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TITLE: Multimodal Intervention Trial for Cognitive Deficits in Neurofibromatosis Type 1: Efficacy of Computerized Cognitive Training and Stimulant Medication

PRINCIPAL INVESTIGATOR: Kristina Hardy, Ph.D.

CONTRACTING ORGANIZATION: Children's National Health System
Washington DC 20010

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6. AUTHOR(S):
Kristina Hardy, Ph.D. (PI)

Danielle Griffin, B.A. (Clinical Research Coordinator)

E-Mail: kkhardy@childrensnational.org;

dgriffin2@childrensnational.org

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Children's National Health System
111 Michigan Ave. NW
Washington, DC 20010

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

During this research period, we successfully coordinated with three participating sites to recruit, screen and follow-up with patients, coached participants through the intervention and trained intervention coaches at the Australia sites, provided support to the Los Angeles site with respect to the IRB continuing review, and submitted personnel and minor administrative amendments. We continue to coordinate with the Boston site to obtain local IRB approval. Additionally, we have maintained a trained study staff which has enabled us to recruit a total of 54 participants, conduct 54 baseline assessments, coach 31 participants through the computerized training intervention, and conduct 31 follow-up assessments across all sites. All data has been entered into the research database.

15. SUBJECT TERMS

Neurofibromatosis, cognition, pediatric, computerized training programs, working memory

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1. INTRODUCTION: The purpose of this research is to assess the efficacy of a home-based, computerized cognitive training (CT) program in a sample of 90 children, aged 8-16 years, with Neurofibromatosis Type 1 (NF1) and working memory (WM) difficulties. Given the high incidence of WM difficulties in children with NF1, it is a critical priority to identify feasible and efficacious interventions. By improving working memory difficulties, children may experience fewer problems with intellectual quotient, executive functioning, and academic performance over time. Participants in this intervention study will be stratified by stimulant medication use and randomized equally between two computerized cognitive training interventions within stratum. Participants will participate in the study for up to 11 weeks. Participants will be assigned a training coach who will work with them weekly via telephone to provide trouble-shooting, brainstorm strategies for maintaining motivation, and provide feedback on training progress to date.

2. KEYWORDS: neurofibromatosis, cognition, pediatric, computerized training programs, working memory

3. ACCOMPLISHMENTS:

What were the major goals of the project?

As stated in the revised SOW (approved 10/16/2018), the major goals of the project include: 1) Developing a plan for patient recruitment and obtaining human subjects approval, 2) Identifying and training study personnel, and maintaining a clinical database, 3) Recruiting and evaluating participants, 4) Cleaning and analyzing patient recruitment and evaluation data, safety data, and neuropsychological data (specifically, reviewing data monthly for completeness and accuracy), and resolving queries with participating sites, and 5) Performing final analysis and writing the report.

What was accomplished under these goals?

Our first major task was to develop a plan for patient recruitment and obtain human subjects approval. This past year, we have continued to successfully coordinate with three other sites regarding material transfer agreements and clinical trial agreements submission, achieved local IRB approval at CNHS, RCH, CHLA and CHW (and supported BCH in obtaining local IRB approval), maintained compliance by submitting personnel and minor administrative amendments, and coordinated with three sites for annual IRB continuing review.

- CNHS: Local IRB approved May 10th, 2016; HRPO protocol approved June 24th, 2016; Continuing Review approved April 26th, 2018
- CHLA: Local IRB approved October 27th, 2016; HRPO protocol approved October 15th, 2017; Continuing Review approved October 10th, 2017
- RCH: Local IRB approved May 23rd, 2017; HRPO protocol approved March 2nd, 2018; Continuing Review submitted to DOD June 28th, 2018
- CHW: Local IRB approved March 23rd, 2017; HRPO protocol approved March 2nd, 2018; Continuing Review submitted to DOD June 28th, 2018
- Boston: Local IRB protocol submitted December 14th, 2017

In terms of stated goals that have not been met, we have not been able to achieve local IRB approval at BCH. The Boston site PI has experienced multiple adverse personal events, which has delayed the IRB protocol submission. To date, the local IRB has been submitted the IRB has made comments on the protocol, and Boston is in the process of responding to these comments. Research coordinators at CNHS are currently working with the PI at Boston to address barriers to IRB approval.

Our second major task was to identify and train study personnel, and to maintain a clinical database. To date, we have completed the training of all study personnel. This past year, we experienced staff turnover both at CNHS and at participating sites. However, we have successfully maintained assessment and intervention clinicians and appropriately trained new study staff. We have successfully coordinated with four sites for Cogmed and MobyMax coach training. Two trained Cogmed and MobyMax coaches at the CNHS site continue to provide coaching training for all participants at CNHS and CHLA, and one trained coach at the CHW site provides coaching for all participants at their site. Additionally, this past year, two study staff members at the RCH site were trained as coaches and will provide coaching for all participants at that site. The coordinating site continues to support and provide supervision to the coaches at CHW and RCH via conference calls and email.

Our third major task was to recruit and evaluate participants. Over the first two years of this study, CNHS successfully recruited and conducted baseline assessments for 22 participants. Fourteen (14) children qualified for the intervention, successfully completed the training intervention, and returned for follow-up assessment. In the third year, CNHS successfully recruited and completed baseline assessments for an additional 11 participants. Seven (7) children qualified for the intervention, successfully completed the training intervention, and returned for follow-up assessment. To date, at CNHS, one participant has been lost to follow-up and one participant qualified for, but did not complete, the intervention due to mental health concerns.

In the third year, CHLA successfully recruited and completed baseline assessments for 14 participants. Eight (8) children qualified for the intervention. Seven (7) children successfully completed the training intervention and returned for follow-up assessment, while 1 child is currently participating in the intervention. To date, at CHLA, three participants have been lost to follow-up. In the third year, CHW successfully recruited and completed baseline assessments for 4 participants. Three (3) children successfully completed the training intervention and returned for follow-up assessment, while 1 child is currently participating in the intervention. In the third year, RCH has successfully recruited 1 participant.

To date, 54 children have been successfully recruited and 31 evaluable participants have achieved follow-up. While our goal for the end of the third year, according to the revised SOW, was to recruit 62 across all sites, we remain optimistic that we will achieve our recruitment goals by the end of Year 4. Specifically, we believe that we will quickly progress towards our target accrual now that the two sites in Australia have received IRB and HRPO approval. Both sites will continue recruiting and evaluating participants who have expressed interest in the study. Additionally, at this point in the study, CNHS has achieved 92% of its predicted enrollment to date, as stated in the revised SOW. CHLA has achieved 84% of its predicted enrollment, as stated in the revised SOW. In summary, with four sites now actively recruiting, we are confident that we will be able to maintain a rate of accrual consistent with that originally planned.

The remainder of the goals subsumed under the third major task are ongoing, including monitoring recruitment process, retention, and completing of the final assessment, monitoring regulatory compliance and GCP compliance, completing follow-up assessments, and coordinating with all sites to discuss progress and engage in problem-solving.

Our fourth major task was to clean and analyze patient recruitment and evaluation data, safety data, and neuropsychological data. Data from participants at CNHS, CHLA, CHW, and RCH have been entered into an online database by the appropriate team member. Data has been reviewed for completeness and accuracy by the database manager. Data is reviewed by the primary research coordinator at CNHS, and discrepancies are identified and rectified. Enrollment has reached greater than 30 participants and data has been summarized.

The remainder of the goals subsumed under the fourth major task are either ongoing or to be performed at a later time. Those that are to be performed at a later time include summarizing data after 60 participants and summarizing all data.

The goals subsumed under the fifth major task are to be performed at a later time. These include performing all analyses per analysis plan, sharing findings with investigators and study funder, and disseminating findings through abstracts, presentations, and publications.

What opportunities for training and professional development has the project provided?

This project has provided multiple opportunities for training and professional development. Specifically, research coordinators at all sites have been given access to the Cogmed professional training program as well as instructor access to MobyMax. By completing the Cogmed training program, research coordinators can now serve as intervention coaches for participants who receive the working memory intervention. By being given instructor access to MobyMax, research coordinators can now monitor participant progress on the reading intervention. Importantly, while an official MobyMax coaching course is not available, the PI of this study has continued to provide training and supervision to research coordinators. This training and supervision allows research coordinators to provide appropriate and effective feedback to participants completing the reading intervention.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period, we anticipate that the Boston site will obtain local IRB approval. This would allow for additional recruitment and enrollment of participants, and would increase our recruitment scope from four to five sites. Additionally, we anticipate rapid recruitment at the two Australian sites, which have recently opened and have multiple patients interested in participating in this study.

Our goal is to screen a total of 130 participants by the time of the next annual report, which will be accomplished by screening a total of two to five participants each quarter at each site. The coordinating site also plans to summarize and review the data after 60 participants have been recruited.

4. **IMPACT**

What was the impact on the development of the principle disciplines of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

In the third year, we did not make any changes in the approach that was approved by the funding agency.

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

1) During the first year, we experienced a myriad of challenges, which delayed the timeline of this project. First, in 2015, Cogmed phased out support for the non-adaptive computerized intervention training – the planned active control for this study. As a result, the study team was tasked with finding a new active control. Following research on multiple control options, MobyMax was identified as the new active control. Because of this unforeseeable circumstance, the submission of the Coordinating Center protocol to the IRB was significantly delayed. Second, it took quite a bit longer than originally anticipated for other sites to obtain local IRB approval. Specifically, IRB analysts and reviewers requested lengthy documentation of explanations regarding protection of privacy and confidentiality. Such significant delays in IRB approval, contract executions, and HRPO approval within the first year has resulted in recruitment delays across sites throughout the second year and into the third year. Local IRB approval and HRPO approval has now been obtained for four sites, which should successfully remedy these delays.

Additionally, the Boston site has experienced major delays in local IRB approval. During the second year of this project, the PI at BCH experienced multiple adverse personal events, which prevented the development of an IRB protocol. During the third year, an IRB protocol was developed and submitted for review. While the IRB protocol has yet to be approved, it is now in the review process. We have continued to coordinate with and support this site as needed. We are confident this will not negatively influence enrollment in the long term as this study was originally designed as a four site study.

Further, it has taken longer than originally anticipated for CHLA, RCH, and CHW to obtain HRPO approval, which has ultimately delayed recruitment. All sites listed above have now obtained approval and recruitment is moving forward at a rapid rate. Additionally, for both the RCH and CHW sites, the continuing review was not processed properly following the first submission and sites were asked to suspend recruitment. While this issue has now been resolved, it did delay recruitment at these sites.

By the end of year three, we have screened 54 participants and enrolled 37 evaluable participants on the intervention study. We expected to enroll 62 evaluable participants by the end of the third year, which means we have enrolled 60% of our anticipated goal. Importantly, we have increased the recruitment goal at each site to 2-5 participants per quarter, which will enable us to meet our screening goal of 130 participants by the end of year four.

2) We have also experienced administrative delays at CNHS within the Grants and Contracts Department. Specifically, we experienced difficulty executing contracts between our site and other sites – an issue which took multiple months to resolve. Additionally, our Grants department experienced significant delays in paying reimbursements out to CHLA, which dated more than six months. By the end of the third year, we have paid out all of the reimbursements owed to CHLA, but the process took many months to remedy (with the issue being identified in April 2017). While the reimbursement delays were being resolved, CHLA ceased recruitment. Our Grants department also paid our per case reimbursements to CHW, which were not owed.

3) Finally, we have experienced multiple staffing transitions at the coordinating site, including the transition from Dr. Maria Acosta to Dr. Kristina Hardy as the study PI, and the addition of two new clinical research coordinators and a postdoctoral fellow to the study team. While all new study staff have successfully been trained on this study, the turn-over in staffing created minor delays in study progress.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

There were no significant changes in the use or care of human subjects, vertebrate animals, biohazards and/or select agents during the reporting period.

Significant changes in use or care of human subjects

There were no significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects.

Significant changes in use or care of vertebrate animals

Vertebrate animals are not used in this study.

Significant changes in use of biohazards and/or select agents

There were no significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of biohazards and/or select agents.

6. Products

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	Maria T. Acosta, M.D.
Project Role:	PI until 7/31/2018
Researcher Identifier:	ORCID ID 0000-0002-7645-0011
Nearest person month worked:	0.3 per quarter, quarters 1-3, 0.15 quarter 4/1.05 per year, cost sharing support by CNMC for an additional 0.3 per quarter /1.05 per year
Contribution to project:	Overseen all details regarding all necessary documents to submit to DoD and IRB
Funding support:	
Name:	Kristina K. Hardy, Ph.D.
Project Role:	PI (as of 8/1/2018)
Researcher Identifier:	ORCID ID 0000-0002-5479-5043
Nearest person month worked:	0.6 per quarter/2.3 per year, cost sharing support by CNHS at 0.15 per quarter/0.6 per year
Contribution to project:	Overseeing neuropsychological assessments and intervention methods as outlined in protocol. Overseeing all details regarding all necessary documents to submit to DoD and IRB.
Funding support:	
Name:	Marni Jacobs, Ph.D.
Project Role:	Statistician
Researcher Identifier:	ORCID ID 0000-0001-6649-6692
Nearest person month worked:	0.23 per quarter/0.9 per year
Contribution to project:	Leads all coordinating center efforts and provides statistical expertise on protocol
Funding support:	
Name:	Dan Zhang
Project Role:	Data Coordinator
Researcher Identifier:	N/A
Nearest person month worked:	0.09 per quarter/0.36 per year
Contribution to project:	CRF and EDC creation
Name:	Kaitlyn Tiplady, M.Ed. (left project 8/10/18)
Project Role:	Clinical Research Coordinator

Researcher Identifier:	N/A
Nearest person month worked	1.5 this quarter/6 per year; only 5.5 Year 3
Contribution to project:	Facilitates communication between all sites, administrative management, coordination of study material and operations, intervention coach
Name:	Danielle Griffin, B.A. (Replaced part of Kaitlyn Tiplady, 08/11/18)
Project Role:	Clinical Research Coordinator
Researcher Identifier:	N/A
Nearest person month worked	1.5 per quarter/6.0 per year, only 0.5 Year 3
Contribution to project:	Facilitates communication between all sites, administrative management, coordination of study material and operations, intervention coach
Name:	Anthony Gioia, B.S. (left project 7/13/18)
Project Role:	Clinical Research Coordinator
Researcher Identifier:	N/A
Nearest person month worked	0.75 this quarter/3.0 per year, 2.5 Year 3
Contribution to project:	Facilitated communication sites, administrative management, intervention coach
Name:	Carly Berger, B.S. (Replaced part of Anthony Gioia)
Project Role:	Clinical Research Coordinator
Researcher Identifier:	N/A
Nearest person month worked	0.6 per quarter/2.4 per year
Contribution to project:	Facilitates communication between all sites, administrative management, coordination of study material and operations, intervention coach
Name:	Laura Kurzius, PhD (Replaced part of Anthony Gioia and added some of Dr. Hardy's responsibilities, 8/27/18)
Project Role:	Post-Doc Fellow
Researcher Identifier:	N/A
Nearest person month worked	0.6 per quarter/2.4 per year
Contribution to project:	Coordinator of coaching

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

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

None.

9. APPENDICES

None included.