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

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CONTRACTING ORGANIZATION: Children's National Hospital, Washington, DC

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

To date, we have successfully coordinated with the four participating sites (CNH, CHLA, RCH, CHW) to recruit, screen and follow-up with participants, coached participants through the intervention, and maintained a fully-trained study staff team across sites. We have consented a total of 96 participants, conducted 96 baseline assessments, randomized 67 children to one of the two computerized intervention programs. Of these, 62 participants have completed training and participated in follow-up assessments. All collected data has been entered into the research database. A no cost extension (NCE) for this project has been submitted.

15. SUBJECT TERMS
Neurofibromatosis, cognition, pediatric, computerized training programs, working memory

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1. INTRODUCTION: This study aims 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, we are hopeful that 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 approved SOW, 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 to 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 CNH, RCH, CHLA and CHW, maintained compliance by submitting personnel and minor administrative amendments, and coordinated with three sites for annual IRB continuing review.

- CNH: Local IRB approved May 10th, 2016; HRPO protocol approved June 24th, 2016; Continuing Review submitted to DOD March 20th, 2020
- CHLA: Local IRB approved October 27th, 2016; HRPO protocol approved October 15th, 2017; Continuing Review submitted to DOD July 20th, 2020
- RCH: Local IRB approved May 23rd, 2017; HRPO protocol approved March 2nd, 2018; Continuing Review submitted to DOD August 18th, 2020
- CHW: Local IRB approved March 23rd, 2017; HRPO protocol approved March 2nd, 2018; Continuing Review submitted to DOD August 18th, 2020

In terms of stated goals that have not been met, local IRB approval has not been obtained at the Boston site. Due to the significant delays experienced in getting IRB approval at the Boston site, BCH was removed from the protocol and will not be participating in the study going forward.

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. We have successfully maintained assessment and intervention clinicians, and appropriately trained new study staff, including coordinating with all sites from Cogmed and MobyMax coach training. Three trained Cogmed and MobyMax coaches at the CNH site continue to provide coaching for all participants at CNH and CHLA, one trained coach at the CHW site provides coaching for all participants at their site, and two study staff members at the RCH site provide coaching for all participants at their 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. During the first four years of the study, CNH successfully recruited and conducted baseline assessments for 39 participants. Twenty-six (26) children qualified for the intervention, and 24 children successfully completed the training intervention and returned for follow-up assessment. During the first four years of the study, 1 participant at CNH was lost to follow-up and 1 participant qualified for, but did not complete, the intervention due to mental health concerns. As noted in previous reports, recruitment in Year 4 was impacted by the departure of Dr. Acosta; it took several months after Dr. Acosta's departure in August 2018 for normal NF1 clinic operations to resume. In the fifth year, CNH successfully recruited and completed baseline assessments for an additional 2 participants. Both children qualified for the intervention – 1 child successfully completed the intervention and returned for follow-up and the other child did not complete the intervention due to mental health concerns. Of note, recruitment in the fifth year was less than anticipated because the COVID-19 virus. Similarly, the previous study coordinators recently stepped down from their roles at CNH. While the new coordinator is trained and actively working on the study, this change has delayed our progress.

Additionally, it is important to note that as of March 17th, 2020, CNH and our collaborating had research recruitment suspensions due to the COVID-19 global pandemic. This regulation halted all recruitment efforts and prevented any additional study enrollments quarters 2, 3, and most of 4 in Year 5. The policies of all participating institutions continue to change regularly, and recruitment is now in the beginning stages of resuming at CNH and CHLA.

During the first four years of the study, CHLA successfully recruited and completed baseline assessments for 20 participants. Fifteen (15) children qualified for the intervention, and 11 children successfully completed the training intervention and returned for follow-up assessment. During the first three years of the study, 4 participants were lost to follow-up. In the fifth year, CHLA successfully recruited and completed baseline assessments for an additional 6 participants. Five (5) children qualified from the intervention – 3 children successfully completed the intervention and returned for follow-up, 1 child is actively participating in the intervention, and 1 child qualified, but was lost to follow up.

During the first four years of the study, CHW successfully recruited and completed baseline assessments for 21 participants. Nineteen (19) children qualified for the intervention, and 13 children successfully completed the training intervention and returned for follow-up assessment. During the first four years of the study, 5 participants were lost to follow-up. In the fifth year, CHW successfully recruited and completed baseline assessments for an additional 2

participants. Both children qualified for the intervention, successfully completed the intervention, and returned for follow-up.

In the first four years of the study, RCH successfully recruited and completed baseline assessments for 6 participants. Six (6) children qualified from the intervention – 3 children successfully completed the intervention and returned for follow-up, 2 children are actively participating in the intervention, and 1 child withdrew from the study. No additional children were recruited in the fifth year.

To date, 96 children have been successfully recruited, 62 evaluable participants have achieved follow-up, and 1 child is actively participating in the intervention. While our goal for the end of the fifth year, according to the SOW submitted in the No Cost Extension from August 2019, was to complete project recruitment, we remain optimistic that we will achieve our recruitment goals by the end of Year 6 (the second NCE year). To date, CNH has achieved 82% of its predicted enrollment, CHLA has achieved 104% of its predicted enrollment, CHW has achieved 74% of its predicted enrollment, and RCH has achieved 60% of its predicted enrollment. Importantly, because the Boston site was not included in Year 5 and will not be included in Year 6, the participants predicted to be enrolled at that site have been re-distributed across the other four sites. To meet our original project goals, we anticipate randomizing an additional 14 participants, with the expectation that 2 of these may be lost to follow up. We originally anticipated that 70% of children participating in screening/baseline testing would meet eligibility criteria for randomization; however, our actual rate is 78%. Therefore, we anticipate needing to recruit approximately 21 participants total to meet our final accrual goal. Specifically, CNH aims to recruit 6 participants, CHLA aims to recruit 5 participants, CHW aims to recruit 6 participants, and RCH aims to recruit 4 participants in the coming year, as outlined in the SOW submitted in September 2020. We are confident that we will be able to maintain a rate of accrual consistent with that planned for the NCE year.

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 CNH, 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 CNH, and discrepancies are identified and rectified. As specified in the protocol, we have also previously conducted a second formal review of data completion and accuracy, triggered when enrollment reached 60 participants in Year 4.

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 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?

Since the last report, we presented a poster characterizing accrual and adherence data in the first three years of the project at the annual meeting of the Children's Tumor Foundation. The citation is as follows:

Hardy, KK., Griffin, D., Berger, C., Weisman, H., Barton, B., Payne, J., Rosser, T., Walsh, K., & Ullrich, N. (2020). Multimodal Intervention Trial for Cognitive Deficits in Neurofibromatosis Type 1: Efficacy of Computerized Cognitive Training and Stimulant Medication. Poster presented at the 35th Annual NF Conference, virtual. **What do you plan to do during the next reporting period to accomplish the goals?**

Our goal is to screen a total of 117 participants by the end of the project, by recruiting another 21 participants across four sites as specified above.

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 fifth 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. Importantly, the Boston site experienced major delays in local IRB approval and will be not be included on this project in the coming year. The participants predicted to be enrolled at the Boston site have been re-distributed across the other four sites. Specifically, CNH will aim to recruit 7 participants, CHLA will aim to recruit 5 participants, CHW will aim to recruit 6 participants, and RCH will aim to recruit 4 participants in the coming year, as outlined in the SOW submitted in September 2020. We are confident that we will be able to maintain a rate of accrual consistent with that planned for the second NCE year.

   Further, it took 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. 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 five, we have screened 96 participants and randomized 77 evaluable participants on the intervention study, which is nearly 83% of our total accrual goals. Given the significant delays in executing contracts, receiving human subjects approval at both the local and HRPO levels in Project Year 2, and the total recruitment pause due to the COVID-19 global pandemic, we feel that our recruitment is roughly one year behind schedule, which the second NCE period should remedy. As noted above, we expect to enroll 117 participants by the end of the sixth year.

   2) As noted in previous reports, we experienced administrative delays at CNH within the Grants and Contracts Department earlier in the project. 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.

3) As noted in previous reports, 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 during the third year of this project, and the change-over of the two clinical research coordinators and postdoc with a new clinical research coordinator and postdoc in year 5 of the project. While all new study staff have successfully been trained on this study, the turn-over in staffing created minor delays in study progress, especially considering these changes occurred in the middle of the COVID-19 pandemic.

There was also a process of transition that occurred following Dr. Acosta's departure from the institution in August 2018. There was a 3-month hiatus in the comprehensive, multi-disciplinary NF1 clinic as a new clinic director was identified and established, and an additional three months in which the new clinic slowly established its previous volume of patients. This clinic, from which we typically recruit participants for the study, is now operating, and we are once again able to identify and approach families for participation with support from the new clinic staff.

4) In Year 5, we have continued to monitor recruitment process, retention and completion of final assessment, and have maintained expected progress until March 17th, 2020, when study enrollments were suspended at all sites due to the COVID-19 pandemic. We have maintained and monitored our regulatory compliance and have continued to coordinate across sites to finalize all participant recruitment, assessment, and data entry requirements. Notably, all funds are being used as originally proposed and the study aims have not changed.

However, recruitment efforts were completely paused due to site research restrictions during the COVID-19 global pandemic. These regulations prevented any additional study enrollments from March 2020 until October 2020. The policies of all institutions involved in the current study continue to change on a weekly basis, and recruitment is slowly resuming at CNH and CHLA. It is believed that study recruitment can be restarted within the next few weeks at all sites. Given our documented success in anticipated enrollment up until the pandemic-related policies were set, we submitted a second NCE which would facilitate screening of the anticipated additional 21 participants needed to achieve our projected sample.

The coordinating study team at CNH continues to meet regularly with members of the collaborating sites to review progress and data collection. The primary site clinical research coordinator is actively monitoring the changing policies related to COVID-19 and will continue to coordinate with all sites to resume recruitment and enrollment.

Procedures have been identified for each site that will maximize recruitment and assessment activities, while minimizing the time patients spend in clinics and adhering to all social distancing and public health practices. This includes identified testing rooms that are frequently cleaned, space that allows for appropriate social distancing, availability of personal protective equipment, and sanitizing protocols for all study materials. The requested second NCE period enable us to screen, enroll, and randomize participants to reach our anticipated sample of 90 randomized participants. Additionally, ongoing efforts coordinated by the study PI and the primary CRC will be taken to complete all assessments and collect all data in order to reach the projected 76 evaluable participants in our final sample. The study PI and the primary site CRC will also work closely to prepare data sets for analyses, thereby facilitating completion of the overarching goals of this study shortly after receipt of the final data points.

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:	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 CNH at 0.15 per quarter /.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.
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
Name:	Dan Zhang
Project Role:	Data Coordinator
Researcher Identifier:	N/A
Nearest person month worked:	0.09 per quarter/.36 per year
Contribution to project:	CRF and EDC creation
Name:	Hannah Weisman, B.S.
Project Role:	Clinical Research Coordinator, as of 8/1/2020
Researcher Identifier:	N/A
Nearest person month worked:	1.5 per quarter/6.0 per year
Contribution to project:	Facilitates communication between all sites, administrative management, coordination of study material and operations, intervention coach
Name:	Danielle Griffin, B.A.
Project Role:	Clinical Research Coordinator, Until 7/31/2020
Researcher Identifier:	N/A
Nearest person month worked	1.5 per quarter/6.0 per year
Contribution to project:	Facilitates communication between all sites, administrative management, coordination of study material and operations, intervention coach
Name:	Carly Berger, B.S.
Project Role:	Clinical Research Coordinator, Until 7/31/2020
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:	Christina Sharkey, PhD
Project Role:	Post-Doc Fellow, as of 8/10/2020
Researcher Identifier:	N/A
Nearest person month worked	0.6 per quarter/2.4 per year
Contribution to project:	Coach
Name:	Laura Kurzius, PhD
Project Role:	Post-Doc Fellow, Until 6/20/2020
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.