group that receives the Cogmed Working Memory Training. Children in this intervention group will complete 5 35-40 minute sessions per week for 5 weeks. We will be asking parents to supervise the child's completion of these sessions. The children might find some of the Cogmed Program activities to be frustrating. However, the system is "adaptive," in that the difficulty level of the tasks is titrated to match a child's abilities, thereby insuring some success and lowering stress. The families might be inconvenienced by having to make three visits to Boston Children's Hospital within a 5 month period.

There is some inconvenience and burden of completing questionnaires and some families may feel uncomfortable answering questions. The parent-completed questionnaires will require approximately 60 minutes to complete. We will aim for questionnaires to be completed prior to the in-person assessment, however there will be little time pressure required for the completion of

the instruments by the parents and teachers as they will be mailed out to parents approximately 3 months prior to the appointment for the in-person evaluation.

Risk Management Response:

- **Neurodevelopmental Testing and CogMed Intervention:** Prior to beginning the evaluation, subjects and families will be told that the information they provide will be held in confidence and not revealed to school officials or other authorities without their permission, and that names will not be associated with answers in our database. Possible referrals will be discussed with the family. Similarly, parents will be told that we are required by law to report any evidence that suggests child abuse. As part of the debriefing, both the child and parent will be asked if they would like additional care or services. If so, we will provide referrals. If a patient's responses suggest engagement in risk-taking behaviors, appropriate resources will be discussed and information provided. An experienced psychiatric clinician will always be available to address with the children or parents who experience any distress that the testing or questionnaires might stimulate.

e) If children and/or parents exhibit any indication of suicidal thoughts or intentions, this will be carefully discussed both with the parent(s) and subject. Suicidal intent, plans, and means will be evaluated by a licensed clinician. Subjects judged to be at risk will be referred for further evaluation and intervention. Referrals for emergency evaluation would be made to our institution's Psychiatric Emergency Service or to hospitals closer to their homes, if appropriate. The on-call and emergency service mental health providers will be notified of the study's existence.

f) If a subject exhibits a significant depression or appears to require psychiatric hospitalization, s/he will have access to referral for treatment. If during the assessment,

the subject has a suicide plan or attempt or the severity of the adolescent's depression requires hospitalization, the psychiatric clinician at the participating center will facilitate hospitalization. If the subject requires additional care but does not require hospitalization, the research team will facilitate the subject's obtaining this care using his or her own health insurance.

- **Ascertaining Vital Status of Subjects:** We will contact the subject's cardiologist before initiating contact with subjects and their families to be sure that the subject is alive. There is a tiny chance that the cardiologist might not have been informed about a subject's death and that we will cause distress by contacting parents of an expired subject not known to have died.
- **Costs:** Tests required by the study will be provided free of charge. The study will also pay for parking for families.
- **Alternatives:** Parents and children will be told that if they decline to participate, the future medical care that the child might receive at Children's Hospital in Boston will not be affected and that if they agree to participate, they are free to withdraw from the study at any time or to decline to participate in specific aspects of the study protocol.
- **Confidentiality:** Investigators will take all reasonable measures to protect the confidentiality of subjects and their families, including the following:

    a) Investigators will arrange for counseling if anxious feelings arise in the family at any time during the study.

    b) Each child and parent is assigned a subject identification number (SID). All interview and clinical research data are stripped of identifiers and labeled with the

study number. The enrollment log with participant identifiers will be maintained at each site in a secured, locked location available only to the study staff.

c) The study will follow good clinical practices at all times. Databases will be secured as previously discussed.

d) The risk of breach of subject confidentiality will be minimized by storage of all study materials in a locked file cabinet in a location separate from the laboratory data.

e) The subject's name and any other identifying information will not appear in any presentation or publication resulting from this study.

f) The study team will contact family members for recruitment according to local guidelines. As per local requirements, contact will be made with those individuals who have expressed a willingness to at least learn about the research study. Other family members will not be informed of who is and is not participating. The subject will also be warned not to disclose their participation in order to protect their own privacy.

g) If important clinical findings are noted during the study, the PI or other qualified member of the research team will take full responsibility for disclosing the findings to the patients/parents, communicating with their primary care physicians with permission, and making appropriate referrals as indicated. The subject may choose to seek a second opinion and/or appropriate clinical care. This might change the subject's insurability as it relates to the clinical finding only. The presumption is that detection of a potentially clinically significant finding will prove to be beneficial to the subject in the long run.

Potential benefits

- Children who complete the Cogmed Working Memory Program might experience an improvement in their executive functioning. This could help them to function more effectively in school, at home, and in their social relationships.
- Subjects and their families who return for neurodevelopmental evaluation will learn about those aspects of the child's neurodevelopmental status that are assessed by the battery of tests. If the family provides consent, this information will also be shared with the pediatrician.
- If there are areas in which a subject is functioning poorly, these can be identified and recommendations for further evaluation or intervention provided, as appropriate.
- An indirect benefit may also come from the awareness that the results of this study may serve to help improve the care of children with similar problems in the future. CHD patients and their families may derive a sense of altruism, accomplishment, and contribution to furthering understanding of the problem through their participation.

Risk/Benefit Ratio and importance of information to be obtained

The risk/benefit ratio is favorable for this study, for the following reasons:

1. The baseline risk is minimal because adverse events are extraordinarily unlikely.
2. Although an individual subject may not benefit from participation, the results of this study will make important contributions to understanding potential treatment of executive function deficits.
3. The CogMed intervention has never been studied in children with CHD.

4. The in-person evaluation for subjects in both treatment groups will provide accurate and rich information about neurocognitive function for use by patients, their families, and schools.

5. Data generated from this study will provide guidance that can be provided to parents and medical care providers of patients with congenital heart disease.

Safety assessment and monitoring

Because no physical interventions will take place, the likelihood of significant adverse events related to the study are relatively small.

a) Specification of Safety Parameters: Any complication during a study evaluation or occurring within 24 hours of a study evaluation will be considered an adverse event and reported as described below.

b) Recording and Reporting Adverse Events: This study is not an intervention study. However, a major component of safety monitoring is ascertainment and reporting of adverse events (AE), including adverse reactions to study procedures. The approach to these activities for this study is summarized in the sections that follow.

c) Definitions of Adverse Event, Suspected Adverse Reaction and Adverse Reaction: For the purposes of this study, adverse events will include any untoward event that occurs during or in close proximity to any study related evaluation including the battery of neurodevelopmental assessments.

d) Classification of Adverse Events: Monitoring AEs requires that they be classified as to seriousness, expectedness, and potential relationship to the study, of which drive the reporting process.

(1) *Seriousness*

ii) A serious adverse event (SAE) is one that:

(1) Results in death,

(2) Is life-threatening (the subject was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred),

(3) Requires inpatient hospitalization or prolongation of existing hospitalization,

(4) Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or

(5) Is an important medical event that may jeopardize the subject or may require medical/surgical intervention to prevent one of the serious adverse event outcomes.

The Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 MedDRA 12.1 (http://ctep.cancer.gov) provides a grading system that is used to categorize the severity of adverse events, as follows:

Grade 1	Mild	Transient, requires no special treatment or intervention, does not interfere with daily activities
Grade 2	Moderate	Alleviated with simple treatments, may limit daily activities
Grade 3	Severe	Requires therapeutic intervention and interrupts daily activities
Grade 4	Life-threatening	

Or disabling

Grade 5 Death

A AE, as defined above, encompasses CTCAE grades 4 and 5, and any Grade 3 event that requires or prolongs hospitalization, or that substantially disrupts the ability of the subject to conduct normal life functions.

2. Expectedness

The purpose of reporting is to provide new, important information on serious reactions or events previously unobserved or undocumented. Therefore, all AEs will be evaluated as to whether their occurrence was unexpected, using the following definitions:

- *Unexpected*: An unexpected AE or adverse reaction is one for which the nature or severity is not consistent with information in the protocol, or consent form. An AE or adverse reaction also may be categorized as unexpected if the event has not previously been observed at the same specificity and/or severity.
- *Expected*: An event is considered expected if it is known to be associated with the particular evaluation

3. Causality

Causality assessment is required to determine which events require expedited reporting. The following criteria will be used to determine causality:

- *Not Related*: The event is clearly related to other factors, such as the subject's clinical state, or non-study drugs or interventions.

- *Possibly Related*: The event follows a compatible temporal sequence from the time of study evaluation, but could have been produced by other factors such as the subject's clinical state or non-study drugs or interventions.
- Probably Related: The event follows a reasonable temporal sequence from the time of study evaluation, and cannot be reasonably explained by other factors such as the subject's clinical state, or non-study drugs or interventions.

g) Identification and Data Collection Procedures: AEs that are not considered adverse reactions or suspected adverse reactions will be identified when they are reported to the clinical center or during scheduled study visits by study coordinators and investigators. AEs will be assessed using self-report, physical examination data, and medical record review.

h) Identification and Data Collection Procedures: AEs that are not considered adverse reactions or suspected adverse reactions will be identified when they are reported to the clinical center or during scheduled study visits by study coordinators and investigators. AEs will be assessed using self-report, physical examination data, and medical record review.

i) Reporting Procedures

Fatal or life-threatening AEs are to be reported to the ACC within 24-hours of first knowledge of the event. Those that are unexpected and considered possibly, probably, or definitely related to the study will be reported as soon as possible, but no later than 7 calendar days after first knowledge of the event, followed by a complete report within 15

calendar days. All other fatal or life-threatening events that are unrelated to the study will be reported semiannually to the DSMB.

All other *SAEs (i.e., non-fatal or not life-threatening)* that are unexpected and considered possibly, probably, or definitely related to the study will be reported within 24-hours of learning of the event.

All other *AEs* not meeting the criteria for expedited reporting will be reported within 7 calendar days of first knowledge of the event.

Reporting of Adverse Events

Seriousness	**Reporting Timeframe**
Fatal or life threatening	Within 24-hours of learning of the event
Serious, but not fatal or life threatening	Within 24-hours of learning of the event
All other	Within 7 calendar days of learning of the event

h) Reporting Adverse Events to Institutional Review Boards: The site Investigator or designee is responsible for reporting all serious adverse events to the local IRB in accordance with local policies and procedures.

i) Follow-up of Subjects after Adverse Events: For AEs with a causal relationship to the study conduct, follow-up by the Investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator.

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This section only to be edited by IRB office.

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Use Plate or Print:

MRN#:

DOB:

Subject's Name:

Gender:

Protocol Title: Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: An Intervention Study

Principal Investigator: Jane Newburger, MD

This consent form gives you important information about a research study. A research study helps scientists and doctors learn new information to improve medical practice and patient care.

Participation in this research study is voluntary. You are free to say yes or no and your decision will not impact the care you receive at Boston Children's Hospital. You can withdraw from the study at any time. A description of the study and its risks, potential benefits and other important information are in this consent form. Please read this consent form carefully and take your time making a decision. The form may contain words that you do not understand. Please ask questions about anything you do not understand. We encourage you to talk to others (for example, your friends, family, or other doctors) before you decide to participate in this research study.

How are individuals selected for this research study?

You are being asked to participate in this research study because your child was born with a congenital heart disease and received care in the Cardiology Clinic at Boston Children's Hospital.

Why is this research study being conducted?

Children with a history of congenital heart disease sometimes experience cognitive and behavioral difficulties. One of the more frequent difficulties involves what are called executive functions. These refer to processes that guide, direct, and manage one's activities (e.g., the ability to initiate and control behavior, to select relevant task goals, to shift strategies flexibly as needed). Problems in these processes can make it harder for a child to learn in school or to maintain good relationships with others. In this research study we want to learn whether children with CHD can improve their executive functioning by using a computer program called the Cogmed Working Memory Program. Although this Program has helped other groups of children with executive function problems (e.g., children born prematurely or children with conditions such as Attention Deficit Hyperactivity Disorder), it is not known whether it can help children with CHD.

Who is conducting this research study, and where is it being conducted?

The study will be conducted only at Boston Children's Hospital by a team led by Dr. Jane Newburger, a pediatric cardiologist and Drs. David Bellinger and Johanna Calderon, research pediatric neuropsychologists. It is funded by a grant from the Department of Defense. Dr. Jane Newburger is the sponsor of this Non-Significant Risk investigational device study.

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It is possible that Dr. Newburger is your child's cardiologist. Although she is an investigator in this study, your child's clinical welfare is her foremost concern. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another health care provider who is in no way associated with this study. You are not under any obligation to participate in any research project offered by your health care provider. If you choose not to participate or not to allow your child to participate, your care at Boston Children's Hospital and/or with your health care provider will not be affected in any way at all.

How many people will participate in this research study?

Approximately 100 7 to 12 year old children and their families will take part in this study.

What do I have to do if I am in this research study?

The duration of your participation in this research study will be 4 to 5 months.

If you decide to join the research study, you will come to the Boston Children's Hospital three times in the next few months. At today's visit, your child will receive a neurodevelopmental assessment consisting of a global cognitive test, the WISC-V and a battery of cognition and executive function tasks from the National Institutes of Health (NIH) Toolbox Assessment of Neurological and Behavioral Function. These are game-like tasks and most are administered on a computer or tablet. This assessment will give us an idea of how your child is doing before receiving the Cogmed intervention and so make it easier to determine if the intervention helps. Also, you will be asked to complete 3 questionnaires that ask about your child's executive function behaviors. These are the Behavior Rating Inventory of Executive Function (BRIEF), the Connors' ADHD DSM-IV Scale (Connors), and the Social Responsiveness Scale. It will take about 45 minutes to complete these. In addition, we will ask you to give the BRIEF and the Connors' questionnaires to your child's teacher to complete. The total time of the visit will be about 2.5 hours.

Your child will then be randomly assigned to either the home-based intervention group, which will receive the Cogmed Working Memory Program, or to a control group. Randomization means that you are put into a group by chance. It is like flipping a coin. Your child will have an equal chance of being placed in the groups. Neither you nor the research investigators can choose what group you will be in. You and your child will know which group you were assigned to, though. Children in the control group will not receive the Cogmed intervention right away but will continue to receive the usual care for children with CHD, which involves surveillance for neurodevelopmental problems, and neurodevelopmental screening and counseling, as needed. When the research study is finished, you will be given the opportunity to have your child receive the same 5-week Cogmed Working Memory Training Program that children assigned to the intervention group received.

If your child is assigned to the intervention group, you will start the Cogmed intervention in the week following the first neurodevelopmental evaluation. A member of the study team will show you and your child how the Cogmed Working Memory Program works and will answer any questions you have on the first visit. Your child will be provided with an iPad on which the Program will be pre-loaded and a secured ID will be created for your child's personal use throughout the intervention. It is child-friendly and web-based. It presents different

game-like tasks for your child to play. The difficulty of the tasks changes to match your child's working memory capacity, so they become more difficult as your child's working memory improves. Your child will complete 25 sessions, each of which lasts 35-40 minutes. These will be spread out over 5 weeks, so that he or she will do one session a day for 5 days per week. The iPad will record your child's responses, and we will be able to securely retrieve these data remotely. We do ask that you supervise your child over this period so help make sure that he or she completes the sessions.

For children in the Cogmed group, Visit 2 (Post-Intervention) will be completed 1 to 2 weeks after completing the Program. For children in the control group, Visit 2 will be completed 6 to 7 weeks after Visit 1. At Visit 2, children in both groups will again be administered the NIH Toolbox tasks, and parents and teachers will complete the same questionnaires they completed at Visit 1. Visit 3 (Follow-Up) will be the final phase of the study. It will take place 4 to 5 months after Visit 1. The same assessments completed at Visit 2 will be done at Visit 3. The purpose of Visit 3 is to see if the beneficial effects of the intervention at Visit 2 (should there be any) are still present after several weeks. Visits 2 and 3 will each take 2 hours.

Study Visit Timeline	Visit 1 Baseline	Visit 2 Post-intervention (6-7 weeks after baseline)	Visit 3 Follow-up (4-5 months after baseline)
Consent /Assent	X		
WISC-V	X		
NIH Toolbox	X	X	X
Behavior Rating Inventory of Executive Function	X	X	X
Connors' ADHD/DSM-IV Scale	X	X	X
Social Responsiveness Scale-2	X	X	X

What are the risks of this research study? What could go wrong?

Some procedures used in this research may present risks that are not well-known or understood. Therefore, there may be unforeseeable risks associated with participating in this research.

There are no invasive procedures involved in participating. Children in the intervention group might find it tiring to complete 5 35-40 minutes sessions per week. You may be asked questions in an interview or on a questionnaire that make you uncomfortable or cause you to remember situations that were upsetting to you. You may become frustrated if you are asked questions that you do not know how to answer. You may not be able to answer all the questions, and you do not need to answer any questions that you do not wish to answer. If

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you or your child becomes upset at any time, you can stop the interview or stop completing an evaluation or a questionnaire. If you wish to speak to someone about how you are feeling, we can help you arrange this.

What are the benefits of this research?

If the Cogmed Working Memory Training Program is effective, children might benefit from improved executive function abilities. All children who enroll in the study will have the opportunity to do the Program, though there will be a delay of a few months before the children randomized to the control group will be able to do so.

If any of the information collected suggests that your child might benefit from additional neuropsychological evaluation, we will tell you and discuss options for following-up.

Are there costs associated with this research? Will I receive any payments?

There are no costs to you to participate in this study.

Families in both the intervention and control groups will need to return the iPad to us after the Cogmed Working Memory Training Program is completed.

Regardless of whether group your child is assigned to, the intervention or standard of care group, you will be paid $100 after Visit 2 is completed, and your child will be given a $25 gift card. If you and your child complete Visit 3, you will receive an additional $100 and your child another $25 gift card. This will add up to a total payment of $200 to you and a total of $50 in gift cards to your child. Parking costs will also be paid for you for all visits. In addition, if you travel from far away for the study visits, transportation costs will be covered with airfare/train for the study participant and one parent or legal guardian, vouchers for taxi transportation, parking and/or mileage reimbursement. If needed, hotel costs for 1 night will also be covered.

This research study will use a service called ClinCard® by the company Greenphire, www.greenphire.com, to manage all payments associated with your participation in study visits, your time and travel related to participation in the study. ClinCard/Greenphire will provide documentation for filing your taxes (1099 form), to the hospital, and may ask for your name and social security number using a secure website to meet that federal requirement. Boston Children's Hospital or the sponsor has contracted with ClinCard/Greenphire to provide this service but Boston Children's Hospital and ClinCard/Greenphire are separate entities and have no other relationship. ClinCard/Greenphire is solely responsible for the security of any information you provide to them.

You will be issued a ClinCard, which is a specially designed debit card for clinical research onto which your funds will be loaded as appropriate. When a study visit is completed, funds will be loaded onto your card. The funds will be available within 1 day and can be used as you wish.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by

signing this form. If you think you have been injured or have experienced a medical problem as a result of taking part in this research, tell the person in charge of the research as soon as possible. The researcher's name and phone number are listed in this consent form.

If I do not want to take part in this research, what are the other choices?

If you do not join this research study, your doctor can discuss other healthcare choices with you. It would be possible for your child to participate in the Cogmed Working Memory Training Program, or some other executive function training, without participating in a research study such as this one.

Are there other things I should know about?

If we find out about new information from this research or other research that may affect your health, safety or willingness to stay in this research we will let you know as soon as possible.

Why would I be taken off the study early?

The research investigator may take you out of this study at any time. This would happen if:

- The research is stopped.
- You are not able to attend the research visits required.
- If your child is not able to complete the Cogmed training sessions as needed.
- The research investigator feels it is in your child's best interest to be taken out of this research.

If this happens, the research investigator will tell you.

Other information that may help you:

Boston Children's Hospital has developed a web-based, interactive educational program for parents called "A Parent's Guide to Medical Research." To find out more about research at Children's, please visit the program at www.researchchildren.org.

Boston Children's Hospital is interested in hearing your comments, answering your questions, and responding to any concerns regarding clinical research. If you have questions or concerns, you may email IRB@childrens.harvard.edu or call (617) 355-7052 between the hours of 8:30 and 5:00, Monday through Friday.

Who may see, use or share your health information?

A copy of this consent form will be placed in your medical record. The results of the tests performed for research purposes will not be placed in your medical record. Because of this, it is unlikely that others within the hospital, an insurance company, or employer would ever learn of such results.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the Web site will include a summary

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of the results. You can search this web site at any time. The US Food and Drug Administration has the right to inspect this study at any time.

Contact for Future Studies: Your participation in any research is completely voluntary and you should feel no pressure to participate if you are contacted about another research study.

Please check and initial one of the options below regarding future contact about other research that we do.

_____ ☐ Yes, I may be contacted about participating in other research projects studying congenital heart disease or related conditions. I give permission for my contact information (name and mailing address and/or phone number) to be given to other researchers working with the study investigator at Boston Children's Hospital.

_____ ☐ No, I do not want to be contacted about other research projects. **Do not** give my contact information to the staff of any other research studies.

What should you know about HIPAA and confidentiality?

Your health information is protected by a law called the Health Information Portability and Accountability act (HIPAA). In general, anyone who is involved in this research, including those funding and regulating the study, may see the data, including information about you. For example, the following people might see information about you:

- Research staff at Boston Children's Hospital involved in this study;
- Medical staff at Boston Children's Hospital directly involved in your care that is related to the research or arises from it;
- Other researchers and centers that are a part of this study, including people who oversee research at that hospital;
- People at Boston Children's Hospital who oversee, advise, and evaluate research and care. This includes the ethics board and quality improvement program;
- People from agencies and organizations that provide accreditation and oversight of research;
- People that oversee the study information, such as data safety monitoring boards, clinical research organizations, data coordinating centers, and others;
- Sponsors or others who fund the research, including the government or private sponsors.
- Companies that manufacture drugs or devices used in this research;
- Federal and state agencies that oversee or review research information, such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and public health and safety authorities;
- People or groups that are hired to provide services related to this research or research at Boston Children's Hospital, including services providers, such as laboratories and others;

- And/or your health insurer, for portions of the research and related care that are considered billable.

If some law or court requires us to share the information, we would have to follow that law or final ruling. Some people or groups who get your health information might not have to follow the same privacy rules. Once your information is shared outside of Boston Children's Hospital, we cannot promise that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect privacy may no longer apply to this information. Other laws may or may not protect sharing of private health information. If you have a question about this, you may contact the Boston Children's Hospital Privacy Officer at (857) 218-4680, which is set up to help you understand privacy and confidentiality.

Because research is ongoing, we cannot give you an exact time when we will destroy this information. Researchers continue to use data for many years, so it is not possible to know when they will be done.

We will also create a code for the research information we collect about you so identifying information will not remain with the data and will be kept separately. The results of this research may be published in a medical book or journal or be used for teaching purposes. However, your name or identifying information will not be used without your specific permission.

Your privacy rights

If you want to participate in this research study, you must sign this form. If you do not sign this form, it will not affect your care at Boston Children's Hospital now or in the future and there will be no penalty or loss of benefits. You can withdraw from the study and end your permission for Boston Children's Hospital to use or share the protected information that was collected as part of the research; however you cannot get back information that was already shared with others. Once you remove your permission, no more private health information will be collected. If you wish to withdraw your health information, please contact the research team.

You may have the right to find out if information collected for this study was shared with others for research, treatment or payment. You may not be allowed to review the information, including information recorded in your medical record, until after the study is completed. When the study is over, you will have the right to access the information again. To request the information, please contact the Hospital's Privacy Officer at (857) 218-4680.

Contact Information

I understand that I may use the following contact information to reach the appropriate person/office to address any questions or concerns I may have about this study. I know:

I can call…	At	If I have questions or concerns about
Investigator:	Phone: 617-554-424	▪ General questions about the research

Boston Children's Hospital

RESEARCH CONSENT FORM

MRN: _____

Pt Name: _____

Jane Newburger	Pager:	▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints
Research Contact: David C. Bellinger	Phone: 617-355-6565 Pager:	▪ General questions about the study ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints
Institutional Review Board	Phone: 617-355-7052	▪ Rights of a research participant ▪ Use of protected health information. ▪ Compensation in event of research-related injury ▪ Any research-related concerns or complaints. ▪ If investigator/research contact cannot be reached. ▪ If I want to speak with someone other than the Investigator, Research Contact or research staff.

Documentation of Informed Consent and Authorization

- I have read this consent form and was given enough time to consider the decision to participate in this research.
- This research has been satisfactorily explained to me, including possible risks and benefits.
- All my questions were satisfactorily answered.
- I understand that participation in this research is voluntary and that I can withdraw at any time.
- I am signing this consent form prior to participation in any research activities.
- I give permission for participation in this research and for the use of associated protected health information as described above (HIPAA).

Parent/Legal Guardian Permission (if applicable)

If the child to be involved in this research is a foster child or a ward of the state please notify the researcher or their staff who is obtaining your consent.

■ _____ _____ _____

Date (MM/DD/YEAR) Signature of **Parent #1** or **Legal Guardian** Relationship to child

Child Assent

■ If child/adolescent's assent is **not** documented above, please indicate reason below (check one):

☐ Assent is documented on a separate IRB-approved assent form
☐ Child is too young
☐ Other reason (e.g. sedated), please specify: _____

Boston Children's Hospital

RESEARCH CONSENT FORM

MRN: _____

Pt Name: _____

Research Investigator /or Associate's Statement & Signature

- I have fully explained the research described above, including the possible risks and benefits, to all involved parties (participant /parents/legal guardian as applicable).
- I have answered and will answer all questions to the best of my ability.
- I will inform all involved parties of any changes (if applicable) to the research procedures or the risks and benefits during or after the course of the research.
- I have provided a copy of the consent form signed by the participant / parent / guardian and a copy of the hospital's privacy notification (if requested).

■ _____ _____

Date (MM/DD/YEAR) Signature of **Research Investigator or Associate**

Witness Statement & Signature

A witness must be present for the entire consent process in the following situations (please check the appropriate box)

☐ The individual cannot read and this consent document was read to the participant or legal representative, **or**

☐ The individual has certain communication impairments that limit the participant's ability to clearly express consent **or**

☐ Situations where the IRB requests a witness be present: please specify _____

I confirm that the information in this consent form was accurately explained to the participant, parent or legally authorized representative, the individual appeared to understand the information and had the opportunity to ask questions, and that informed consent was given freely.

☐ _____ _____

Date (MM/DD/YEAR) Signature of Witness

Or

☐ The individual is not English or Spanish speaking and, through an interpreter, a short form consent document was presented orally to the participant or legal representative and this consent document serves as the summary for such consent.

I confirm that the information in this consent form was presented orally to the participant, parent or legally authorized representative, in a language they could understand and the individual had the opportunity to ask questions.

☐ _____ _____

Date (MM/DD/YEAR) Signature of Witness

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym. **Page 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry. **Page 2**
	2b	All items from the World Health Organization Trial Registration Data Set. **Page 2, Trial Registration Number NCT03023644 on ClinicalTrials.gov**
Protocol version	3	Date and version identifier. **Page 20**
Funding	4	Sources and types of financial, material, and other support. **Page 27**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Page 27**
	5b	Name and contact information for the trial sponsor **Page 27**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **Page 27**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **Page 27**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Pages 4-8**
	6b	Explanation for choice of comparators **Pages 4-8**
Objectives	7	Specific objectives or hypotheses **Pages 8-9**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Page 9**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained. **Page 10**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists). **Page 10**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Pages 11-13**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **Pages 11-13**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Pages 11-13**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **Pages 11-13**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended. **Pages 13-17**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure). **Page 17**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations. **Pages 17-18**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size. **Page 10**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions. **Page 11**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned. **Page 11**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Page 11**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how. **Page 9**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **Page 9**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol. **Pages 13-17**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols. **Page 13**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol. **Page 17-18 and Appendix 1.**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol. **Pages 18-21**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **Pages 18-21**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **Pages 18-21**

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **Page 17-18 and Appendix 1.**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial. **Page 17-18 and Appendix 1.**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct. **Page 18 and Appendix 1.**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor. **Not applicable as this is a minimal risk study.**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval. **Page 21**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators). **Page 21.**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32). **Pages 11 and 20.**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial. **Page 21**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site. **Page 26**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators. **Page 26**

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation. **This is a minimal risk study. Risks management is presented in Appendix 1.**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions. **Page 21**
	31b	Authorship eligibility guidelines and any intended use of professional writers. **Page 21**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code. **Page 21**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates. **Appendix 2.**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable. **Not applicable.**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: Protocol for a Randomized Controlled Trial of Working Memory Training

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Running Head: Executive Function Intervention for Children with CHD

Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: Protocol for a Randomized Controlled Trial of Working Memory Training

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Running Head: Executive Function Intervention for Children with CHD

Abstract

Introduction: Executive function (EF) impairments are among the most prevalent neurodevelopmental morbidities in youth with congenital heart disease (CHD). To date, no studies have investigated the efficacy of cognitive interventions to improve EF outcomes in children with CHD.

Methods and analysis: This is a single center, single-blinded, two-arm randomized controlled trial (RCT) to test the efficacy of Cogmed Working Memory Training (Cogmed) *versus* standard of care in children with CHD after open-heart surgery in infancy. Participants will consist of 100 children with CHD aged 7-12 years who underwent open-heart surgery before the age of 12 months. Participants are randomly allocated to either an intervention group including training on the home-based Cogmed intervention for a duration of approximately 5 weeks or a control group who receive the standard of care. We will evaluate the efficacy of Cogmed at post-treatment and 3-months after completion of the intervention. Baseline, post-treatment, and 3-month follow-up assessments will include specific measures of EF, cognitive and social functioning, and Attention Deficit Hyperactivity Disorder (ADHD) symptoms. The primary outcome of this study is the change in standardized mean score on the List Sorting Working Memory test from the National Institutes of Health (NIH) Toolbox for the Assessment of Neurological and Behavioral Function. Secondary outcomes include measures of social skills, inhibitory control, cognitive flexibility, and behavioral EF as well as ADHD symptoms as measured by the Behavior Rating Inventory of Executive Function, Second Edition and the Conners 3rd Edition. The efficacy of the intervention will be evaluated by comparing within-subject differences (baseline to post-treatment, baseline to 3-month follow-up) between the two groups using an intention-to-treat analysis.

Ethics and dissemination: This study has received Institutional Review Board (IRB) approval from Boston's Children's Hospital IRB (P00022440) and the Human Protection Agency from the US Department of Defense.

Trial Registration Number: NCT03023644

Running Head: Executive Function Intervention for Children with CHD

Strengths and limitations of this study

- To our knowledge, this is the first randomized controlled trial (RCT) investigating the efficacy of an executive function intervention in improving outcomes for children with congenital heart disease (CHD).
- The home-based Cogmed Working Memory Training (Cogmed) is among the most widely-used evidence-based programs targeting core executive function skills and will directly address the most frequent neurodevelopmental impairment for children with critical CHD that strongly impacts their ability to succeed in academic and social environments. This intervention is individually adapted to each child's own executive function level, which ensures an optimal level of performance throughout the sessions.
- As a home-based intervention, Cogmed reduces the need for hospital-based treatment visits, potentially reducing the burden for families of children with chronic health conditions such as critical CHD.
- This RCT includes computerized individual measures of neurodevelopment and parent- and teacher-rating scales of behavioral and social outcomes as well as collection of patient-specific factors to investigate their potential relationship with response to treatment.
- This is a phase II RCT with the goal of providing the first proof of concept that a cognitive intervention can improve outcomes in children with CHD. It is single-blinded (investigators are blinded to intervention status and patient characteristics but participants know their treatment group) and has a relatively short duration of follow-up (3 months).

Running Head: Executive Function Intervention for Children with CHD

INTRODUCTION

Congenital heart lesions are among the most common birth defects,[1-2] as approximately 1% of infants are born with congenital heart disease (CHD). Of these, more than one-third will present with critical CHD, most broadly defined as forms of CHD requiring surgical or catheter interventions or resulting in death in the first year of life.[1,3] Advances in prenatal diagnosis as well as medical and surgical care have reduced mortality rates for all forms of CHD. However, evidence of central nervous system damage, including delayed brain maturation *in utero* and abnormal brain metabolism and microstructure associated with hypoxic-ischemic injury, has been reported by a wealth of studies of critical CHD.[4-7] A dramatic increase in the population of survivors of infant heart surgery has been accompanied by the increased recognition of their long-term postoperative morbidities. Neurodevelopmental disabilities, particularly executive function (EF) impairments, are currently the most prevalent long-term morbidity in the population with CHD.[4] EF refers to a set of higher-order neurocognitive abilities that serve to coordinate and organize actions towards a goal, allowing the individual to adapt to new or complex situations.[8] Impairments in EF manifest as behavioral dysregulation and attention problems, impaired working memory (i.e., the ability to keep information in mind and manipulate it over a short period of time), and problems with organization and planning abilities. EF is more strongly associated with school readiness than is Intelligence Quotient (IQ), predicts both mathematics and reading competence throughout the school years[8-10] and is strongly associated with social cognition (i.e., decoding other people's mental and emotional states and responding to rapid-paced social interactions).[9]

Executive dysfunction can profoundly impact all dimensions of a child's development[11-14] and is a core feature of attention deficit hyperactivity disorder (ADHD)[15] and autism spectrum

symptoms.[16-17] If untreated, deficits in EF may also predispose individuals to later addiction,[18] eating disorders and obesity,[19] and risk-taking behaviors.[20] These adverse sequelae may carry profound implications for the educational achievement, future employment, and quality of life of individuals with CHD.[4]

EF in critical CHD

Impairments in EF are at the heart of the neurodevelopmental phenotype associated with critical CHD after open-heart surgery.[21-34] EF deficits in children with CHD were first reported in school-aged children with dextro-transposition of the great arteries (d-TGA).[25] Standardized neuropsychological testing showed that patients with d-TGA had substantial difficulty planning and alternating between tasks, which suggested impairments in cognitive flexibility and working memory as well as deficits in planning and sustained attention. On the Behavior Rating Inventory of Executive Function (BRIEF), parents and teachers of adolescents with CHD reported significant difficulties, particularly with regard to working memory.[22] Compared to normative values, parents' ratings were worse by ~0.5 Standard Deviation (SD) and those of teachers by ~1 SD, suggesting not only statistically significant but clinically meaningful impairments. More recent findings also reported specific EF impairments in preschool and school-aged children with d-TGA.[21,23-24] In particular, children had important difficulties in behavioral regulation and cognitive control of attention, and they had worse performances on verbal and visual working memory tasks. Consistent findings have been reported by studies that included children with other types of critical CHD such as tetralogy of Fallot[28] or single ventricle physiology requiring the Fontan operation.[29] Finally, EF impairments have been associated with

worse psychosocial health status and worse quality of life in youth with critical CHD,[31] highighting the potential impact of long-term executive dysfunction on mental health in CHD.[32]

Working memory intervention for children with CHD

The American Heart Association (AHA) recommends routine neurodevelopmental screening of all CHD survivors.[4] A burgeoning literature documents the prevalence and importance of impaired EF and ADHD in CHD survivors,[21-40] and brain imaging studies have provided key information on the underlying disturbances in brain structure and microstructure in patients with CHD.[5-7] Yet to date, no trials have been undertaken to test interventions targeting EF and attention deficits in the CHD population.[34]

Cogmed Working Memory Training (Cogmed) is the most widely used computerized evidence-based intervention that targets EF, specifically providing intensive structured training of working memory.[41-54] It has been shown to improve executive performance in several clinical and non-clinical pediatric populations, including children with ADHD,[41-42;46-47] low working memory and low achievement,[43-44] and children who were born preterm or extremely low-birth weight.[53-54] Unlike hospital- or laboratory-based interventions, Cogmed can be implemented as a home-based intervention for children. Studies using Cogmed have shown that subjects demonstrate the ability to transfer skills to non-trained tests of working memory as well as to tasks that involve similar processes, including attention, inhibition, and non-verbal reasoning.[51-53] The positive effect of training has been observed on parental ratings of inattention, including the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) Parent Rating Scale, ADHD Rating Scale, fourth edition (ADHD-RS-IV), BRIEF, and Conners' Parent Rating

Scale. Sustained improvements in behavior as measured by rating scales have also been observed in ADHD,[48] brain injury,[49-50] and non-clinical groups.[51-52]

In summary, several randomized controlled trials evaluating the use of Cogmed in healthy children[44; 51-52] and in children with various conditions[41-42;47;53-54] have demonstrated that this neurocognitive intervention produces significant generalized and sustained enhancement on measures of EF, and also on everyday life learning and behavioral skills. It is proposed that training working memory using Cogmed is a promising intervention for school-aged children with critical CHD because: (1) it addresses the most frequent neurodevelopmental morbidities that strongly impact the ability to succeed in academic and social environments; (2) it allows for intensive and structured practice of targeted skills, with possible transfer to other neurodevelopmental domains; (3) it is individually adapted to each child's own EF levels, which ensures an optimal level of performance throughout the sessions; (4) it is closely monitored, and various parameters of the child's performance are systematically recorded (e.g., correct answers, speed at which tasks are completed); (5) it is child-friendly and rewarding, which facilitates children's compliance; and, finally, but importantly (6) as a home-based intervention, it reduces the need for hospital/clinic-based visits and multiple costs of individual therapy, potentially reducing the burden for families of children with chronic health conditions such as critical CHD.

In this project, we conduct a randomized controlled trial (RCT) to provide the first proof-of-concept that Cogmed intervention improves neurodevelopmental outcomes in children with CHD, and that the improvements persist to 3 months. We will enroll children with CHD who underwent infant open-heart surgery as this population corresponds to the highest risk category for developmental disorders and disabilities as per the AHA guidelines (Class I; Level of Evidence A).[4] We propose to determine immediate and 3-month post-treatment effects on both

laboratory-based tests and ecological measures of children's EF, ADHD, and social difficulties in everyday life. Our study will also provide insight into factors that are associated with response to treatment, identifying children who may be most likely to benefit from the intervention.

Aims and hypotheses

Specific Aim 1: To evaluate the immediate efficacy of home-based Cogmed intervention for neurodevelopmental outcomes in children with CHD. We hypothesize that children who receive the Cogmed intervention, compared with controls receiving standard of care, will display greater improvement from baseline to post-treatment assessment in EF and social development, and greater reduction in symptoms of ADHD.

Our primary outcome measure will be the change in standardized mean score on the working memory test from the National Institutes of Health Toolbox for the Assessment of Neurological and Behavioral Function (NIH Toolbox)[55] from baseline to post-treatment. Secondary outcomes include changes in standardized mean scores on tests of cognitive flexibility, attention, inhibitory control, and speed of processing from the NIH Toolbox; the Global Executive Composite from the Behavior Rating Inventory of Executive Function, 2nd Edition (BRIEF-2)[56], the Global Index and the ADHD Index from the Conners 3rd Edition (Conners-3)[57], and the Social Responsiveness Scale, 2nd Edition (SRS-2).[58]

Specific Aim 2: To assess the effects of the Cogmed intervention at 3-month follow-up. We predict that significant gains in neurodevelopmental and behavioral outcomes will persist 3 months after cessation of intervention for children who received Cogmed as compared to controls.

The primary and secondary outcomes will be the same as those in Specific Aim 1, except that the change in scores will be from baseline to 3-month follow-up (i.e., approximately 3 months after the last Cogmed session).

Specific Aim 3: To explore cognitive, medical, and sociodemographic factors associated with changes in neurodevelopmental and behavioral scores for children who received Cogmed intervention.

METHODS AND ANALYSIS

Study design

This is a single center, single-blinded, two-arm RCT to test the efficacy of Cogmed intervention *versus* standard of care in children with CHD after neonatal and/or infant open-heart surgery (n=50 in each group). All eligible subjects undergo a baseline neurodevelopmental assessment and then are randomly assigned to either the home-based Cogmed intervention or to a control group receiving the standard of care for children with CHD. All participants will undergo a post-treatment and a 3-month follow-up assessment. All investigators collecting outcome data are blinded to patients' group assignment (Cogmed intervention *versus* standard of care) and to medical and surgical histories. Participants and their parents know their group assignment and thus are not blinded. For children assigned to the Cogmed group, post-treatment assessments are performed one to two weeks after the end of the intervention (i.e., approximately 7-8 weeks after baseline assessment) and follow-up will be performed 3 months after the end of the intervention (i.e., approximately 5 months after baseline assessment). For children in the control group, post-treatment and 3-month follow-up assessments are performed approximately 7-8 weeks and 5 months after baseline assessment, respectively.

Running Head: Executive Function Intervention for Children with CHD

Participants and recruitment

Participants are included if they meet the following criteria: (1) diagnosis of CHD requiring at least one open-heart surgery before one year of age; (2) age between 7 and 12 years at baseline assessment; (3) ≥6 months post cardiac surgery; (4) had received cardiovascular care at Boston Children's Hospital; (5) English or Spanish speaking; (6) informed consent from parent/guardian as well as assent of the child. Exclusion criteria will be: (1) diagnosed chromosomal anomalies and/or genetic syndromes; (2) severe physical and/or sensory impairments (hearing, visual, or psychomotor) that would prevent the use of the computerized program; (3) confirmed diagnosis of an autism spectrum disorder and/or severe developmental or intellectual disorder that would prevent successful completion of the planned study testing; (4) placement in a separate classroom for severe sensory, motor, language or other developmental disability receiving individual support; (5) scheduled to undergo major cardiac interventions in the 6 months following enrollment; (6) received, receiving, or scheduled to receive Cogmed or any other computerized behavioral training program targeting EF or ADHD. We will not exclude children who underwent multiple heart or other surgeries, children with a pre-existing neurological history (e.g., epilepsy, stroke) or with a history of a concurrent diagnosis of ADHD (treated or untreated). Rather, we will account for these factors in the data analysis.

Eligible children living in the United States are recruited through patient databases of Boston Children's Hospital Cardiology Clinic and affiliated New England medical centers. Families are invited to participate in the study via a mail packet and follow-up phone call. Flyers and study brochures are displayed in Boston Children's Hospital Cardiology Clinic and affiliated medical centers as well as in some local advocacy parent organizations. Participants are assessed for eligibility and enrolled by a study coordinator and a research nurse. Informed consent and

assent from the child are obtained by a study coordinator or a research neuropsychologist before the baseline assessment at the hospital. Parents and children receive monetary compensation for participation in the study. These incentives are given at the second and third visits. Additionally, in order to further facilitate participants' compliance and reduce drop-outs, the second and third study assessments may be completed at a child's home. The study start date (i.e., start of active enrollment) was February 27, 2017 and it is anticipated that enrollment will be completed in September, 2019.

Patient and Public Involvement

Patients, patient/family advocacy groups, or the public were not involved in the design, recruitment and conduct of this study. Participants are informed of the burden of the intervention and are given the option to stop at any time point. All eligible patients completing the study will receive an individual report of the results of his or her baseline assessment as well as a general report on study results for the group with CHD when data analyses are completed.

Randomization and stratification

All eligible subjects undergo a baseline neurodevelopmental assessment (Figure 1) and then are randomly assigned to either the standard home-based Cogmed intervention group or to a control group (standard of care). Allocations are assigned using a computerized system only seen by the research assistant or study coordinator after confirming all eligibility criteria and consent. Subjects are assigned in the order in which they are enrolled into the study. Randomization is done by computerized permuted blocks design with blocks of varying sizes. Once a subject has been assigned to a group, he/she will remain in the same trial arm for the duration of the study. The randomization scheme involves two stratification factors: type of CHD (univentricular or

biventricular) and baseline level of EF (a score <85 or ≥85 on the working memory test from the NIH Toolbox). Figure 1 shows the flowchart of the trial design.

Intervention group: Home-based Cogmed Working Memory Training

Children randomly assigned to receive the Cogmed intervention will complete the standard home-based format of the program, Cogmed RM, for children aged 7 years and older. The training program contains 12 child-friendly visual-spatial and verbal working memory tasks (e.g., remembering the order in which lamps light up on a 4x4 grid; recalling a series of numbers of increasing length on the screen). All tasks are adaptive, i.e., task complexity levels are automatically adjusted to match each child's working memory capacity, to improve performance and to limit non-compliance to the intervention due to lack of motivation. Tasks become more difficult, on a session-by-session basis, as a child's performance improves. Each training session lasts approximately 40-50 minutes, and the child is instructed to complete one session per day 5 days each week for 5 weeks, for a total of 25 sessions. The program yields individual session-by-session and task-by-task training results, including the children's responses, time spent on each task, and evolution curves. Cogmed is not FDA-regulated. Based on our specific aims, Cogmed is considered a Non-Significant Risk Device.

Study tablets (i.e., iPads) are provided to families randomized to the Cogmed group in order to standardize the method of delivery. Families receive a link for downloading a web-based software program to the tablet. The program is installed on the tablet by a study coordinator who explains how the training program works and how to log into the system and complete training. The training session and installation of the program are completed after baseline assessment and randomization. Parents and children will be actively involved, and during the installation session, children will complete several practice trials under the supervision of the study coordinator. The

25 sessions will be completed by the child, supervised by a parent. For the first 5 sessions, the child trains on the same set of games; on the 6th session and every 5th session thereafter, a new task is introduced and replaces one of the initial tasks. At the end of each session, the child can play an age-appropriate tablet game as a reward. After each session, a parent will upload the results to a secure website. Families are contacted weekly to check program function and discuss concerns. Compliance is automatically registered by the computerized program and is defined as completing at least 20 sessions, the criterion by which children are categorized as compliant or non-compliant to treatment.[41-42]

To implement this intervention, each investigator and study coordinator involved in coaching is certified as a "Cogmed Coach." The Cogmed Coaches will monitor children's performance on mycogmed.com secured website every week during the intervention to permit continuous evaluation of treatment compliance and fidelity. The Cogmed coach specifically monitors performance of each child and contacts the parents and the child by phone on a weekly basis to discuss progression and any issues arising during the training week. A designated Cogmed coach will be available during the trial to respond to any questions or help with any difficulties during the training. Families and children are encouraged to continue the training for at least 20 sessions. If parents or children struggle with some aspects of the intervention such as the time commitment or a lack of motivation to persist with the training, the Cogmed coach discusses alternative options for accommodating each individual child's needs (i.e., rewards systems available, best time of the day to practice, number of breaks necessary during each session, etc.) We provide weekly feedback sessions and close monitoring in order to discourage drop-outs and increase compliance with the intervention. Parents are asked to complete a training evaluation scale following completion of Cogmed; this scale is an integrated component of

Cogmed that gathers information regarding the child's motivation and attention during the training as well as parents' feedback. As soon as a child finishes the intervention, a blinded post-treatment assessment will be scheduled to occur within the following weeks.

Control group: Standard of care

Children randomly assigned to the control group will receive the standard of care recommended for patients with critical CHD. This includes cardiac surveillance and, if needed, neurodevelopmental counseling and screening at Boston Children's Hospital Cardiac Neurodevelopmental Program. Once enrolled in the study, a child in the control group will not receive Cogmed intervention or any other cognitive intervention that targets executive functions or ADHD symptoms until after the 3-month follow-up assessment is completed, i.e., 5-6 months after initial enrollment. Like children assigned to the intervention group, children in the control group can continue treatments that are already in place for other neurodevelopmental disabilities (e.g., speech therapy, occupational services). For children in the control group, post-treatment and 3-month follow-up assessments will be performed 6 to 7 weeks and 4 to 5 months after baseline assessment, respectively. After the study is completed, children in the control group will be offered the possibility of completing the Cogmed intervention at no cost.

Primary outcome measure

The NIH Toolbox[55] is a set of computerized assessments designed to measure outcomes in longitudinal or intervention trials. This battery is particularly appropriate for our study because it is presented in a computerized child-friendly version, paralleling that of the Cogmed intervention. The *List Sorting Working Memory Test* from the NIH Toolbox is the primary outcome of the trial. This standardized measure assesses the ability to process information across a series of modalities (visual-spatial and verbal), to hold this information in a short-term buffer,

and to actively manipulate it mentally. It is considered an excellent composite indicator of children's EF skills, as it requires the simultaneous implementation of control of attention and working memory abilities on tasks of increasing complexity. Mean scores are automatically computed and are compared to a standardization sample of US children of the same age. Scores are normally distributed [mean=100, SD=15] in the standardization sample. The construct validity of the NIH Toolbox working memory tasks is 0.58 for convergent validity and 0.30 for divergent validity. This test has a test-retest reliability of 0.89 (95% confidence interval (CI): 0.85 to 0.92).

Secondary outcome measures

NIH Toolbox Cognition Battery.[55] We include tests that measure cognitive flexibility, attention and inhibitory control, episodic memory, language, and processing speed. Mean scores on the following tests will be our secondary outcomes: (1) *Flanker Inhibitory Control and Attention Test*, which measures a child's ability to control automatic response tendencies that may interfere with achieving a goal; (2) *Dimensional Change Card Sort Test*, which assesses a child's capacity to switch among multiple aspects of a task; (3) *Picture Sequence Memory Test*, which measures a child's ability to remember the sequence of pictures shown on the screen; (4) *Picture Vocabulary Test* and *Oral Reading Recognition*, which assess receptive vocabulary and reading decoding skills; and (5) *Pattern Comparison Processing Speed Test*, which assesses the amount of time it takes a child to process a set amount of information. All scores are standardized and normally distributed (mean=100, SD=15) in the standardization sample. The test-retest reliability of these tests varies between 0.82 and 0.96.

Behavior Rating Inventory of Executive Function, Second Edition.[56] The BRIEF-2 is a standardized questionnaire that measures children's executive functioning in every-day life. It

includes nine scales: Inhibit, Self-Monitor, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Task-Monitor, and Organization of Materials. Parent and teacher versions of the BRIEF-2 will be included. We will analyze the General Executive Composite T score (mean=50, SD=10 for the standardization sample) for each version (Parent and Teacher), which integrates a child's scores on all of the clinical scales. The composite indices of the BRIEF-2 have high internal consistency (0.94 to 0.98 in the normative sample) and high test-retest reliability (0.84 to 0.88 for parents over a 2-week interval; 0.90 to 0.92 for teachers over a 3.5-week interval).

Conners, 3rd Edition.[57] The Conners-3 is a questionnaire which assesses ADHD-related behaviors in children 3 to 17 years old. We will analyze mean T scores (mean=50, SD=10 in the standardization sample) for the ADHD Inattentive and the ADHD Hyperactive-Impulsive DSM-5 Symptom Scales as well as the ADHD Index for both the Parent and Teacher versions. For children 6-11 years old, the Cronbach's alpha coefficients for scores on the scales range from 0.87 to 0.95 for both parent and teacher ratings, indicating satisfactory internal consistency. Test-retest reliability for the scales ranges from 0.67 to 0.72 for parents and 0.47 to 0.80 for teachers.

Social Responsiveness Scale (SRS-2), Second Edition.[58] The SRS-2 questionnaire evaluates autism spectrum symptoms, including those relating to social awareness, social cognition, communication, social motivation, and autistic traits, in individuals older than 2.5 years. We will analyze T scores (mean=50, SD=10 in the standardization sample) from both versions (Parent and Teacher). Ratings show good internal consistency and interrater reliability.

The schedule of neurodevelopmental data collection is presented in Table 1.

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Table 1. Schedule of neurodevelopmental assessment data collection

	Assessment	Informant	Baseline	Post-treatment*	Follow-up**
Primary Outcome	NIH Toolbox List Sorting Working Memory Test	Child	**X**	**X**	**X**
Secondary Outcomes	NIH Toolbox Cognition Battery	Child	**X**	**X**	**X**
	Behavior Rating Inventory of Executive Function, Second Edition	Parent	**X**	**X**	**X**
		Teacher	**X**	**X**	**X**
	Conners, Third Edition	Parent	**X**	**X**	**X**
		Teacher	**X**	**X**	**X**
	Social Responsiveness Scale, Second Edition	Parent	**X**	**X**	**X**
		Teacher	**X**	**X**	**X**

*Post-treatment (one to two weeks after cessation of intervention and/or 6 to 7 weeks after baseline).

**3-month follow-up (3 months after completion of the intervention and/or 4 to 5 months after baseline).

Covariate measures

We will investigate cognitive, medical, and sociodemographic patient-specific factors as predictors of response to the intervention, at both post-treatment and 3-month follow-up assessments. The following variables will be investigated: baseline Full-Scale IQ scores and all subscales on the Wechsler Intelligence Scale for Children, Fifth Edition[59], and perinatal medical history, including birth weight, gestational age, type of CHD, history of neurological abnormalities, number of open-heart surgeries, intensive care unit length of stay, and total number of hospitalizations.

Data Management and Safety Monitoring

Overall integration of the statistics, data management and administrative functions of this trial occur in the Department of Cardiology's Research Support and Statistics Core (RSSC) led by Drs. Jane Newburger and David Wypij. The RSSC provides the infrastructure necessary to

facilitate the conduct of this clinical trial including biostatistical analysis, computerized data entry, data base programming and development, data management, quality control, assistance with manuscript preparation and administrative functions. The RSSC provides a centralized resource for maintaining database. Study documents are being stored in individual subject folders, each folder containing a tracking page. All study materials are stored in a locked file cabinet accessible only to authorized study staff. All study data are recorded on Case Report Forms and entered into a REDCap (Research Electronic Data Capture) database.

A Data and Safety Monitoring Board (DSMB) is comprised of expert members in Cardiology, Neuropsychology and Biostatistics. Members will be independent of the study investigators and their Departments at Boston Children's Hospital as well as from the sponsors of this study. The function of the DSMB will be to advise the funding sources, Boston Children's Hospital and the study investigators on (1) final study designs and protocols prior to the beginning of data collection, (2) problems encountered protocol implementation, (3) frequency of occurrence of adverse events and their relation to study protocols, (4) withdrawals and losses to follow-up, (5) data interpretation and ethical issues, and (6) recommendations arising from the study. The DSMB Chair will receive reports of any serious events that occur in the conduct of the study. This trial has been considered as a Non-Significant Risk device study and reviewed accordingly by the Boston Children's Hospital Institutional Review Board and the Human Research Protection Office (HRPO), US Department of Defense.

A complete description of this trial's data management plan, Safety Monitoring Board and Risk/Benefits Assessment is presented in Appendix 1.

Sample size and power considerations

Our specific aims are to determine whether there are significant differences between the intervention and control groups in the change in scores on the List Sorting Working Memory Test between measurements at baseline and post-treatment (Specific Aim 1) and between baseline and 3-month follow-up (Specific Aim 2). Although this test has a good test-retest reliability of $\rho=0.87$, to be conservative, we will assume a value of $\rho=0.70$ between baseline and post-treatment and between baseline and 3-month follow-up on the same subject. Given a sample size of 100 subjects, $\rho=0.70$ for within-subject correlations, and a two-sided Type I error rate of 5%, we have 81.4% power to detect a mean difference of 0.5 SD between treatment groups, with a conservative 20% attrition rate (hence, analyzing a minimum of 80 subjects) in our primary outcome measure. This corresponds to a mean difference of 7.5 units, given an expected SD of 15 for the List Sorting Working Memory Test of the NIH Toolbox.

Among children who receive the Cogmed intervention, we also seek to assess associations of cognitive, sociodemographic, and medical factors with changes in the scores for our primary outcome measure (Specific Aim 3). Given a sample size of 50 children in the Cogmed group and a two-sided Type I error rate of 5%, we have 79.9% power to detect a correlation of 0.43 (or $R^2 = 0.43^2 = 0.185$ from a linear regression) between a patient-specific factor and the primary outcome variable even with a conservative 20% attrition rate (analyzing a minimum of 40 subjects).

Data analysis plan

For Specific Aims 1 and 2, the efficacy of the intervention will be evaluated by comparing within-subject differences (baseline to post-treatment, baseline to 3-month follow-up,

and, in secondary analyses, post-treatment to 3-month follow-up) across treatment groups using an intention-to-treat analysis.

Descriptive statistics will be calculated, including means, standard deviations, medians, and interquartile ranges for continuous variables and frequency counts and percentages for categorical variables. The primary outcome measure, the List Sorting Working Memory Test of the NIH Toolbox, and most other study outcomes are continuous variables. T tests and linear regression will be used to assess differences between the intervention and control groups for continuous outcomes (i.e., differences in means, 95% CI). Proportions and logistic regression will be used to examine group differences in binary outcomes (i.e., chi square tests, odds ratios, 95% CI). We expect that randomization will produce balance between treatment groups in terms of demographic and baseline factors, but we will use regression methods to adjust for any factors that may be unbalanced. All analyses will be accompanied by graphical exploration of the data to identify outlying and influential observations. Data transformations and nonparametric methods (e.g., Wilcoxon rank sum tests) will be used as appropriate when parametric assumptions are violated. Primary analyses of treatment group differences will focus on complete cases. In secondary analyses, we will assume no change over time for subjects who do not return for their post-treatment assessment (i.e., last value carried forward approach), but we will also carry out other sensitivity analyses to assess the strength of our findings based on other missing data assumptions.

For Specific Aim 3, we will explore the associations between patient factors and within-subject differences (baseline to post-treatment, baseline to 3-month follow-up) using correlation and linear regression methods, including consideration of possible confounding or effect modification. Specific attention will be given to certain patient-specific risk factors including age

at first heart surgery (neonatal *versus* non-neonatal), number of surgeries and neurological complications. Because we will be conducting multiple analyses with several predictors and primary and secondary outcomes in an exploratory fashion, we will interpret results cautiously, based not only on significance levels ($p<0.05$, two-tailed) but also on the magnitude of differences, correlations, or regression effects. As appropriate, we will also consider the use of other statistical methods, such as generalized additive models, partial and sparse partial least squares, and family-wise error rates, in our approach. Analyses will be conducted primarily using SAS, Stata, SPSS, and R.

ETHICS AND DISSEMINATION

This study has received full Institutional Review Board (IRB) approval from Boston's Children's Hospital IRB (P00022440) and has also been reviewed and approved by the Human Protection Agency from the United States Department of Defense. Protocol modifications and amendments will be submitted to the ethical committees for approval. Amendments to the study protocol will be added to publications reporting the study outcomes. This trial has been registered with the American Clinical Trials Registry (NCT03023644). Prior to entering into the trial, all parents or legal guardians and children will give written informed consent or assent to participate. Appendix 2 presents the study consent form. All information will follow IRB and Human Protection guidelines for confidentiality and data protection. The study results will be disseminated through publications in scientific journals, presentations at scientific conferences, and directly to the families who participated in the study. Co-investigators will be co-authors of the publications describing trial outcomes, without the use of professional writers. Data will be provided upon request.

Trial Progress

The trial is currently in the active recruitment phase (first baseline assessment February, 2017). This is Protocol V.4, 10 July 2018. Substantial protocol amendments will be communicated to investigators via email and to other parties as required. All changes are submitted to Boston Children's Hospital's IRB, to the Sponsor of this trial (US Department of Defense) and updated in clinicaltrials.gov.

Discussion

This article has presents the background and design of a RCT investigating the efficacy of a 5-week working memory intervention for children with CHD who underwent open-heart surgery in infancy. This is the first study to investigate the effects of a neurocognitive intervention targeting EF in school-aged children with CHD. We will evaluate children's cognitive and social outcomes including autism spectrum and ADHD symptoms. Furthermore, the results from this trial will provide information on potential patient-specific factors associated with response to the intervention. As a first clinical trial, we will test the efficacy of the intervention at 3-months after the cessation of training. If the intervention is proven effective at this time, longer-term effects should be investigated (e.g., at 6- or 12- months post-intervention). Assessment of longer-term effects of working memory training will provide key information about the cost-efficacy of Cogmed in CHD patients, the likelihood that lasting benefits generalize to other areas of development, and the duration of its benefits.

Executive dysfunction may have cascading adverse effects on a myriad of domains ranging from specific neurocognitive abilities to school achievement, social adaptation, and, ultimately, quality of life. Timely prevention and treatment of these issues is a priority in the care of patients with CHD. If proven effective, this type of neurocognitive intervention could be implemented in a clinical outpatient practice for patients at increased neurodevelopmental risk.

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Running Head: Executive Function Intervention for Children with CHD

Contributors JC, DCB, and JWN are the primary investigators and together with DW designed and established this research study. JC and JWN were responsible for ethics applications and reporting. JC, DCB, CH, and AL are responsible for data collection and implementation of the intervention. JC will take lead roles on preparation for publication of the clinical outcomes of the study. JWN, DCB, DW, CS, CH, and AL will contribute to the preparation of publications within their respective fields of expertise. DW and CS will take on a lead role of the statistical analysis for the study. JC drafted the final version of this manuscript. All authors critically reviewed and approved the final version. All data from this study will be submitted to peer-review journals and for presentation at national and international scientific conferences.

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Competing interests No competing interests are reported. Authors do not have any commercial or scientific affiliation with Pearson, Inc., distributor of Cogmed Working Memory Training.

Ethics approval Full ethical approval for this study has been obtained by the Boston Children's Hospital's Institutional Review Board (IRB) (IRB number P00022440) and has also been reviewed and approved by the Human Protection Agency from the United States Department of Defense. All parent/guardians and children will give written informed consent or assent to participate prior to entering into the trial.

Running Head: Executive Function Intervention for Children with CHD

Figure 1. Flowchart of trial design (ND=neurodevelopmental)

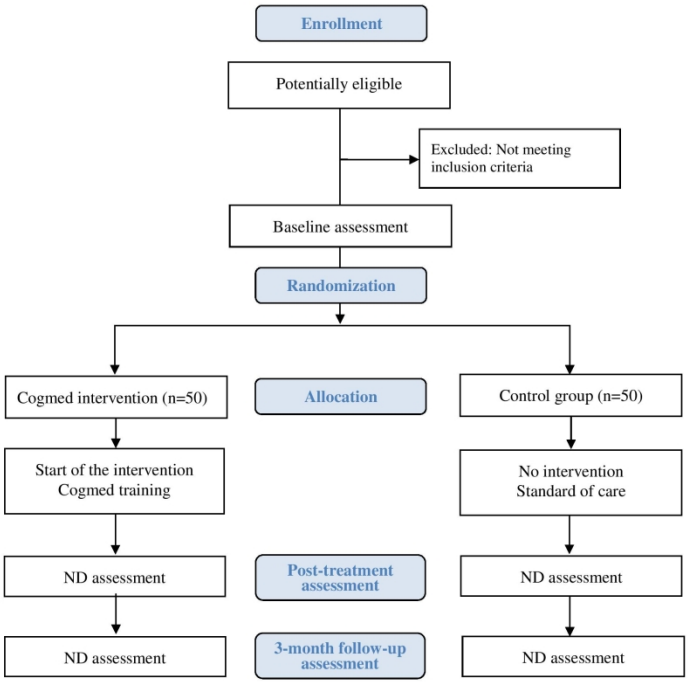

Figure 1. Study flow-chart

215x279mm (300 x 300 DPI)

Appendix 1

Calderon J, Bellinger DC, Hartigan C, Lord A, Stopp C, Wypij D, Newburger JW. Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: Protocol for a Randomized Controlled Trial of Working Memory Training.

1) Data Management and Quality Control

2) Data and Safety Monitoring Board

3) Risk/Benefits Assessment and Risk Management

1) Data management and quality control

Overall integration of the statistics, data management, and administrative functions of this trial will occur in the Department of Cardiology's Research Support and Statistics Core (RSSC). The RSSC will be led by Drs. Jane Newburger and David Wypij. Key support personnel in the RSSC will be a Master's level statistician/statistical programmer (Christian Stopp) and Study Coordinator (Carolyn Dunbar-Masterson).

The purposes of the Research Support and Statistics Core are as follows:

1. To support final protocol development during the Planning Phases of the clinical trial, including refinement of study design, eligibility criteria, baseline and outcome measures, power and sample size calculations, randomization methods, statistical analysis plans (including early stopping rules), and ethical considerations.
2. To assist in overall study coordination of patient follow-up, training of study personnel, quality control and quality assurance, development of Case Report Forms and Manuals of Operations, database development, data entry, database checks and updates, and maintenance of blinding and firewalls.
3. To perform statistical analyses and study monitoring (including adverse event monitoring and Data and Safety Monitoring Board reports).
4. To plan and perform final data analyses, support publication and abstract preparation, and create final data sets for archival purposes.
5. To plan and analyze ancillary studies, such as mechanistic studies or analyses of the association of clinical variables with the outcomes of the intervention.
6. To provide administrative support as needed for research excellence in the trial.

The Research Support and Statistics Core will provide the infrastructure necessary to facilitate the conduct of the proposed clinical trial. Its functions include biostatistical analysis, forms design, data base programming and development, clinical data management, quality control, clinical research study coordination, assistance with manuscript preparation, and administrative functions. It provides a centralized core of key program project staff. In addition to including facilities needed to conduct clinical research studies at Boston Children's Hospital, it provides a centralized resource for maintaining databases and facilitating quality-control procedures for all patient–related data. Individuals in the RSSC will provide computerized data entry and quality control of data. The policies, procedures, and resources already in existence in the Statistical and Data Coordinating Center of the Department of Cardiology at Boston Children's Hospital provide the infrastructure to facilitate these efforts. Computing resources and biostatistical collaboration will be provided for the design, conduct, analysis, and reporting of the trial. Computing resources will also be supported by the RSSC.

Study documents will be stored in individual subject folders; each folder will contain a tracking page that enables study staff and investigators to record annotations and comments regarding the clinical data. All study materials will be stored in a locked file cabinet that is accessible only to authorized study staff. For data analyses, all de-identified Cogmed records will be downloaded and stored with the corresponding subject identification number for each subject. The majority of neurodevelopmental tests have a computerized format that automatically calculates children's score as a function of their performance. Subject confidentiality will be maintained by recording subject data with use of a unique subject identifier. Identifiable data, such

as contact information and medical record numbers, will be recorded and stored separately from the clinical study data.

Case Report Forms will be developed jointly by the clinical, biostatistical, and data coordination team members working on this clinical trial. Forms design features include the selection of valid, reliable measurements that are less burdensome, development and testing of reliability measures, pre-testing of forms, formatting of forms to ensure clarity (standard conventions for coding close-ended questions, minimal use of open-ended questions), and smooth flow in question patterns to reduce missing data. A detailed Manual of Operations will be developed to ensure efficient, consistent, and accurate data collection and ease of communication. The Manual of Operations will allow updating, as needed, using dated footers. The Case Report Forms and Manual of Operations for this trial will be based on those successfully used in previous studies by the investigative team.

All study data will be recorded and maintained on Case Report Forms and entered into a REDCap (Research Electronic Data Capture) database. REDCap is a secure, fully customizable, web-based application designed to support data capture for clinical research studies. REDCap provides user-friendly Case Report Forms, audit trails, calculated fields, queries, and the ability to set up a calendar to schedule and track critical study events, such as participant visits. Auto-validation, branching/skip logic, and other features provide real-time data entry validation to prevent logic errors, range checks to reduce out-of-range values, context-specific help actions, and conditional logic to ensure accurate data collection. Designated users from the research study team can be assigned different levels of access. REDCap is designed to comply with HIPAA regulations,

and allows data export to common analysis packages such as SAS, Stata, R, or Excel. Daily database backup routines are executed to ensure data safety, security, and reliability.

2) Data and Safety Monitoring Board

A Data and Safety Monitoring Board will be comprised of five members, each of whom is eminent in one of the specific areas at issue in the study: Pediatric Cardiology, Psychiatry and Neurodevelopment, and Biostatistics. Members of the DSMB must be independent of the study investigators and their departments at Boston Children's Hospital. The function of the DSMB will be to advise the funding sources, Boston Children's Hospital, and study investigators on: (1) final study designs and protocols prior to the beginning of data collection, (2) problems with protocol implementation, (3) frequency of occurrence of adverse events and their relation to study protocols, (4) withdrawals and losses to follow-up, (5) data interpretation and ethical issues, and (6) recommendations arising from the study. The DSMB Chair will receive reports of all serious events throughout the conduct of the study. The exact schedule and procedures for monitoring or stopping a study will be established by the DSMB during the first year of the study.

Research Support and Statistics Core staff will assemble and maintain the required data on enrollment, adverse events and data quality for regular reporting to the DSMB, on a schedule to be dictated by the DSMB, and to prepare and present such reports. The methods of analysis for the clinical project and the criteria for early stopping will be developed by Dr. Wypij, with input and approval from the DSMB in general and the DSMB statistician in particular. Statistical analyses

pertinent to early-stopping decisions will be conducted by Dr. Wypij and presented for evaluation to the DSMB on the agreed-upon schedule.

3) Risks/Benefits Assessment

This trial has been considered as a Non-Significant Risk device study and reviewed accordingly by the Boston Children's Hospital Institutional Review Board and the Human Research Protection Office (HRPO), US Department of Defense.

Foreseeable risks:

This RCT does not involve any drugs or invasive procedures, and the injury associated with participation is highly unlikely. Therefore, the trial is likely to entail minimal risk to participants. The NSR determination for this study will not impact the risk/benefit ratio. Participating will require considerable time, particularly in the group that receives the Cogmed Working Memory Training. Children in this intervention group will complete 5 35-40 minute sessions per week for 5 weeks. We will be asking parents to supervise the child's completion of these sessions. The children might find some of the Cogmed Program activities to be frustrating. However, the system is "adaptive," in that the difficulty level of the tasks is titrated to match a child's abilities, thereby insuring some success and lowering stress. The families might be inconvenienced by having to make three visits to Boston Children's Hospital within a 5 month period.

There is some inconvenience and burden of completing questionnaires and some families may feel uncomfortable answering questions. The parent-completed questionnaires will require approximately 60 minutes to complete. We will aim for questionnaires to be completed prior to the in-person assessment, however there will be little time pressure required for the completion of

the instruments by the parents and teachers as they will be mailed out to parents approximately 3 months prior to the appointment for the in-person evaluation.

Risk Management Response:

- **Neurodevelopmental Testing and CogMed Intervention:** Prior to beginning the evaluation, subjects and families will be told that the information they provide will be held in confidence and not revealed to school officials or other authorities without their permission, and that names will not be associated with answers in our database. Possible referrals will be discussed with the family. Similarly, parents will be told that we are required by law to report any evidence that suggests child abuse. As part of the debriefing, both the child and parent will be asked if they would like additional care or services. If so, we will provide referrals. If a patient's responses suggest engagement in risk-taking behaviors, appropriate resources will be discussed and information provided. An experienced psychiatric clinician will always be available to address with the children or parents who experience any distress that the testing or questionnaires might stimulate.

e) If children and/or parents exhibit any indication of suicidal thoughts or intentions, this will be carefully discussed both with the parent(s) and subject. Suicidal intent, plans, and means will be evaluated by a licensed clinician. Subjects judged to be at risk will be referred for further evaluation and intervention. Referrals for emergency evaluation would be made to our institution's Psychiatric Emergency Service or to hospitals closer to their homes, if appropriate. The on-call and emergency service mental health providers will be notified of the study's existence.

f) If a subject exhibits a significant depression or appears to require psychiatric hospitalization, s/he will have access to referral for treatment. If during the assessment,

the subject has a suicide plan or attempt or the severity of the adolescent's depression requires hospitalization, the psychiatric clinician at the participating center will facilitate hospitalization. If the subject requires additional care but does not require hospitalization, the research team will facilitate the subject's obtaining this care using his or her own health insurance.

- **Ascertaining Vital Status of Subjects:** We will contact the subject's cardiologist before initiating contact with subjects and their families to be sure that the subject is alive. There is a tiny chance that the cardiologist might not have been informed about a subject's death and that we will cause distress by contacting parents of an expired subject not known to have died.
- **Costs:** Tests required by the study will be provided free of charge. The study will also pay for parking for families.
- **Alternatives:** Parents and children will be told that if they decline to participate, the future medical care that the child might receive at Children's Hospital in Boston will not be affected and that if they agree to participate, they are free to withdraw from the study at any time or to decline to participate in specific aspects of the study protocol.
- **Confidentiality:** Investigators will take all reasonable measures to protect the confidentiality of subjects and their families, including the following:

  a) Investigators will arrange for counseling if anxious feelings arise in the family at any time during the study.

  b) Each child and parent is assigned a subject identification number (SID). All interview and clinical research data are stripped of identifiers and labeled with the

study number. The enrollment log with participant identifiers will be maintained at each site in a secured, locked location available only to the study staff.

c) The study will follow good clinical practices at all times. Databases will be secured as previously discussed.

d) The risk of breach of subject confidentiality will be minimized by storage of all study materials in a locked file cabinet in a location separate from the laboratory data.

e) The subject's name and any other identifying information will not appear in any presentation or publication resulting from this study.

f) The study team will contact family members for recruitment according to local guidelines. As per local requirements, contact will be made with those individuals who have expressed a willingness to at least learn about the research study. Other family members will not be informed of who is and is not participating. The subject will also be warned not to disclose their participation in order to protect their own privacy.

g) If important clinical findings are noted during the study, the PI or other qualified member of the research team will take full responsibility for disclosing the findings to the patients/parents, communicating with their primary care physicians with permission, and making appropriate referrals as indicated. The subject may choose to seek a second opinion and/or appropriate clinical care. This might change the subject's insurability as it relates to the clinical finding only. The presumption is that detection of a potentially clinically significant finding will prove to be beneficial to the subject in the long run.

Potential benefits

- Children who complete the Cogmed Working Memory Program might experience an improvement in their executive functioning. This could help them to function more effectively in school, at home, and in their social relationships.
- Subjects and their families who return for neurodevelopmental evaluation will learn about those aspects of the child's neurodevelopmental status that are assessed by the battery of tests. If the family provides consent, this information will also be shared with the pediatrician.
- If there are areas in which a subject is functioning poorly, these can be identified and recommendations for further evaluation or intervention provided, as appropriate.
- An indirect benefit may also come from the awareness that the results of this study may serve to help improve the care of children with similar problems in the future. CHD patients and their families may derive a sense of altruism, accomplishment, and contribution to furthering understanding of the problem through their participation.

Risk/Benefit Ratio and importance of information to be obtained

The risk/benefit ratio is favorable for this study, for the following reasons:

1. The baseline risk is minimal because adverse events are extraordinarily unlikely.
2. Although an individual subject may not benefit from participation, the results of this study will make important contributions to understanding potential treatment of executive function deficits.
3. The CogMed intervention has never been studied in children with CHD.

4. The in-person evaluation for subjects in both treatment groups will provide accurate and rich information about neurocognitive function for use by patients, their families, and schools.

5. Data generated from this study will provide guidance that can be provided to parents and medical care providers of patients with congenital heart disease.

Safety assessment and monitoring

Because no physical interventions will take place, the likelihood of significant adverse events related to the study are relatively small.

a) Specification of Safety Parameters: Any complication during a study evaluation or occurring within 24 hours of a study evaluation will be considered an adverse event and reported as described below.

b) Recording and Reporting Adverse Events: This study is not an intervention study. However, a major component of safety monitoring is ascertainment and reporting of adverse events (AE), including adverse reactions to study procedures. The approach to these activities for this study is summarized in the sections that follow.

c) Definitions of Adverse Event, Suspected Adverse Reaction and Adverse Reaction: For the purposes of this study, adverse events will include any untoward event that occurs during or in close proximity to any study related evaluation including the battery of neurodevelopmental assessments.

d) Classification of Adverse Events: Monitoring AEs requires that they be classified as to seriousness, expectedness, and potential relationship to the study, of which drive the reporting process.

(1) *Seriousness*

ii) A serious adverse event (SAE) is one that:

(1) Results in death,

(2) Is life-threatening (the subject was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred),

(3) Requires inpatient hospitalization or prolongation of existing hospitalization,

(4) Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or

(5) Is an important medical event that may jeopardize the subject or may require medical/surgical intervention to prevent one of the serious adverse event outcomes.

The Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 MedDRA 12.1 (http://ctep.cancer.gov) provides a grading system that is used to categorize the severity of adverse events, as follows:

Grade 1	Mild	Transient, requires no special treatment or intervention, does not interfere with daily activities
Grade 2	Moderate	Alleviated with simple treatments, may limit daily activities
Grade 3	Severe	Requires therapeutic intervention and interrupts daily activities
Grade 4	Life-threatening	

Or disabling

Grade 5 Death

A AE, as defined above, encompasses CTCAE grades 4 and 5, and any Grade 3 event that requires or prolongs hospitalization, or that substantially disrupts the ability of the subject to conduct normal life functions.

2. Expectedness

The purpose of reporting is to provide new, important information on serious reactions or events previously unobserved or undocumented. Therefore, all AEs will be evaluated as to whether their occurrence was unexpected, using the following definitions:

- *Unexpected*: An unexpected AE or adverse reaction is one for which the nature or severity is not consistent with information in the protocol, or consent form. An AE or adverse reaction also may be categorized as unexpected if the event has not previously been observed at the same specificity and/or severity.
- *Expected*: An event is considered expected if it is known to be associated with the particular evaluation

3. Causality

Causality assessment is required to determine which events require expedited reporting. The following criteria will be used to determine causality:

- *Not Related*: The event is clearly related to other factors, such as the subject's clinical state, or non-study drugs or interventions.

- *Possibly Related*: The event follows a compatible temporal sequence from the time of study evaluation, but could have been produced by other factors such as the subject's clinical state or non-study drugs or interventions.
- Probably Related: The event follows a reasonable temporal sequence from the time of study evaluation, and cannot be reasonably explained by other factors such as the subject's clinical state, or non-study drugs or interventions.

g) Identification and Data Collection Procedures: AEs that are not considered adverse reactions or suspected adverse reactions will be identified when they are reported to the clinical center or during scheduled study visits by study coordinators and investigators. AEs will be assessed using self-report, physical examination data, and medical record review.

h) Identification and Data Collection Procedures: AEs that are not considered adverse reactions or suspected adverse reactions will be identified when they are reported to the clinical center or during scheduled study visits by study coordinators and investigators. AEs will be assessed using self-report, physical examination data, and medical record review.

i) Reporting Procedures

Fatal or life-threatening AEs are to be reported to the ACC within 24-hours of first knowledge of the event. Those that are unexpected and considered possibly, probably, or definitely related to the study will be reported as soon as possible, but no later than 7 calendar days after first knowledge of the event, followed by a complete report within 15

calendar days. All other fatal or life-threatening events that are unrelated to the study will be reported semiannually to the DSMB.

All other *SAEs (i.e., non-fatal or not life-threatening)* that are unexpected and considered possibly, probably, or definitely related to the study will be reported within 24-hours of learning of the event.

All other *AEs* not meeting the criteria for expedited reporting will be reported within 7 calendar days of first knowledge of the event.

Reporting of Adverse Events

Seriousness	**Reporting Timeframe**
Fatal or life threatening	Within 24-hours of learning of the event
Serious, but not fatal or life threatening	Within 24-hours of learning of the event
All other	Within 7 calendar days of learning of the event

h) Reporting Adverse Events to Institutional Review Boards: The site Investigator or designee is responsible for reporting all serious adverse events to the local IRB in accordance with local policies and procedures.

i) Follow-up of Subjects after Adverse Events: For AEs with a causal relationship to the study conduct, follow-up by the Investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator.

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This section only to be edited by IRB office.

Use Plate or Print:

MRN#:

DOB:

Subject's Name:

Gender:

Protocol Title: Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: An Intervention Study

Principal Investigator: Jane Newburger, MD

This consent form gives you important information about a research study. A research study helps scientists and doctors learn new information to improve medical practice and patient care.

Participation in this research study is voluntary. You are free to say yes or no and your decision will not impact the care you receive at Boston Children's Hospital. You can withdraw from the study at any time. A description of the study and its risks, potential benefits and other important information are in this consent form. Please read this consent form carefully and take your time making a decision. The form may contain words that you do not understand. Please ask questions about anything you do not understand. We encourage you to talk to others (for example, your friends, family, or other doctors) before you decide to participate in this research study.

How are individuals selected for this research study?

You are being asked to participate in this research study because your child was born with a congenital heart disease and received care in the Cardiology Clinic at Boston Children's Hospital.

Why is this research study being conducted?

Children with a history of congenital heart disease sometimes experience cognitive and behavioral difficulties. One of the more frequent difficulties involves what are called executive functions. These refer to processes that guide, direct, and manage one's activities (e.g., the ability to initiate and control behavior, to select relevant task goals, to shift strategies flexibly as needed). Problems in these processes can make it harder for a child to learn in school or to maintain good relationships with others. In this research study we want to learn whether children with CHD can improve their executive functioning by using a computer program called the Cogmed Working Memory Program. Although this Program has helped other groups of children with executive function problems (e.g., children born prematurely or children with conditions such as Attention Deficit Hyperactivity Disorder), it is not known whether it can help children with CHD.

Who is conducting this research study, and where is it being conducted?

The study will be conducted only at Boston Children's Hospital by a team led by Dr. Jane Newburger, a pediatric cardiologist and Drs. David Bellinger and Johanna Calderon, research pediatric neuropsychologists. It is funded by a grant from the Department of Defense. Dr. Jane Newburger is the sponsor of this Non-Significant Risk investigational device study.

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MRN: _____

Pt Name: _____

It is possible that Dr. Newburger is your child's cardiologist. Although she is an investigator in this study, your child's clinical welfare is her foremost concern. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another health care provider who is in no way associated with this study. You are not under any obligation to participate in any research project offered by your health care provider. If you choose not to participate or not to allow your child to participate, your care at Boston Children's Hospital and/or with your health care provider will not be affected in any way at all.

How many people will participate in this research study?

Approximately 100 7 to 12 year old children and their families will take part in this study.

What do I have to do if I am in this research study?

The duration of your participation in this research study will be 4 to 5 months.

If you decide to join the research study, you will come to the Boston Children's Hospital three times in the next few months. At today's visit, your child will receive a neurodevelopmental assessment consisting of a global cognitive test, the WISC-V and a battery of cognition and executive function tasks from the National Institutes of Health (NIH) Toolbox Assessment of Neurological and Behavioral Function. These are game-like tasks and most are administered on a computer or tablet. This assessment will give us an idea of how your child is doing before receiving the Cogmed intervention and so make it easier to determine if the intervention helps. Also, you will be asked to complete 3 questionnaires that ask about your child's executive function behaviors. These are the Behavior Rating Inventory of Executive Function (BRIEF), the Connors' ADHD DSM-IV Scale (Connors), and the Social Responsiveness Scale. It will take about 45 minutes to complete these. In addition, we will ask you to give the BRIEF and the Connors' questionnaires to your child's teacher to complete. The total time of the visit will be about 2.5 hours.

Your child will then be randomly assigned to either the home-based intervention group, which will receive the Cogmed Working Memory Program, or to a control group. Randomization means that you are put into a group by chance. It is like flipping a coin. Your child will have an equal chance of being placed in the groups. Neither you nor the research investigators can choose what group you will be in. You and your child will know which group you were assigned to, though. Children in the control group will not receive the Cogmed intervention right away but will continue to receive the usual care for children with CHD, which involves surveillance for neurodevelopmental problems, and neurodevelopmental screening and counseling, as needed. When the research study is finished, you will be given the opportunity to have your child receive the same 5-week Cogmed Working Memory Training Program that children assigned to the intervention group received.

If your child is assigned to the intervention group, you will start the Cogmed intervention in the week following the first neurodevelopmental evaluation. A member of the study team will show you and your child how the Cogmed Working Memory Program works and will answer any questions you have on the first visit. Your child will be provided with an iPad on which the Program will be pre-loaded and a secured ID will be created for your child's personal use throughout the intervention. It is child-friendly and web-based. It presents different

game-like tasks for your child to play. The difficulty of the tasks changes to match your child's working memory capacity, so they become more difficult as your child's working memory improves. Your child will complete 25 sessions, each of which lasts 35-40 minutes. These will be spread out over 5 weeks, so that he or she will do one session a day for 5 days per week. The iPad will record your child's responses, and we will be able to securely retrieve these data remotely. We do ask that you supervise your child over this period so help make sure that he or she completes the sessions.

For children in the Cogmed group, Visit 2 (Post-Intervention) will be completed 1 to 2 weeks after completing the Program. For children in the control group, Visit 2 will be completed 6 to 7 weeks after Visit 1. At Visit 2, children in both groups will again be administered the NIH Toolbox tasks, and parents and teachers will complete the same questionnaires they completed at Visit 1. Visit 3 (Follow-Up) will be the final phase of the study. It will take place 4 to 5 months after Visit 1. The same assessments completed at Visit 2 will be done at Visit 3. The purpose of Visit 3 is to see if the beneficial effects of the intervention at Visit 2 (should there be any) are still present after several weeks. Visits 2 and 3 will each take 2 hours.

Study Visit Timeline	Visit 1 Baseline	Visit 2 Post-intervention (6-7 weeks after baseline)	Visit 3 Follow-up (4-5 months after baseline)
Consent /Assent	X		
WISC-V	X		
NIH Toolbox	X	X	X
Behavior Rating Inventory of Executive Function	X	X	X
Connors' ADHD/DSM-IV Scale	X	X	X
Social Responsiveness Scale-2	X	X	X

What are the risks of this research study? What could go wrong?

Some procedures used in this research may present risks that are not well-known or understood. Therefore, there may be unforeseeable risks associated with participating in this research.

There are no invasive procedures involved in participating. Children in the intervention group might find it tiring to complete 5 35-40 minutes sessions per week. You may be asked questions in an interview or on a questionnaire that make you uncomfortable or cause you to remember situations that were upsetting to you. You may become frustrated if you are asked questions that you do not know how to answer. You may not be able to answer all the questions, and you do not need to answer any questions that you do not wish to answer. If

you or your child becomes upset at any time, you can stop the interview or stop completing an evaluation or a questionnaire. If you wish to speak to someone about how you are feeling, we can help you arrange this.

What are the benefits of this research?

If the Cogmed Working Memory Training Program is effective, children might benefit from improved executive function abilities. All children who enroll in the study will have the opportunity to do the Program, though there will be a delay of a few months before the children randomized to the control group will be able to do so.

If any of the information collected suggests that your child might benefit from additional neuropsychological evaluation, we will tell you and discuss options for following-up.

Are there costs associated with this research? Will I receive any payments?

There are no costs to you to participate in this study.

Families in both the intervention and control groups will need to return the iPad to us after the Cogmed Working Memory Training Program is completed.

Regardless of whether group your child is assigned to, the intervention or standard of care group, you will be paid $100 after Visit 2 is completed, and your child will be given a $25 gift card. If you and your child complete Visit 3, you will receive an additional $100 and your child another $25 gift card. This will add up to a total payment of $200 to you and a total of $50 in gift cards to your child. Parking costs will also be paid for you for all visits. In addition, if you travel from far away for the study visits, transportation costs will be covered with airfare/train for the study participant and one parent or legal guardian, vouchers for taxi transportation, parking and/or mileage reimbursement. If needed, hotel costs for 1 night will also be covered.

This research study will use a service called ClinCard® by the company Greenphire, www.greenphire.com, to manage all payments associated with your participation in study visits, your time and travel related to participation in the study. ClinCard/Greenphire will provide documentation for filing your taxes (1099 form), to the hospital, and may ask for your name and social security number using a secure website to meet that federal requirement. Boston Children's Hospital or the sponsor has contracted with ClinCard/Greenphire to provide this service but Boston Children's Hospital and ClinCard/Greenphire are separate entities and have no other relationship. ClinCard/Greenphire is solely responsible for the security of any information you provide to them.

You will be issued a ClinCard, which is a specially designed debit card for clinical research onto which your funds will be loaded as appropriate. When a study visit is completed, funds will be loaded onto your card. The funds will be available within 1 day and can be used as you wish.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by

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MRN: _____

Pt Name: _____

signing this form. If you think you have been injured or have experienced a medical problem as a result of taking part in this research, tell the person in charge of the research as soon as possible. The researcher's name and phone number are listed in this consent form.

If I do not want to take part in this research, what are the other choices?

If you do not join this research study, your doctor can discuss other healthcare choices with you. It would be possible for your child to participate in the Cogmed Working Memory Training Program, or some other executive function training, without participating in a research study such as this one.

Are there other things I should know about?

If we find out about new information from this research or other research that may affect your health, safety or willingness to stay in this research we will let you know as soon as possible.

Why would I be taken off the study early?

The research investigator may take you out of this study at any time. This would happen if:

- The research is stopped.
- You are not able to attend the research visits required.
- If your child is not able to complete the Cogmed training sessions as needed.
- The research investigator feels it is in your child's best interest to be taken out of this research.

If this happens, the research investigator will tell you.

Other information that may help you:

Boston Children's Hospital has developed a web-based, interactive educational program for parents called "A Parent's Guide to Medical Research." To find out more about research at Children's, please visit the program at www.researchchildren.org.

Boston Children's Hospital is interested in hearing your comments, answering your questions, and responding to any concerns regarding clinical research. If you have questions or concerns, you may email IRB@childrens.harvard.edu or call (617) 355-7052 between the hours of 8:30 and 5:00, Monday through Friday.

Who may see, use or share your health information?

A copy of this consent form will be placed in your medical record. The results of the tests performed for research purposes will not be placed in your medical record. Because of this, it is unlikely that others within the hospital, an insurance company, or employer would ever learn of such results.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the Web site will include a summary

of the results. You can search this web site at any time. The US Food and Drug Administration has the right to inspect this study at any time.

Contact for Future Studies: Your participation in any research is completely voluntary and you should feel no pressure to participate if you are contacted about another research study.

Please check and initial one of the options below regarding future contact about other research that we do.

_____ ☐ Yes, I may be contacted about participating in other research projects studying congenital heart disease or related conditions. I give permission for my contact information (name and mailing address and/or phone number) to be given to other researchers working with the study investigator at Boston Children's Hospital.

_____ ☐ No, I do not want to be contacted about other research projects. **Do not** give my contact information to the staff of any other research studies.

What should you know about HIPAA and confidentiality?

Your health information is protected by a law called the Health Information Portability and Accountability act (HIPAA). In general, anyone who is involved in this research, including those funding and regulating the study, may see the data, including information about you. For example, the following people might see information about you:

- Research staff at Boston Children's Hospital involved in this study;
- Medical staff at Boston Children's Hospital directly involved in your care that is related to the research or arises from it;
- Other researchers and centers that are a part of this study, including people who oversee research at that hospital;
- People at Boston Children's Hospital who oversee, advise, and evaluate research and care. This includes the ethics board and quality improvement program;
- People from agencies and organizations that provide accreditation and oversight of research;
- People that oversee the study information, such as data safety monitoring boards, clinical research organizations, data coordinating centers, and others;
- Sponsors or others who fund the research, including the government or private sponsors.
- Companies that manufacture drugs or devices used in this research;
- Federal and state agencies that oversee or review research information, such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and public health and safety authorities;
- People or groups that are hired to provide services related to this research or research at Boston Children's Hospital, including services providers, such as laboratories and others;

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MRN: _____

Pt Name: _____

- And/or your health insurer, for portions of the research and related care that are considered billable.

If some law or court requires us to share the information, we would have to follow that law or final ruling. Some people or groups who get your health information might not have to follow the same privacy rules. Once your information is shared outside of Boston Children's Hospital, we cannot promise that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect privacy may no longer apply to this information. Other laws may or may not protect sharing of private health information. If you have a question about this, you may contact the Boston Children's Hospital Privacy Officer at (857) 218-4680, which is set up to help you understand privacy and confidentiality.

Because research is ongoing, we cannot give you an exact time when we will destroy this information. Researchers continue to use data for many years, so it is not possible to know when they will be done.

We will also create a code for the research information we collect about you so identifying information will not remain with the data and will be kept separately. The results of this research may be published in a medical book or journal or be used for teaching purposes. However, your name or identifying information will not be used without your specific permission.

Your privacy rights

If you want to participate in this research study, you must sign this form. If you do not sign this form, it will not affect your care at Boston Children's Hospital now or in the future and there will be no penalty or loss of benefits. You can withdraw from the study and end your permission for Boston Children's Hospital to use or share the protected information that was collected as part of the research; however you cannot get back information that was already shared with others. Once you remove your permission, no more private health information will be collected. If you wish to withdraw your health information, please contact the research team.

You may have the right to find out if information collected for this study was shared with others for research, treatment or payment. You may not be allowed to review the information, including information recorded in your medical record, until after the study is completed. When the study is over, you will have the right to access the information again. To request the information, please contact the Hospital's Privacy Officer at (857) 218-4680.

Contact Information

I understand that I may use the following contact information to reach the appropriate person/office to address any questions or concerns I may have about this study. I know:

I can call…	At	If I have questions or concerns about
Investigator:	Phone: 617-554-424	▪ General questions about the research

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MRN: _____

Pt Name: _____

Jane Newburger	Pager:	▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints
Research Contact: David C. Bellinger	Phone: 617-355-6565 Pager:	▪ General questions about the study ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints
Institutional Review Board	Phone: 617-355-7052	▪ Rights of a research participant ▪ Use of protected health information. ▪ Compensation in event of research-related injury ▪ Any research-related concerns or complaints. ▪ If investigator/research contact cannot be reached. ▪ If I want to speak with someone other than the Investigator, Research Contact or research staff.

Documentation of Informed Consent and Authorization

- I have read this consent form and was given enough time to consider the decision to participate in this research.
- This research has been satisfactorily explained to me, including possible risks and benefits.
- All my questions were satisfactorily answered.
- I understand that participation in this research is voluntary and that I can withdraw at any time.
- I am signing this consent form prior to participation in any research activities.
- I give permission for participation in this research and for the use of associated protected health information as described above (HIPAA).

Parent/Legal Guardian Permission (if applicable)

If the child to be involved in this research is a foster child or a ward of the state please notify the researcher or their staff who is obtaining your consent.

■ _____ _____ _____

Date (MM/DD/YEAR) Signature of **Parent #1** or **Legal Guardian** Relationship to child

Child Assent

■ If child/adolescent's assent is **not** documented above, please indicate reason below (check one):

☐ Assent is documented on a separate IRB-approved assent form
☐ Child is too young
☐ Other reason (e.g. sedated), please specify: _____

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RESEARCH CONSENT FORM

MRN: _____

Pt Name: _____

Research Investigator /or Associate's Statement & Signature

- I have fully explained the research described above, including the possible risks and benefits, to all involved parties (participant /parents/legal guardian as applicable).
- I have answered and will answer all questions to the best of my ability.
- I will inform all involved parties of any changes (if applicable) to the research procedures or the risks and benefits during or after the course of the research.
- I have provided a copy of the consent form signed by the participant / parent / guardian and a copy of the hospital's privacy notification (if requested).

■ _____ _____

Date (MM/DD/YEAR) Signature of **Research Investigator or Associate**

Witness Statement & Signature

A witness must be present for the entire consent process in the following situations (please check the appropriate box)

☐ The individual cannot read and this consent document was read to the participant or legal representative, **or**

☐ The individual has certain communication impairments that limit the participant's ability to clearly express consent **or**

☐ Situations where the IRB requests a witness be present: please specify _____

I confirm that the information in this consent form was accurately explained to the participant, parent or legally authorized representative, the individual appeared to understand the information and had the opportunity to ask questions, and that informed consent was given freely.

☐ _____ _____

Date (MM/DD/YEAR) Signature of Witness

Or

☐ The individual is not English or Spanish speaking and, through an interpreter, a short form consent document was presented orally to the participant or legal representative and this consent document serves as the summary for such consent.

I confirm that the information in this consent form was presented orally to the participant, parent or legally authorized representative, in a language they could understand and the individual had the opportunity to ask questions.

☐ _____ _____

Date (MM/DD/YEAR) Signature of Witness

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym. **Page 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry. **Page 2**
	2b	All items from the World Health Organization Trial Registration Data Set. **Page 2, Trial Registration Number NCT03023644 on ClinicalTrials.gov**
Protocol version	3	Date and version identifier. **Page 20**
Funding	4	Sources and types of financial, material, and other support. **Page 27**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Page 27**
	5b	Name and contact information for the trial sponsor **Page 27**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **Page 27**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **Page 27**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Pages 4-8**
	6b	Explanation for choice of comparators **Pages 4-8**
Objectives	7	Specific objectives or hypotheses **Pages 8-9**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Page 9**

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained. **Page 10**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists). **Page 10**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Pages 11-13**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **Pages 11-13**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Pages 11-13**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **Pages 11-13**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended. **Pages 13-17**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure). **Page 17**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations. **Pages 17-18**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size. **Page 10**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions. **Page 11**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned. **Page 11**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Page 11**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how. **Page 9**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **Page 9**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol. **Pages 13-17**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols. **Page 13**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol. **Page 17-18 and Appendix 1.**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol. **Pages 18-21**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **Pages 18-21**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **Pages 18-21**

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **Page 17-18 and Appendix 1.**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial. **Page 17-18 and Appendix 1.**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct. **Page 18 and Appendix 1.**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor. **Not applicable as this is a minimal risk study.**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval. **Page 21**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators). **Page 21.**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32). **Pages 11 and 20.**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial. **Page 21**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site. **Page 26**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators. **Page 26**

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation. **This is a minimal risk study. Risks management is presented in Appendix 1.**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions. **Page 21**
	31b	Authorship eligibility guidelines and any intended use of professional writers. **Page 21**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code. **Page 21**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates. **Appendix 2.**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable. **Not applicable.**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.