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AWARD NUMBER: W81XWH-16-1-0741

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

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

RECIPIENT: Boston Children's Hospital Corporation

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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:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

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 approximately 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:** Provide a brief list of keywords (limit to 20 words).

-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, months 10-12**, 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*

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

1) As indicated in our Year 2 Annual report, 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 this quarterly report (Year 3, months 1-3), 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*

For the period report **Year 3, months 4-6**, we had the following target milestones:

1) As indicated in earlier reports, we had some unavoidable delays in enrollment. Moreover, we recently hired and trained a new research coordinator to replace the previous one who left her position on 11/30/18. One of our research assistants, Catherine Hartigan, also left her position and this also caused an additional delay in recruitment as the new coordinator needed to receive comprehensive training in all aspects of the study. We therefore modified our time table to continue enrollment through Months 1-2 of Year 4. 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. Our new research coordinator is now fully trained on all tasks and is working under the direct supervision of Dr. Calderon.
2) Continue visits to participants' homes to administer the iPad and instruct parents and children on accessing and using the Cogmed Program.
3) Continue 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*

For this period report **Year 3, months 7-9**, we had the following target milestones:

1) As indicated in our revised statement of work and previous quarterly report, we have now extended the duration of enrollment to Year 4, months 1-2. The No-Cost Extension request for this study is now approved for a projected end date of 09/30/2020. During this period (Year 3, months 7-9), we 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. Our new research coordinator, Daniel Albers, is now fully trained on all tasks under the supervision of Dr. Calderon.
2) Continue visits to participants' homes to administer the iPad and instruct parents and children on accessing and using the Cogmed Program.
3) Continue 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 extension of the enrollment in this period, all milestones have been successfully 100% completed.*

For the period report **Year 3, months 10-12** we had the following target milestones:

1) We have successfully continued eligibility screening as well as enrollment, baseline assessment and randomization of children to the intervention versus the control group following our revised time table. Our enrollment is projected to end by Year 4 Month 2.
2) Continue visits to participants' homes to administer the iPad and instruct parents and children on accessing and using the Cogmed Program.
3) Continue 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 extension of the enrollment in this 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. Of 2,077 potentially eligible patients in our cardiology clinic medical records, n=1,266 were found eligible, n=498 ineligible and n=313 remain to be potentially screened (85% of our records screened). Of those eligible of medical records, 812 families have received a mailing packet, 112 (14%) have opted out, 214 (26%) are lost to follow-up, 333 (41%) can be still contacted for a phone interview screening and 153 (19%) total phone screens have been completed. At the time of this report, 133 patients have been found to be eligible on phone screening and 20 non-eligible due to criteria not previously identified on medical records (e.g., recent diagnosis of autism spectrum disorders, placed in a specialized classroom, previous or ongoing training with Cogmed, etc.). As of today, 112 baseline visits have been scheduled. We have now completed 101 baseline visits. Two children were excluded after baseline due to clinical reasons (i.e., severe learning disability that would prevent them from continuing the testing). A total of 97 children have been randomized to one of the groups (intervention *versus* control). Two children who were initially randomized were excluded due to a minor protocol deviation (i.e., assignment of a lower intervention intensity: 35 minutes/session *versus* the standard 40-50 minutes). Information regarding this minor protocol deviation was submitted and approved by our local IRB and all documentation was sent to the DoD with our Year 3 Quarterly report 3.

We have now 47 children in the intervention group and 50 children in the control group. All children 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 83 of our enrolled patients and 65 patients have completed follow-up testing (third visit) as well. Five more second and third visits are currently scheduled for October and November.

On 10/8/19, we have received approval of our 5th amendment regarding a minor increase in sample size to a total of 110 eligible patients enrolled. We had initially targeted the enrollment of 100 children with CHD and have now attained 97 eligible participants. However, 9 of these participants have dropped-out of the study. In order to maintain our estimated power to detect clinically meaningful differences between the groups, we have now obtained approval from our local IRB to increase our sample size of 10 additional participants to total 110 in sample size. This change will not add any other modifications to the consent or assent forms and will not change our methods or extend the project beyond its anticipated schedule. We have attached the IRB approval amendment as well as our latest continuing review to this report.
Our statistical team continues to operate periodic data quality control and cleaning. 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.

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 now been published. 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 and at the 8th Annual Scientific Sessions of the Cardiac Neurodevelopmental Outcome Collaborative in Toronto next October, 2019.

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 4 months 1-3 of the study), we will continue 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 100% of our enrollment target by the end of Month 2, Year 4. 90% of post-intervention (visit 2) are also expected to be completed by the end of the next reporting period.

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 before the end of Year 4 that will advise the sponsor, Boston Children's Hospital, and study investigators.

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.

We had initially targeted the enrollment of 100 children with CHD and have now attained 97 eligible participants enrolled in our trial. However, 9 of these enrolled participants have dropped-out of the study after the baseline neurodevelopmental assessment. In order to maintain our estimated power to detect clinically meaningful differences between the groups, we would need a total of 100 eligible children with available data in the trial. We have now obtained approval from our local IRB to increase our sample size of 10 additional participants to total 110 in sample size. The IRB approval amendment has been attached to this report. This change will not add any modifications to the consent or assent forms and will not change our methods or extend the project beyond its anticipated schedule. Our research coordinator has already established a waiting list of potentially eligible patients who will schedule a visit before the end of Year 4, month 2. Our data will continue to be blinded to study investigators, therefore the study team is not aware of any anticipated results at this point.

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).

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 randomised controlled trial of working memory training *BMJ Open* 2019;9:e023304. doi: 10.1136/bmjopen-2018-023304.

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.*

Methods and study design have been presented at the Sixth Pediatric Anesthesia and Neuro-Development Assessment Symposium in New York City in April 2018 and at the 8th Annual Scientific Sessions of the Cardiac Neurodevelopmental Outcome Collaborative in Toronto next October, 2019

- **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."

Name: Jane Newburger, MD, MPH
Project Role: Principal investigator
Research Identifier ORCID number: 0000-0002-7794-9017
Nearest person month worked: 0.3 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: 1.4 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: 0.3 months
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: 0.02 months
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, Valerie Rofeberg.

Name: Valerie Rofeberg, MS
Project Role: Biostatistician
Research Identifier ORCID number: 0000-0002-6360-5993
Nearest person month worked: .3 months

Ms. Rofeberg is responsible for data quality control and statistical analyses under the supervision of Dr. Wypij and Calderon.

Name: Daniel Albers, BS
Project Role: Study Coordinator
Research Identifier ORCID number: 0000-0003-2275-878X
Nearest person month worked: 3 months
Mr. Albers has undergone neurodevelopmental assessment and Cogmed Working Memory Training in order to administer the intervention to children with CHD. He has participated in the logistic organization of this study. In collaboration with Alexandra Roseman, he performs the medical record screening of potentially eligible patients as well as enrolling and consenting those found to be eligible. He then provides patients and their parents an iPad and training necessary to complete the intervention. He participates to data checking and cleaning under the supervision of Ms. Rofeberg and Dr. Wypij.

Name: Alexandra Roseman, BA
Project Role: Research Assistant
Research Identifier ORCID number: 0000-0001-7080
Nearest person month worked: 0.6 months
Ms. Roseman is currently undergoing training to administer the neurodevelopmental tests as well as the Cogmed Working Memory program. In collaboration with Daniel Albers, she performs the medical record screening of potentially eligible patients as well as enrolling and consenting those found to be eligible.

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."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

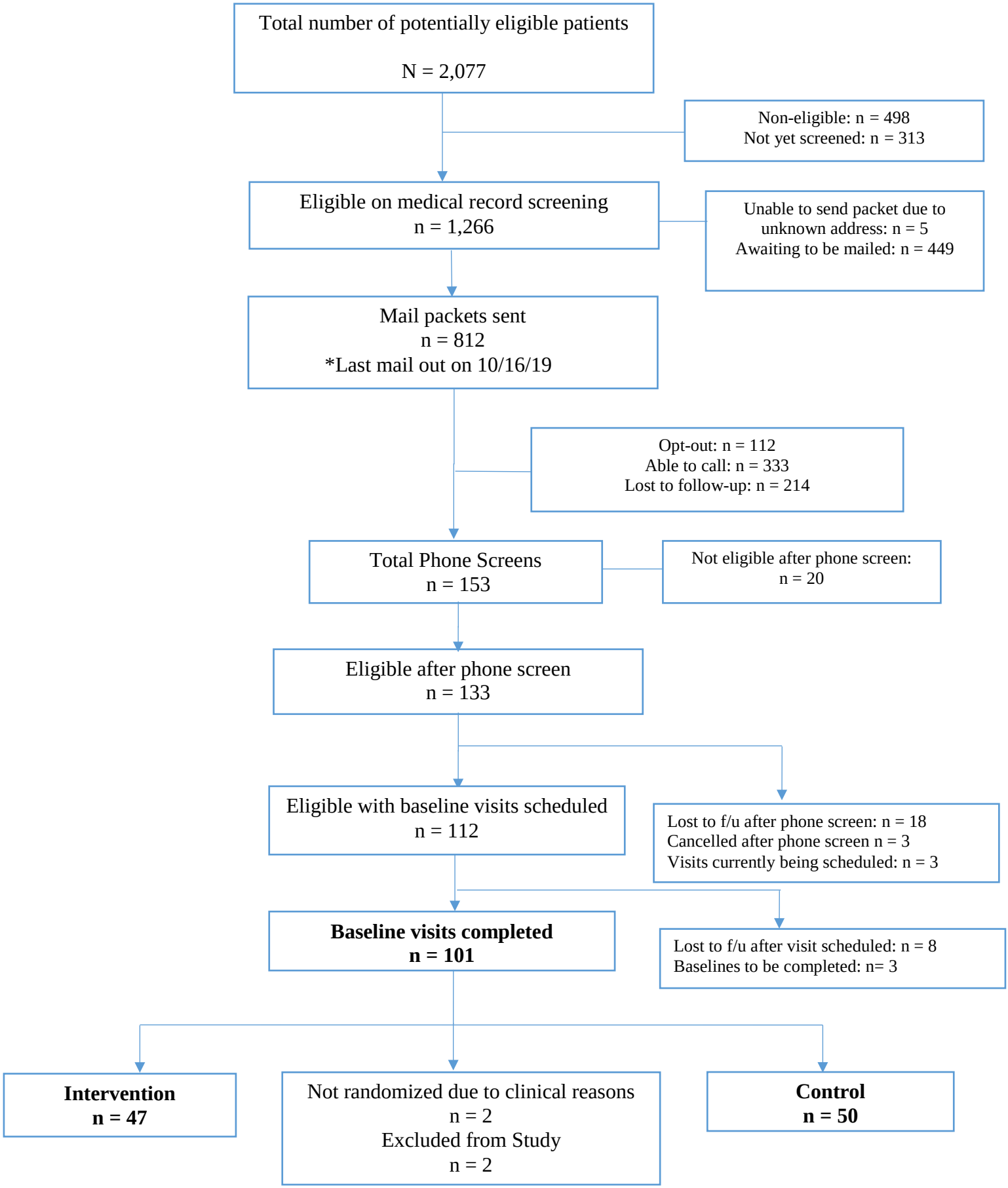

Figure 1. Flow-chart of current enrollment for DoD Y03 Annual Report

Boston Children's Hospital
Institutional Review Board (IRB)
300 Longwood Avenue
Mailstop BCH 3164
Boston, MA 02115
Tel: (617) 355-7052
Fax: (617) 730-0226
www.bostonchildrens.org/research/irb

Principal Investigator	Jane Newburger, MD
Protocol Title	Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: An intervention Study
Protocol Number	IRB-P00022440
Date:	October 9, 2019

NOTICE OF EXPEDITED APPROVAL – AMENDMENT

IRB Amendment approval Date: 10/8/2019
IRB Protocol Expiration Date: 11/6/2019

The Institutional Review Board has approved the amendment submitted 9/19/2019. This amendment proposes the following changes:

- The study team requests a minor increase in the total sample size of eligible participants enrolled in our randomized controlled trial due to unanticipated drop-outs from the trial. We had initially targeted the enrollment of 100 children with CHD and have now attainted 96 eligible participants enrolled in our trial. However, approximately 10 of these enrolled participants have dropped-out of the study after baseline and/or the first neurodevelopmental visit. In order to maintain our estimated power to detect clinically meaningful differences between the groups, we would need a total of 100 eligible children with available data in the trial. Thus, we request an increase of 10 additional participants to total 110 in sample size.
  This change will not add any modifications to the consent or assent forms, will not change the current methods and will not extend the project beyond its anticipated schedule. Our data will continue to be blinded to study investigators, therefore the study team is not aware of any anticipated results at this point.

The approved consent form is available on-line through the BCH Informed Consent Library. To obtain the consent form, please go to http://chbcfapps/research/consents. The ICLibrary should be accessed each time you need a consent form to ensure that the current version of the consent is always used. Do not store the consent forms on your computer or make copies for future use. Note that the activation/expiration date on the consent form can only be changed or modified by the staff of the IRB Office. Please also note that subjects cannot be enrolled in a study if the consent form has expired. A copy of the signed consent should be kept in your files. The subject/family must also be given a signed copy.

The occurrence of unanticipated problems should promptly be reported to this office. Any revisions, amendments, or changes to the protocol require prior IRB approval. The IRB has asked this office to notify investigators that clinical investigation protocol files are subject to audits at some future time.

Sincerely,

Anna Mitchell, IRB Administrator
For the Institutional Review Board

Tell us how we are doing! https://www.surveymonkey.com/s/irbsatisfactionsurvey

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Principal Investigator	Jane Newburger, MD
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Date:	October 9, 2019

NOTICE OF EXPEDITED CONTINUING APPROVAL

IRB Approval Date:	**9/29/2019**
IRB Activation/Release Date:	**10/9/2019**
IRB Expiration Date:	**9/28/2020**

The Institutional Review Board has approved the continuing renewal of the above referenced protocol through expedited review procedures.

The approved consent/assent document(s) are available on-line through the BCH Informed Consent Library. To obtain the consent form, please go to http://chbcfapps/research/consents. The IC Library should be accessed each time you need a consent form to ensure that the current version of the consent is always used. Do not store the consent forms on your computer or make copies for future use. Note that the activation/expiration date on the consent form can only be changed or modified by IRB Office staff. Children and adolescents are required to sign the consent or assent form in addition to the parent(s)/guardian(s). If you determine a particular child is not capable of providing assent, you will need to provide the rationale on the consent form, after the parental signatures. Please also note that subjects cannot be enrolled in a study if the consent form has expired. A copy of the consent should be kept in your files. The subject/family must also be given a signed copy.

The occurrence of unanticipated problems should promptly be reported to this office. Any revisions, amendments, or changes to the protocol require prior IRB approval.

The IRB has asked me to notify all investigators that files are subject to audit at any time.

Sincerely,

Anna Mitchell, IRB Administrator
For the Institutional Review Board

Tell us how we are doing! https://www.surveymonkey.com/s/irbsatisfactionsurvey