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

PRINCIPAL INVESTIGATOR: Jane W. Newburger, M.D, MPH

RECIPIENT: Children's Hospital, Boston
Boston, MA 02115-5724

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Jane W. Newburger, M.D, MPH

EMAIL: jane.newburger@cardio.chboston.org

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Children's Hospital, Boston
Boston, MA 02115-5724

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14. ABSTRACT
Neurodevelopmental (ND) disabilities, particularly executive function impairments, are currently the most prevalent, and arguably the most distressing, long-term morbidity in the burgeoning population with congenital heart disease (CHD). Deficits in executive function pose serious threats to the educational achievement and consequent future employability, insurability and quality of life of millions of children with CHD. These adverse sequelae carry profound clinical and financial implications. While accumulating evidence exists on the deficits of patients with CHD, research evaluating effective therapeutic strategies is notably absent. The Cogmed intervention has been shown to improve executive function in several pediatric populations, but has not been studied in the CHD population.

15. SUBJECT TERMS-

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION:

Each year, approximately 1 child in every 100 is born with Congenital Heart Disease (CHD), making it the most common birth defect. Neurodevelopmental disabilities, particularly executive function (EF) impairments, are currently the most prevalent, and arguably the most distressing, long-term morbidity in the population with CHD. Deficits in executive function pose serious threats to the educational achievement and future employability, insurability and quality of life of millions of children with CHD. The Cogmed Working Memory intervention has been shown to improve executive function in several pediatric populations, but has not been studied in the CHD population. This is the first randomized controlled trial to evaluate the efficacy of Cogmed in improving neurodevelopmental outcomes of children with critical CHD after infant open-heart surgery. Children who meet eligibility criteria and who agree to participate will be randomly assigned to an intervention or control group. Children in the intervention group will complete 25 35-40 minute sessions of Cogmed training for a duration of 5 weeks. Cogmed is a set of home-based, child-friendly, computerized activities that targets the active training of EF including visual and spatial working memory, attention and impulse control. The control group will receive the standard of care. Children in both groups will undergo a total of 3 neurodevelopmental assessments: 1) a baseline evaluation prior to group randomization, 2) a post-treatment evaluation (or a 5 to 7-week post-baseline evaluation for the control group) and 3) a 3 month-follow-up assessment after the cessation of the intervention (or around 4-5 months after the baseline for the control group). The latter assessment will indicate whether any gains in EF skills of the children in the intervention group are sustained after training. Parents and teachers will also complete questionnaires about children's EF, attention, and social behaviors to determine whether training affects behaviors of the intervention group at home and in school. The investigators will also identify the medical and surgical characteristics of children associated with intervention efficacy. This information will be helpful in targeting the intervention most efficiently in the future.

2. KEYWORDS:

-Congenital Heart Disease
-Neurodevelopmental Disorders
-School-aged Children
-Executive Function
-Working Memory
-Cognitive interventions
-Infant Open Heart Surgery
-Cogmed

3. ACCOMPLISHMENTS: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific aims:

1. To evaluate the immediate efficacy of home-based Cogmed Working Memory Intervention for neurodevelopmental outcomes including executive function, social development and ADHD symptom reduction in children with critical CHD after open-heart surgery.
2. To evaluate the longer-term effects of the Cogmed Working Memory Intervention at 3-month follow-up.
3. To explore cognitive, medical and socio-demographic factors associated with changes in neurodevelopmental and behavioral scores in children assigned to receive the intervention.

For the period Year 1, month 1-3, we had the following target milestones:

1) Submit protocol to the USAMRMC office and HRPO
2) Hire and train research staff (develop job descriptions for study coordinator, advertise, interview and hire the study coordinator, identify space for new staff).

→ *All milestones have been successfully 100% completed*

For the period report Year 1, months 3-6, we had the following target milestones:

1) Acquire all study materials including neurodevelopmental tests, licenses for Cogmed working memory intervention as well as initiate the order of iPads.
2) Complete staff training and finalize data report forms and REDCap protocol.
3) Obtain and review records of Cardiology Clinic to identify potentially eligible children.
4) Conduct a pilot training using the Cogmed Working Memory intervention with two healthy volunteers, ages 7-12 years old.
5) Initiate further eligibility screening by phone with potentially eligible families.
6) Initiate enrollment and complete first baseline assessment with randomization of the first participant to one of the trial arms (intervention or control).

→ *All milestones have been successfully 100% completed*

For the period report Year 1, months 7-9, we had the following target milestones:

1) Continue the eligibility screening as well as the enrollment, baseline assessments and randomization of children to the intervention versus the control group.
2) Continue visits to participants' homes to administer the iPad and instruct parents and children on accessing and using the Cogmed Program.
3) Schedule and conduct the post-intervention evaluations (Visit 2) for the first time.
4) Monitor all participants' performances on Cogmed intervention.
5) Hold bi-monthly research study meetings to discuss ongoing progress and milestones.

→ *All milestones have been successfully 100% completed*

For the period report Year 1, months10-12, we had the following target milestones:

1) Continue the eligibility screening as well as the enrollment, baseline assessments and randomization of children to the intervention versus the control group.
2) Continue visits to participants' homes to administer the iPad and instruct parents and children on accessing and using the Cogmed Program.
3) Schedule and conduct the follow-up evaluations (Visit 3) for the first time.
4) Monitor all participants' performances on Cogmed intervention.
5) Hold bi-monthly research study meetings to discuss ongoing progress and milestones.

→ *All milestones have been successfully 100% completed*

For the period report (Year 2, months 1-3), we had the following target milestones:

1) Continue the eligibility screening as well as the enrollment, baseline assessments and randomization of children to the intervention versus the control group.
2) Continue visits to participants' homes to administer the iPad and instruct parents and children on accessing and using the Cogmed Program.
3) Continue conducting the post-intervention evaluations (Visit 2) and follow-up evaluations (Visit 3).
4) Monitor all participants' performances on Cogmed intervention.
5) Hold bi-monthly research study meetings to discuss ongoing progress and milestones.

→ *All milestones have been successfully 100% completed*

For the period report (Year 2, months 4-6), we had the following target milestones:

1) Continue the eligibility screening as well as the enrollment, baseline assessments and randomization of children to the intervention *versus* the control group.
2) Continue visits to participants' homes to administer the iPad and instruct parents and children on accessing and using the Cogmed Program.
3) Continue conducting the post-intervention evaluations (Visit 2) and follow-up evaluations (Visit 3).
4) Monitor all participants' performances on Cogmed intervention.
5) Hold bi-monthly research study meetings to discuss ongoing progress and milestones.
6) Submit a continuing review to the IRB
7) Conduct the first Data Safety Monitoring Board meeting

→ *All milestones have been successfully 100% completed*

For the period report (Year 2, months 7-9), we had the following target milestones:

1) Continue the eligibility screening as well as the enrollment, baseline assessments and randomization of children to the intervention *versus* the control group.
2) Continue visits to participants' homes to administer the iPad and instruct parents and children on accessing and using the Cogmed Program.
3) Continue conducting the post-intervention evaluations (Visit 2) and follow-up evaluations (Visit 3).
4) Monitor all participants' performances on Cogmed intervention.
5) Hold bi-monthly research study meetings to discuss ongoing progress and milestones.
6) Prepare and submit a first article presenting our study, background and methods for publication.

→ *All milestones have been successfully 100% completed*

For the period report (Year 2, months 10-12), we had the following target milestones:

1) Our original grant proposal called for termination of enrollment by the end of the 9th month of Year 2. As mentioned in earlier reports, we had some unavoidable delay in beginning enrollment and also had a period of time in which enrollment was slower than anticipated. We therefore modified our time table to continue enrollment through the end of Year 03. In the final quarter of Year 2, we thus have continued eligibility screening as well as the enrollment, baseline assessments and randomization of children to the intervention *versus* the control group in accordance with the revised time table.
2) Continue visits to participants' homes to administer the iPad and instruct parents and children on accessing and using the Cogmed Program.
3) Continue conducting the post-intervention evaluations (Visit 2) and follow-up evaluations (Visit 3).
4) Monitor all participants' performances on Cogmed intervention.
5) Hold bi-monthly research study meetings to discuss ongoing progress and milestones.

→ *With our planned extension of the enrollment in this project period, all milestones have been successfully 100% completed*

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

All activities for this annual report were successfully accomplished.

We have continued the eligibility screening of cardiology clinic records. On November 9th, 2017, the Boston Children's Hospital IRB and the Department of Defense Human Research Protection Office (HRPO) approved our fourth amendment that proposed to expand the inclusion criteria to children with CHD currently living further away from Boston Children's Hospital (i.e., in the United States but beyond driving distance from the Hospital) and meeting all other eligibility criteria. This brought our list of potentially eligible patients from 1,019 to 1,909.

Currently, nearly 70% of these records have been meticulously screened. Of those eligible from this initial screening, 562 families have received mail-packets detailing information from the study. The study coordinator, Alison Lord, BS, continues to collaborate with Drs. Newburger, Calderon, and Bellinger as well as the cardiology research nurse to screen for potential children eligible for our study. From those who have received mail-packets, 92 (16%) have opted-out, 105 (19%) have been lost to follow-up and 17 (3%) were found ineligible after the phone screening. 280 more patients eligible on medical records are being contacted by our study coordinator and research assistant. At the time of this report, 70 eligible patients have been scheduled for baseline visits, 64 baseline visits have been completed and 63 children have been randomized to one of the groups (intervention versus control). Several more visits are already scheduled over the fall. Those randomized to the intervention have had home visits in which they are instructed on using the iPad and Cogmed program. These patients are continuously monitored on their Cogmed performances. We have also completed post-intervention (second visit) testing with 50 of our enrolled patients and 36 patients have completed follow-up testing (third visit) as well.

During this reporting period, on February 14th, 2018, we held our Data Safety Monitoring Board (DSMB) meeting. The DSMB unanimously supported the ongoing enrollment and conduct of the trial. They advised us to continue the monitoring of potential adverse events and reasons for drop outs. It is projected that the next DSMB meeting will take place when a total of 50 (1/2 of the cohort) have completed their 3rd follow-up visits (anticipated to be by February, 2019).

Finally, we prepared and submitted a first protocol manuscript including our trial's methods to BMJ Open Protocols. The manuscript has received positive reviews and recommendations and our revised manuscript is currently under review for publication.

We do not have any results or outcomes according to treatment group at this point, because results are blinded to investigators and overseen by the DSMB. We have enclosed the "open" section of our first DSMB report from February 14, 2018. We have also appended the DSMB letter recommending continuation of enrollment. Finally, we have enclosed a revised version of our Statement of Work as well as the current flow-chart for enrollment.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to Report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

The study protocol, including details about the Cogmed intervention, study design, and analysis plan, have been detailed in a manuscript in BMJ open, which has been resubmitted with requested revisions. Dr. Calderon also presented an overview of the protocol at the Sixth Pediatric Anesthesia and Neuro-Development Assessment Symposium in New York City in April 2018.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."
Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

In the next reporting period (Year 3 months 1-3 of the study), we will continue the eligibility screening as well as the enrollment, baseline assessments and randomization of children to the intervention *versus* the control group. We will also continue the visits to participants' homes to set up the iPad and instruct parents and children on accessing and using the Cogmed program. We will continue to conduct post-intervention (visit 2) and follow-up (visits 3) visits as well. We anticipate that we will complete approximately 80% of our enrollment target by the end of Month 6, Year 3.

We will monitor all participants' performances on Cogmed intervention as well as continue to have bi-monthly research study meetings to discuss ongoing progress and milestones. We will also hold a second Data Safety Monitoring Board meeting that will advise the sponsor, Boston Children's Hospital, and study investigators.

We will also request a no-cost extension beyond Year 3 because we anticipate reaching our enrollment target by month 12 of Year 3 and would like to complete the post-intervention and follow-up visits for the last recruited participants and for preparation of the final manuscript(s) during the no-cost extension period.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The identification and treatment of neurodevelopmental morbidity constitute a primary aim in medical care and a public health priority as the number of individuals with CHD soars. The proposed innovative study bridges important bodies of research in the fields of neuropsychology and CHD, representing the first RCT to evaluate the efficacy of remediation strategies for children with CHD. If proven effective, this type of neurocognitive intervention could be implemented in a clinical outpatient practice.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Currently, there is a large population of patients with long-term neurodevelopmental dysfunction that negatively impact their quality of life. Deficits in executive function, in particular, pose serious threats to their educational achievement and consequent future employability, insurability and quality of life. The results of this study are likely to improve clinical and public knowledge about the available preventive and/or treatment strategies for youth with CHD. This, in turn, may positively affect policies regarding the clinical implementation of evidence-based interventions in this population which will likely have a significant economic and social impact.

5. CHANGES/PROBLEMS: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

In recent reporting periods, we have experienced a slower pace of enrollment of new participants. In order to increase our enrollment rates, we have sent packets to additional families and placed brochures on additional clinic offices. We have expanded our inclusion criteria to children living outside the Boston area (i.e., national patients). We have also hired a research assistant to support our efforts for screening and assessment of potentially eligible patients. Thanks to these strategies, we have seen a substantial increase in participation, with a total of 63 eligible children enrolled, as of today. However, despite these efforts, we believe that it is necessary to extend the enrollment period from the current plan of Year 2 to Year 3, month 12. We will request a one-year no-cost extension of our project from September 30, 2019 to September 30, 2020. This extension will allow us to finalize all patients' follow-up, prepare for the final data analyses and disseminate the first trial results to the scientific community.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals.

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

"Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: Protocol for a Randomized Controlled Trial of Working Memory Training"
This manuscript is currently being given full consideration for publication in BMJ Open.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

clinicaltrials.gov
This website is a NIH online database of private and public clinical studies. Currently only a description of the study and contact information are displayed as there are no findings yet.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

**Effort is based on the quarter covering 07/01/18 – 09/29/18
Name: Jane Newburger, MD, MPH
Project Role: Principal investigator
Research Identifier ORCID number: 0000-0002-7794-9017
Nearest person month worked: 1 months
Contribution to Project: Dr. Newburger (PI) has written and prepared the protocol. She assures the coordination and supervision of this study. She has reviewed patient enrollment criteria, ensured data quality forms and maintained effective communication with study investigators.

Name: Johanna Calderon, PhD
Project Role: Co-Investigator
Research Identifier ORCID ID: 0000-0002-2644-6858
Nearest person month worked: 2 months
Contribution to Project: Dr. Calderon has written and prepared the protocol and has taken responsibility for the hiring and training of neurodevelopmental specialists and the study coordinators. She has prepared the case-report and REDcap forms as well as the randomization strategy in consultation with the team's biostatisticians. She supervises all aspects of the study and conducts neurodevelopmental assessments.

Name: David C. Bellinger, PhD
Project Role: Co-Investigator
Research Identifier ORCID number: 0000-0003-3393-0119
Nearest person month worked: 1 month
Dr. Bellinger has participated in study preparation. He has participated in the logistic preparation of staff training as well as in the neurodevelopmental aspects of the trial. He has supervised the research coordinators.

Name: David Wypij, PhD
Project Role: Co-Investigator
Research Identifier ORCID number: 0000-0001-8367-8711
Nearest person month worked: 1 month
Dr. Wypij has served as this trial's senior biostatistician. He has supervised all aspects of study design, protocol development, database management, data entry and quality control. He has supervised the development of form design, data base structure and procedures and has oversight a Master's Level biostatistician, Christian Stopp.

Name: Christian Stopp, MS
Project Role: Biostatistician

Research Identifier ORCID number: 0000-0002-6360-5993
Nearest person month worked: 1 month
Mr. Stopp has been responsible for formatting, programing needs and has developed the REDCap forms, in collaboration with Drs. Wypij and Calderon.

Name: Alison Lord, BS
Project Role: Study Coordinator
Research Identifier ORCID number: 0000-0003-2275-878X
Nearest person month worked: 3 months
Ms. Lord has undergone neurodevelopmental testing and Cogmed Working Memory Training in order to administer the intervention to children with CHD. She has participated in the logistic organization of this study. In collaboration with Dr. Newburger, Carolyn Dunbar Masterson, RN, and Donna Donati, she performs the medical record screening of potentially eligible patients as well as enrolling and consenting those found to be eligible. She then provides patients and their parents an iPad and training necessary to complete the intervention.

Name: Alexandra Roseman, BA
Project Role: Research Assistant
Research Identifier ORCID number: 0000-0001-7080
Nearest person month worked: 1 months
Ms. Roseman is currently undergoing training to administer the neurodevelopmental tests as well as the Cogmed Working Memory program. In collaboration with Alison Lord, she performs the medical record screening of potentially eligible patients as well as enrolling and consenting those found to be eligible.

Name: Carolyn Dunbar-Masterson
Project Role: Staff Nurse
Research Identifier ORCID number: 0000-0003-2975-0641
Nearest person month worked: No Change
Ms. Dunbar-Masterson has participated in medical aspects of data forms and patient screening. She has supervised the research coordinator in her tasks regarding the medical record information.

Name: Donna Donati
Project Role: Senior Study Coordinator
Research Identifier ORCID number: 0000-0001-7435-4504
Nearest person month worked: No Change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. APPENDICES: N/A

STATEMENT OF WORK – October 30*, 2018- UPDATED VERSION
START DATE - September 30, 2016

Site: Boston Children's Hospital
300 Longwood Avenue
Boston, MA 02115
PI: Jane W. Newburger, MD, MPH (JWN)
Co-PI: David C. Bellinger, PhD (DCB)
Key investigators: Johanna Calderon, PhD (JC); David Wypij, PhD (DW)
Data Core Manager: David Wypij, PhD (DW); Christian Stopp, MS (CS)
Research Coordinator: Alison Lord
Senior Study Coordinator and Study Supervisor: Donna Donati

Clinical Trial Specific Aims

Specific Aim 1: To evaluate the immediate efficacy of home-based Cogmed Working Memory Intervention for neurodevelopmental outcomes including executive function, social development and ADHD symptom reduction in children with critical CHD after open-heart surgery

Specific Aim 2: To evaluate the longer-term effects of the Cogmed Working Memory Intervention at 3-month follow-up

Specific Aim 3: To explore cognitive, medical, and socio-demographic factors associated with changes in neurodevelopmental and behavioral scores in children assigned to receive the intervention

	Timeline			
	Year 1	**Year 2**	**Year 3**	**Year 4**
Major Task 1: Clinical trial preparation	Months	Months	Months	
Subtask 1: Prepare Regulatory Documents and Research Protocol for Study				
Boston Children's Hospital IRB protocol approval (completed)	-			
Submit protocol to the U.S. Army Medical Research and Materiel Command (USAMRMC) office if Research Protections (ORP) and Human Research Protection Office (HRPO)	1			
Milestone Achieved: USAMRMC, ORP and HRPO approval	3-5	-	-	
Major Task 2: Staffing and equipment				
Subtask 1: Acquire required equipment and licenses				
Order WISC-V, BRIEF, Conners, and SRS assessment tools	3-4	-	-	
Acquire licenses for Cogmed Working Memory Program	3-4	-	-	
Acquire license for NIH Toolbox	3-4	-	-	
Order iPads	3-4	-	-	
Subtask 2: Hire and Train Study Staff				
Develop job descriptions for Study Coordinator	1-3	-	-	

Advertise, interview, and Hire Study Coordinator	3-5	-	-	
Identify space for new staff	3-5	-	-	
Train investigators and Research Assistant on Cogmed Intervention	4-5	-	-	
Train and Develop Quality control protocol for neurodevelopmental specialists	3-5	-	-	
Subtask 3: Data entry protocol		-	-	
Design REDCap protocol and train coordinator	4-5	-	-	
Milestones Achieved: Research staff trained; all equipment and licenses acquired	4-5	-	-	
Major Task 3: Patient recruitment, baseline assessments, and randomization				
Eligibility screening: obtain and review records of Cardiology Clinic to identify potentially eligible children	4-5	-	-	
Baseline assessments	6-12	1-12	1-12	
Milestones Achieved: first baseline assessment completed; first child is randomized	6	-	-	
Major Task 4: Intervention				
RA visits participants' homes to set up iPAD and instruct parents and children on accessing and using Cogmed Program	7-12	1-12	1-12	
Milestone Achieved: First home Intervention visit is completed	7	-	-	
Major Task 5: Post-intervention				
Participants complete Visit 2; child repeats NIH Toolbox tasks, parent completes questionnaires	8-12	1-12	1-12	1-2
Milestone Achieved: First Post-intervention evaluation (Visit 2) is completed	8	-	-	
Major Task 6: 3-month follow-up		-	-	
Participants complete Visit 3; child repeats NIH Toolbox tasks, parent completes questionnaires	-	1-12	1-12	1-5
Milestone Achieved: First Follow-up evaluation (Visit 3) is completed	-	1		
Major Task 7: Analysis of data		-	-	
Milestone Achieved: Study findings are determined and prepared for incorporation into manuscripts	-	-		6-10
Major Task 8: Preparation of manuscripts for publication				
Milestone Achieved: First manuscript submitted for publication in a peer-reviewed journal	-	-		11-12

Enrollment actual and projected status

	Year 1				Year 2				Year 3				Total
Target Enrollment Clinical Trial (per quarter)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
Original SOW (cumulative)	-	-	20	48	76	88	100						**100**
Actual Enrollment (cumulative)	-		**14**	**20**	**33**	**43**	**52**	**64**					**64**
Projected Revised Enrollment for Year 3 (cumulative)	-								72	82	92	100	**100**

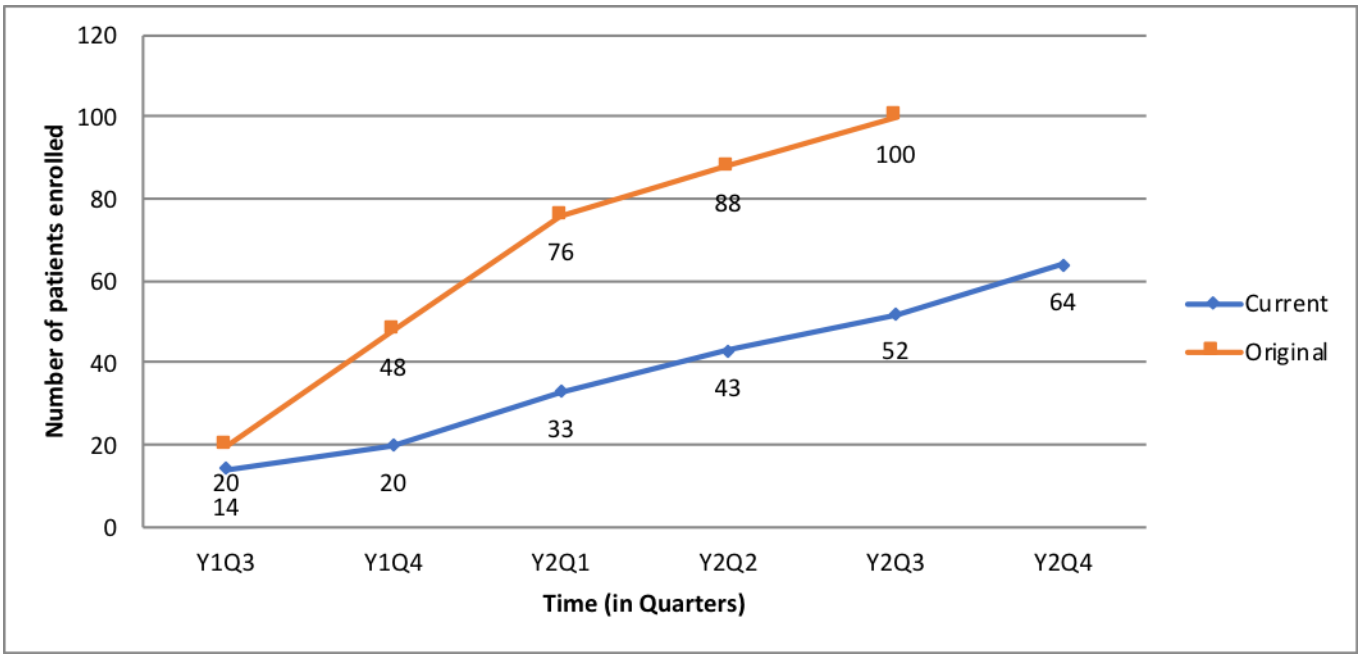


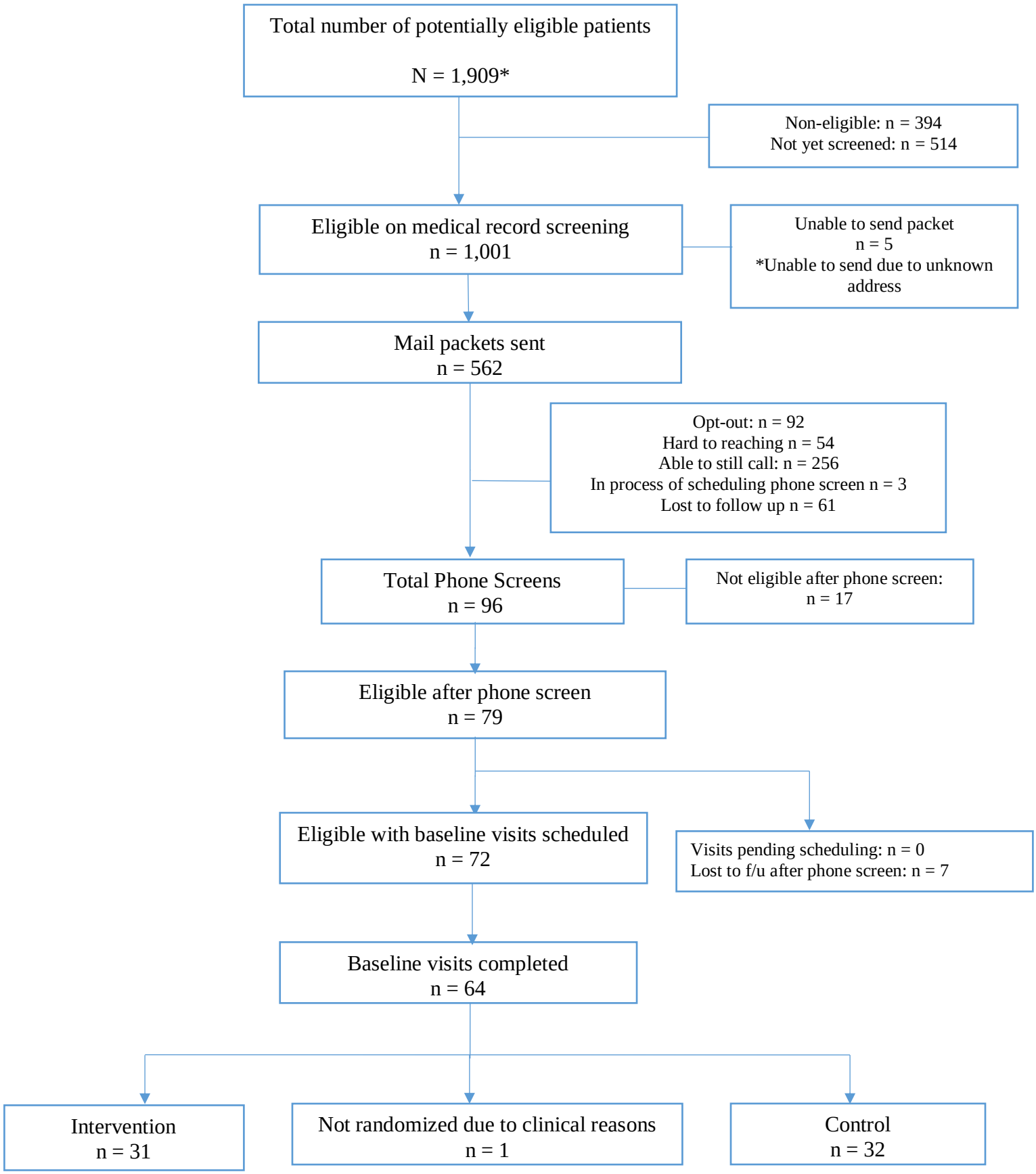
Figure 1. Number of patients in the original *versus* the current enrollment by quarter from Year 1 Q3 to Y2 Q4.

With the proposed revised enrollment, we project reaching 80% of our sample size goal by Year 3 Q2 and 100% by the end of Year 3 Q4. The projected timeline will be as follows:

- Projected Enrollment until October 2019 (Year 3, Q4).
- Last patient enrolled expected to finish 3-month follow-up (5 months total trial) by March, 2020 (Year 4, Q2).

Screening and Enrollment

Figure 1: Flowchart of Screening and Enrollment Data – Through 10/10/2018



Randomized Controlled Trial of Executive Function Intervention in Children with CHD

DSMB Conference call

February 14, 2018

DSMB members present: Caren Goldberg, John Orav, Dawn Ilardi

Study team representatives: Jane Newburger*, Johanna Calderon*, David Wypij, Christian Stopp, Alison Lord*, Catherine Hartigan*, Donna Donati*

Absent: J William Gaynor^, David Urion^

Those marked with * were present for the open session only. Those marked with ^ were contacted following the DSMB call

The DSMB is appreciative of the excellent work of the study team and the review/presentation of the analyses to date in both the open and closed sessions.

Recommendations include:

1) The DSMB unanimously supports the ongoing enrollment and conduct of the trial.

2) Continue to track events including episodes of headaches, vomiting, etc in case pattern is present.

3) Please continue to collect reason for study drop out from those who have dropped out- this may be related to undesirable effects as above or increased stress/frustration with Cogmed treatment and may be important to note/report.

4) Consider the potential need to adjust in analyses for practice effect related to outcome measurements.

5) Plan next DSMB meeting when a total of 50 (1/2 of the cohort) have completed their follow-up visits.)

Respectfully submitted,

Caren Goldberg, MD, MS, Chair, on behalf of Drs. Dawn Ilardi, John Orav, J William Gaynor and David Urion.