AWARD NUMBER: W81XWH-15-1-0508

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 Hospital
111 Michigan Ave NW, Washington DC 20010

REPORT DATE: DECEMBER 2021

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
DECEMBER 2021	Final	30SEPT2015 - 29SEPT2021

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER
W81XWH-15-1-0508

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S):
Kristina Hardy, PhD (PI)
Kaitlyn Tiplady, PhD (Post-Doctoral Fellow)

E-Mail: KKHardy@childrensnational.org and KMTiplady@childrenational.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Children's National
Hospital
111 Michigan Ave, NW
Washington, DC 20010

8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Children with NF1 demonstrate working memory difficulties which impacts cognitive and academic functioning. One hundred and three children with NF1, age 8-16 years (M = 11.37 years, SD = 2.21) at four participating sites (50.5% Male, 78.6% Not Hispanic/Latino, 68.0% White, 14.6% on stimulant medication), were screened using a battery of neurocognitive tests and parent-completed questionnaires. The intervention phase included 82 children (who were stratified by stimulant medication use and randomized equally between two interventions: CogmedRM (n = 41), or the active control, MobyMax, an online reading program (n = 41). Children who completed CogmedRM did not outperform children who completed MobyMax but demonstrated improvement on digit span backward and spatial span forward. This computerized, home-based working memory training program was acceptable, feasible, and enjoyable for children and adolescents with NF1.

15. SUBJECT TERMS

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

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRDC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *area code)*
Unclassified	Unclassified	Unclassified	Unclassified	14	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

1. INTRODUCTION: This study assessed the efficacy of a home-based, computerized cognitive training (CT) program in a sample of 82 children, aged 8-16 years, with Neurofibromatosis Type 1 (NF1) and working memory difficulties. Given the high incidence of working memory difficulties in children with NF1, it is a critical priority to identify feasible and efficacious interventions. By improving working memory difficulties, researchers are hopeful that children may experience fewer problems with intellectual quotient, executive functioning, and academic performance over time. Participants in this intervention study were stratified by stimulant medication use and randomized equally between two computerized cognitive training interventions within stratum. Participants participated in the study for up to 11 weeks. Participants were assigned a training coach who worked with them weekly via telephone to provide troubleshooting, brainstorm strategies for maintaining motivation, and provide feedback on training progress to date. Participants returned for follow up testing to measure abilities following completion of the intervention.

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

3. ACCOMPLISHMENTS:

What were the major goals of the project?
As stated in the SOW, the major goals of the project included: 1) Develop a plan for patient recruitment and obtaining human subjects approval, 2) Identify and train study personnel, and maintain a clinical database, 3) Recruit and evaluate participants, 4) Clean and analyze patient recruitment and evaluation data, safety data, and neuropsychological data (specifically, review data monthly for completeness and accuracy), and resolve queries with participating sites and 5) Perform final analysis and write 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. Over the past six years, we obtained IRB approval at CNHS, CHLA, RCH, and CHW and maintained proper institutional and DOD approval. Continuing reviews were appropriately maintained across sites. While Children's Hospital of Boston was also supposed to participate in this study, they never obtained IRB approval and therefore, did not ultimately recruit participants. IRB protocols have been maintained at each site to ensure we can continue analyzing data and disseminating the findings.

- CNHS: Coordinating Center IRB protocol submitted in February 2016 and was approved by the local IRB on 05/10/2016, HRPO protocol application was submitted on 06/ 02/2016 and was approved on 06/24/2016, and the 2021 Continuing Review was approved by Children's National on 03/10/2021 and submitted to the DOD on 3/16/2021.
- CHLA: IRB protocol approved 10/27/2016; protocol submitted to HRPO on 12/13/16, requested revisions submitted to HRPO 03/03/2017 and approved 10/15/2017, Continuing Review submitted to DOD 07/20/2020
- RCH: IRB protocol submitted 09/06/16 and approved 05/23/17, HRPO protocol submitted 09/19/2017 and approved 03/02/18, Continuing Review submitted to DOD 08/18/2020.
- CHW: IRB protocol submitted 09/06/16 and approved 05/23/17, HRPO protocol submitted 09/19/2017 and approved 03/02/18, Continuing Review submitted to DOD 08/18/2020

Our second major task was to identify and train study personnel, and to maintain a clinical database. Given that this study is concluding, all study personnel were appropriately trained and completed research activities as described. Study staff maintained properly trained assessment and intervention clinicians. New staff were trained and the coordinating site ensured participants received CogmedRM and MobyMax coaching. The coordinating site coached all participants at CHLA and CNMC and was a resource for coaches at RCH and CHW if they needed support.

Our third major task was to recruit and evaluate participants. Recruitment was delayed across sites due to difficulties obtaining HRPO and IRB approval. CNHS obtained HRPO approval first (06/24/2016), followed by CHLA (10/15/2017), and then RCH and CHW (03/02/2018.) In year 4, recruitment was impacted by

the departure of the original PI, Dr. Maria Acosta. After several months of obtaining the appropriate approval, Dr. Kristina Hardy became the PI and recruitment resumed. Recruitment was impacted again in year five given the COVID-19 pandemic and institutional restrictions on research at CNHS, CHLA, RCH, and CHW. A no-cost extension was submitted in August 2019 to allow time for additional recruitment. Each site involved in this study had target screening numbers which were outlined in the statement of work. The numbers in the statement of work were not ultimately achieved. This study has faced a myriad of difficulties with recruitment related to administrative delays in the initial approval and the onset of the COVID-19 pandemic which impacted recruitment at multiple time points. Further, the Australia sites, CHW and RCH, have been in lockdown multiple times which has impacted their ability to recruit participants since March 2020. Given these delays, the research team is satisfied with the final number of participants and can move forward with data analysis and dissemination. No additional participants will be recruited at this time.

Across the four sites, researchers screened 103 children with a diagnosis of Neurofibromatosis Type 1 (NF1) who showed signs of cognitive deficits related to NF1. Participants were between the ages of 8-16 years (M = 11.37 years, SD = 2.21) and were seen across four participating sites (50.5% Male, 78.6% Not Hispanic/Latino, 68.0% White, 14.6% on stimulant medication). The goal was to screen 120 participants screened across all sites, meaning 86% of the predicted enrollment was achieved. Study participants who demonstrated deficits in working memory were randomized (n=82) and asked to complete 25 at-home training session of either CogmedRM or MobyMax. The goal was to randomize 90 participants, so 91% of the randomization goal was achieved. After completion of the at-home training session (3-5 sessions per week) participants returned for a follow-up visit (n=68), which is 83% of the randomized sample.

The number of participants screened and randomized differed across sites. CNHS was scheduled to screen 52 participants by the end of the study with the goal of randomizing 36 participants. Upon completion of this study, CNHS screened 48 participants (92% of the target enrollment) and randomized 35 (97% of target randomization). At CNHS, 3 participants were lost to follow up. CHLA was scheduled to screen 29 participants by the end of this study with the goal of randomizing 21 participants. Upon completion of this study, CHLA screened 26 participants (90% of the target enrollment) and randomized 20 (95% of target randomization). At CHLA, 5 participants were lost to follow up. CHW was scheduled to screen 29 participants by the end of this study with the goal of randomizing 24 participants. Upon completion of this study, CHW screened 23 participants (79% of the target enrollment) and randomized 21 (88% of target randomization). At CHW, 5 participants were lost to follow up. RCH was scheduled to screen 10 participants by the end of this study with the goal of randomizing 9 participants. Upon completion of this study, RCH screened 6 participants (60% of the target enrollment) and randomized 6 (67% of target randomization). At RCH, 1 participant was lost to follow up.

Of note, we discovered a few discrepancies from previous quarterly reports stating enrollment and/or randomization totals in previous reports. Specifically, upon review of the quarterly reports and our final data set, it appears errors were made in the tracking of screened versus randomized participants. It appears that a few children who were screened for participation were inadvertently documented as being randomized participants. These errors have been reviewed in detail by the coordinating center and study PI and have been rectified for this final report.

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 were entered into an online database by the appropriate team member. Data has been reviewed for completeness and accuracy by the database manager. As specified in the protocol, we conducted a full review of data when participant enrollment reached 60. A major task over the last year was to maintain and then finalize the clinical database. The coordinating site reviewed all data for completeness and sent data inquires to each site which highlighted missing or incomplete data. CHLA reviewed the data inquiry and entered the missing data into the clinical database. Of importance, RCH and CHW are in Australia which is currently in lockdown due to the COVID-19 Pandemic. As a result, RCH and CHW were unable to go on site to complete the data review. They have reviewed the data inquiries and entered as much data as they can remotely. The coordinating site is aware of this situation and continues to communicate with RCH and

CHW. RCH and CHW have agreed to look for missing data when they are able to visit the office, in-person. The missing data is minor and all major outcome data has been collected and is complete.

The goals subsumed under the fifth major task are related to dissemination of findings. At this time, we have performed most major analysis related to outcome measures, with the exception of analyses related to academic measures. These findings are summarized here for final report purposes, but additional analyses are being prepared for publication. Information regarding individual CogState tasks referenced below is included in *Appendix A*.

The primary objective of this study was to statistically determine whether CogmedRM improves scores on the CogState One-back subtest when compared to the adaptive MobyMax control. All analyses were based on an intention to treat (ITT) approach. This means that if a participant is randomized, they will be included in analyses, regardless of the number of sessions that they completed in the assigned intervention. This was a Phase II study with two hypotheses within the primary aim. Each was tested at a two-sided alpha=0.025. All other analyses were considered exploratory.

The specific aim of this study was to assess the efficacy of a home-based, computerized cognitive training (CT) program in children with NF1 and working memory difficulties. Researchers hypothesized that CogState One-back score errors in working memory results (primary endpoint) would be lower in the CogmedRM group than in the MobyMax group. Researchers used a two-way analysis of covariance (ANCOVA), analyzed the post-intervention in the CogState One Back Accuracy Z-score assessing working memory. One factor in the analysis was the intervention group (CogmedRM vs MobyMax), and the second factor was the stratification group (on vs. off stimulant medication). The model used baseline CogState One-back Accuracy performance as the covariate. For analysis purposes, CogmedRM was considered effective if the mean One-back Accuracy score for participants assigned to the CogmedRM condition was significantly higher than that of participants assigned to MobyMax. Researchers found that participants in the CogmedRM and MobyMax did not demonstrate significant differences in their CogState One-Back score errors in working memory ($F(1,53) = 1.34$, $p = 0.25$)). Within the first hypothesis, researchers also hypothesized that participants who were on stimulants and completed CogmedRM would perform better on the CogState One-Back subtest for working memory than those participants who completed the MobyMax training. While we proposed that we would perform an ANCOVA within the “on-stimulants” stratum, this analysis was not appropriately powered due to the small sample size of children who qualified for randomization while being treated with stimulants (n = 12).

In addition, a linear regression model was fit using the performance-based (CogState One-back accuracy) scores at follow up assessment as the outcome and intervention group, age, and CogState performance and ADHD-RS IV scores from the baseline assessment included as covariates. The overall model was not significant, with the intervention groups showing no difference in CogState One-Back scores ($F(1,50) = 0.82$, $p = 0.37$) at follow-up, and baseline CogState performance, ADHD-RS IV scores, and age did not significantly contribute.

The exploratory aim of this study was to assess the efficacy of working memory training on other outcomes of interest, including both performance-based and questionnaire measures of working memory and attention. We used repeated measures linear model with alpha set at .05 to analyze the change in performance-based and questionnaire ratings scores between the baseline and follow up visits. Specifically, the following performance-based measures were included in the exploratory analyses: WISC-V Digit Span Backward, Spatial Span, One-card Learning and Groton Maze Learning. The research study team is awaiting data from the Australia sites in order to complete the analyses of CogState Detection and Identification. In addition, the following questionnaire variables were included in the exploratory analyses: BRIEF Working Memory Index, Behavioral Regulation Index, and Metacognition Index. Based on this analysis, we found that WISC-V Digit Span Backward scores ($F(1,27) = 5.83$, $p = 0.023$) and Spatial Span Forward scores ($F(1,27) = 12.20$, $p = 0.002$) significantly improved with cognitive training. CogState One-card Learning trended toward improvement ($F(1,27) = 3.88$, $p = 0.059$), but there were no significant improvements in Groton Maze Learning or any questionnaire variables ($ps > 0.05$).

Some preliminary findings have been submitted to the International Neuropsychological Society (INS) in the form of an abstract and the team is awaiting notification of acceptance to the conference. The team has already shared findings with investigators and we plan to continue disseminating findings through abstracts, presentations, and publications. We are currently drafting a publication for the study which we will submit to a peer reviewed journal in hopes of disseminating these important findings.

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 CogmedRM professional training program as well as instructor access to MobyMax. By completing the CogmedRM 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 have a better understanding of how progress is monitored within educational settings. Training and supervision provided by the PI and study staff allowed research coordinators to provide appropriate and effective feedback to participants completing the reading intervention. These training opportunities have allowed coordinators to engage in rapport building and refine their skills as executive function and academic coaches. Multiple professional development opportunities have been afforded to those who work on this project as well.

How were the results disseminated to communities of interest?
Data collection concluded on October 6th, 2021 when the final participant returned for their follow-up visit at CNHS. As a result, initial analyses recently began, and researchers have not yet disseminated the final results. Researchers will continue analyzing data and publishing findings to share with the community.

In the past, preliminary data from this study was used for conference posters and presentations. Specifically, data collected as part of this study was presented at the Children's Tumor Foundation annual conference in 2018 and 2020. The CTF conference is attended by multidisciplinary medical providers who work with individuals with NF1. A poster was also submitted to the International Neuropsychological Society 2022 annual conference, but it is currently under review and researchers are awaiting notification.

Hardy KK, Tiplady K, Walsh KW, Gioia AR, Rosser T, Barton B, Payne J, Ullrich N, Griffin D, Berger C, Packer RJ, Acosta MT. *Computerized cognitive training intervention for children with neurofibromatosis type 1 (NF1): Accrual and adherence in a multi-site trial.* Poster presented at the annual meeting of the Children's Tumor Foundation; November 2018; Paris, France

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.

Hardy KK, Sharkey, C, Tiplady K, Weisman H, Barton B, Rosser, T, Payne, J, Walsh KW, Ullrich, N, North, K, Acosta MT. *Efficacy of a computerized cognitive training for cognitive deficits in neurofibromatosis type 1: A randomized trial.* Submitted poster to the annual meeting of the International Neuropsychological Society; February 2022; New Orleans, United States.

Currently, the research team is the process of preparing this data for additional analysis and dissemination. The primary goal is to draft a research paper on the major findings to be published in a peer reviewed journal. The team is hopeful findings will be published in a journal which can be accessed by other researchers and medical professional who work with individuals with NF1. Researchers also plan to summarize findings in hopes of presenting at the Children's Tumor Foundation annual conference in June 2022.

What do you plan to do during the next reporting period to accomplish the goals?
Now that this study has closed recruitment and started the final data analysis, researchers plan to continue analyzing data and disseminating information. The research team is currently working on a publication that addresses the primary aims of this study and plans to use this data to publish information

on the exploratory aims. In order to continue disseminating the work, the PI's from each institution will continue to meet and work together to create publications.

4. **IMPACT**

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

Children with NF1 may experience executive function deficits which impact their functioning at home, school, and in the community. These executive function deficits are best identified and treated by working with a neuropsychologist, psychologist, or executive function coach within a clinical setting. Unfortunately, many children with NF1 do not have access to these specialized services based on socioeconomic status, transportation, and geographic location. Increasing access to technology, including the internet and computers, has improved the availability of health-related information and services for a wide range of individuals, including those in remote or underserved areas. For this reason, intervention approaches that include electronic or technological aspects may be particularly well-suited for individuals with physical, cognitive, mental health, or socio-economic difficulties that limit access to more traditional, neuropsychological services. Children, adolescents, and adults with NF1 often have limited access to intervention services that target core executive function difficulties. As a result, it is important to understand if computerized cognitive training (CT) programs can be used to treat children with NF1. The findings from this study suggest that children with NF1 benefit from using CogmedRM to improve their auditory and spatial working memory abilities on select tasks.

CT programs are not contraindicated with pharmacological interventions, are cost-effective, and easy to administer at home with parental oversight. CT programs, if included as part of remediation for cognitive deficits, thus have the benefit of being accessible to a large proportion of the population. MobyMax was also used as an online reading comprehension intervention. In this study, participants were able to complete both training programs in the convenience of their own homes, with support provided with the aid of a phone-based coach to guide and focus the activities. The technological requirements of each program were basic and easy to support, making both programs a patient-friendly, low-cost alternative to traditional hospital- or clinic-based care. Each family was trained to use the technology in one session and coaches were able to provide technological support remotely when needed.

This study evaluated the cognitive improvements associated with computerized CT and computerized reading intervention programs. Based on the results of this study, we know there are some benefits to working memory if children completed the computerized intervention, but we also know that parents did not report observable behavioral changes in their children. These are risks and benefits that should be discussed by providers if parents' express interest in using CT for children with NF1. Additional analysis is needed to determine the impact of the computerized training interventions on reading abilities.

Parents, children, and adolescents found both interventions to feasible and acceptable interventions, suggesting that other adaptive CT programs should be explored as a neuropsychological intervention option for children with NF1. Given that children with NF1 cannot easily access neuropsychological intervention services, these interventions should continue to be explored. As a result, it is important for neuropsychologists to continue identify interventions like CT that are easily accessible to children and adolescents with NF1.

What was the impact on other disciplines?

Across healthcare disciplines, providers experience difficulties referring patients for appropriate intervention services to address executive dysfunction. Barriers to intervention include time, location, socio-economic difficulties, and motivation to engage in long-term intervention services. Adaptive computerized inventions offer an alternative, easily accessible options for families who want access to intervention services but face barriers. In this study, parents, children, and adolescents reported they were able to navigate the technology and sufficiently complete sessions as directed by their intervention coach. While CogmedRM or MobyMax may not be appropriate given the individualized needs of the child, the format in which the interventions were delivered were well received. Given that these adaptive

computerized programs were well received by parents and children with NF1, other disciplines should consider whether adaptive computerized programs may also be beneficial for other populations.

What was the impact on technology transfer?
This study used two computer-based interventions for children with NF1. While CogmedRM targets working memory, Mobymax targets reading comprehension. Given that children with NF1 are more likely to experience working memory and reading comprehension difficulties than typically developing children with NF1 may benefit from these interventions. The results of this study suggest children who received CogmedRM did not demonstrate a significant improvement in visual working memory abilities as measured by Cogstate in comparison to children who received MobyMax, but performance on WISC-V digit span backward and spatial span forward did significantly improve for children who received CT. This means CT is not only feasible and acceptable, but it may improve at least some aspects of working memory.

CogmedRM is an adaptive, computer-based intervention. It consists of game-like exercises that involve repeated practice of simple visual-spatial and verbal span tasks. CogmedRM has been assessed in several studies in children with ADHD and other cognitive deficits associated with working memory problems. This program is considered a fixed training “dose” (i.e., 25 training sessions), which is important given it is a short-term intervention for children. CogmedRM consists of exercises that are continuously adapted to the child’s skill level on a trial-by-trial basis. While there is evidence to suggest that children with ADHD maintain gains over time and progress academically, additional analysis is needed to determine if this is true for individuals with NF1. In addition, parents did not report significant behavioral changes in their children’s behavioral or metacognitive functioning, suggesting that CogmedRM may not result in behavioral changes. Given the small sample size of children on stimulant, researchers were unable to run analyses to understand the effect of stimulant medication and the intervention on working memory abilities in children with NF1. Additional research is needed in this area to determine if there is a significant effect.

Mobymax is an adaptive, computer-based academic program. For this study, researchers used the paired reading stories program. Paired reading stories allowed children to read fictional and informational text and then answer questions about what they read. Given it was an adaptive program, the stories would become easier or harder depending on participant responses. Coaches were able to monitor the progress of participants using typical educational progress monitoring tools, like those used in Response to Intervention (RTI). At this time, additional data analysis is needed to better understand the impact of MobyMax training on working memory and reading comprehension abilities in children who completed the intervention. That being said, the goal was to understand if parents and children felt they could complete the intervention within the suggested time period using the technology provided by study staff.

The goal of this study was to determine if CogmedRM is a feasible, acceptable, and efficacious intervention. Findings suggest these computerized, home-based programs were acceptable, feasible, and enjoyable for children and adolescents with NF1, with some indication of clinical benefit. Given this support for the acceptability and efficacy of CogmedRM, translation of this intervention into clinical practice may be warranted.

What was the impact on society beyond science and technology?

This study impacted society by increasing knowledge about executive function and reading difficulties for individuals with NF1. Families volunteered to be apart of this study because children with NF1 who have executive dysfunction are impacted across settings and parents have a better understanding of the brain-based behavioral difficulties children with NF1 have.

Further, cognitive deficits are the most important cause of long-term dysfunction in patients with NF1. Remediation and interventions to improve those deficits will significantly impact the quality of life and long-term prognosis in this population. Given the high incidence of neuropsychological dysfunction in children with NF1, identifying accessible, safe, feasible and efficacious interventions is a critical priority for this population. There is evidence that CT interventions could be helpful and consistently implemented for

children with NF1. This does have the potential to impact long-term functioning for individuals with NF1, which could result in a greater societal impact.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

In the sixth year, we did not make any changes in the approach that was approved by the funding agency. This study has stopped recruitment and is in the data analysis phase, therefore, no additional changes will be made.

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

During the first year, we experienced a myriad of challenges, which delayed the timeline of this project. First, in 2015, CogmedRM 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. The team researched multiple alternative options and 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 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 resulted in recruitment delays across sites throughout the second year and into the third year. Importantly, the Boston site experienced major delays in local IRB approval and ultimately, was not included as a site in this study. The participants predicted to be enrolled at the Boston site were then re-distributed across the other four sites, increasing recruitment targets for each site. Further, it took longer than originally anticipated for CHLA, RCH, and CHW to obtain HRPO approval, which has ultimately delayed recruitment. 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. These issues caused significant delays at the beginning of this study.

As noted in previous reports, we experienced administrative delays at CNH within the Grants and Contracts Department earlier in the project. Specifically, we had trouble executing contracts between our site and other sites – an issue which took multiple months to resolve within the first year of this study. Additionally, our Grants department experienced significant delays in paying reimbursements out to CHLA, which dated more than six months. The issue was identified in April 2017 and was remedied by the end of Year 3, but CHLA stopped recruitment during this period.

Over the course of this study, we have experienced multiple staffing transitions at the coordinating site. In August 2018, Dr. Maria Acosta left CNHS and Dr. Kristina Hardy became the new study PI. 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. At the same time Dr. Acosta left, the coordinating center also experienced a transition in study coordinators. Two research coordinators left and two new research coordinators and a postdoctoral fellow were hired. Two years later, the two research coordinators and postdoctoral fellow left CNHS and one new research coordinator and postdoctoral fellow were hired. While all new study staff were successfully trained, the turn-over in staffing at multiple time points created delays in study progress and created challenges tracking participants.

Finally, the COVID-19 pandemic also created extensive delays in recruitment of new participants and ultimately impacted the attainment of our planned accrual. On March 17th, 2020, study enrollments were suspended at all sites due to the COVID-19 pandemic. CNHS resumed recruitment in Year 6, Quarter 1, but recruitment did not resume at other sites. Again, it is important to discuss the impact of the pandemic on the site located in Australia as they were impacted differently than sites in the United States. Australia has been in and out of lockdown since March 2020, which means CHW and RCH have not been able to recruit or screen participants for much of the pandemic. While both sites had the intention to recruit, given the pandemic and government regulations, they were unable to complete planned accruals.

At this time, this study has concluded recruitment and is the data analysis stage. Moving forward, the coordinating study team will continue to meet with collaborating sites periodically to review data and

discuss dissemination of finds. Once the CHW and RCH are no longer in lockdown, both sites will complete their data review and all data will be finalized for additional analyses.

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
As described above, the following conference presentations have resulted from this study:

Hardy KK, Tiplady K, Walsh KW, Gioia AR, Rosser T, Barton B, Payne J, Ullrich N, Griffin D, Berger C, Packer RJ, Acosta MT. *Computerized cognitive training intervention for children with neurofibromatosis type 1 (NF1): Accrual and adherence in a multi-site trial.* Poster presented at the annual meeting of the Children's Tumor Foundation; November, 2018; Paris, France

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.

Hardy KK, Sharkey, C, Tiplady K, Weisman H, Barton B, Rosser, T, Payne, J, Walsh KW, Ullrich, N, North, K, Acosta MT. *Efficacy of a computerized cognitive training for cognitive deficits in neurofibromatosis type 1: A randomized trial.* Submitted poster to the annual meeting of the International Neuropsychological Society; February 2022; New Orleans, United States.

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/2.4 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. Overseeing data review.
Name:	Hannah Weisman, B.S.
Project Role:	Clinical Research Coordinator, as of 8/1/2020
Researcher Identifier:	N/A

Nearest person month worked:	1.2 per quarter/3.6 per year
Contribution to project:	Administrative management, coordination of study materials and operations, and intervention coach
Name:	Kaitlyn Tiplady, PhD
Project Role:	Post-Doc Fellow, as of 12/28/2020
Researcher Identifier:	N/A
Nearest person month worked	1.2 per quarter/3.6 per year
Contribution to project:	Facilitates communication between all sites, administrative management, coordination of study material and operations, intervention coach

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

Appendix A

Table 1. Cogstate battery and test descriptions

Task	Task Description	Cognitive Domain	Outcome Measure
Detection	A playing card is presented face down in the center of the screen. When the card flips over the participant must press “Yes” as quickly as possible.	Processing Speed	Response speed
Identification	A playing card is presented face down in the center of the screen. When the card flips over the participant must decide whether the card is red or not.	Attention	Response speed
One-Back	A playing card is presented face up in the center of the screen. The participant must decide whether the card is the same as the previous card.	Working Memory	Response speed, Response accuracy
One-Card Learning	A playing card is presented face up in the center of the screen. The participant must decide whether he has seen the card before in this test.	Visual Memory	Response accuracy
Continuous Paired Associate Learning	The participant must learn and remember the pictures hidden beneath different locations on the screen.	Visual Memory	Response accuracy
Groton Maze Learning	The participant must find a hidden pathway. Once the participant successfully finds the hidden pathway, he is returned to the start location to repeat the test and must try to remember the pathway previously learned.	Executive Function	Response accuracy