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.