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

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

Multicenter protocol Version 3: January 10, 2022

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As a site principal investigator I will conduct, record, and report this study in compliance with the IRB/Ethics Committee, International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice Guidelines, and Declaration of Helsinki. No protocol deviation will be implemented without prior review and approval of the Sponsor and IRB/Ethics Committee except where necessary to prevent immediate hazard to research participants. In this case, the deviation will be immediately reported to the Sponsor and IRB/Ethics Committee.

Signature of Investigator	Date
Print Investigator Name	Investigator Title
Name of Clinical Site	

1. PROTOCOL SYNOPSIS

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

Protocol Number: COGTRAIN

Objective: To assess the efficacy of a home-based, computerized cognitive training (CT) program, called *Cogmed*^{RM}, targeted to improve working memory in children with NF1 and working memory difficulties.

Study Design: This is a Phase II randomized parallel group controlled clinical trial comparing two interventions on cognitive outcomes. Participants will be stratified by stimulant medication use and randomized equally between the two interventions within stratum. Participants will be in the study for to 11 weeks.

Number of Participants:
Approximately 90 patients with Neurofibromatosis 1 (NF1) will be enrolled in the study.

Study Centers and Coordinating Center: Five study centers, 2 in the United States and 2 in Australia will participate in this clinical study. The Coordinating Center located at Children's National Health System will manage the clinical study operations, data management, statistical management and study reporting.

Eligibility Criteria:
Patients must meet all of the following inclusion criteria to be eligible for enrollment:

1. 8-16 years old at time of screening
2. NF1 Diagnosis based on National Institute of Health (NIH) criteria
3. Has an identified caregiver who is willing and able to oversee the training practice during the intervention period
4. Has access to a telephone and phone number where they can be reached
5. Both patient and caregiver have reading, speaking, and listening comprehension of English
6. Treated with a stable dose of stimulant medication for at least the last 30 days and not planning to change the dose during study participation *or* receiving no stimulant medications for at least the last 30 days and not planning to initiate a trial of stimulant medications for the duration of the study.
7. Score $\geq$1 SD below the mean on either the WISC-V-Integrated Spatial Span Forward or Backwards tasks or Digit Span Forward or Backwards tasks *or* score $\geq$1 SD below the participant's estimated IQ on either Spatial Span Forward or Backwards or Digit Span Forward or Backwards.

Patients will be excluded from enrollment in this study if they meet any of the following exclusion criteria:

1. Full scale IQ≤70, as estimated by WASI-II (Block Design, Vocabulary, Matrix Reasoning, Similarities).
    - Note: In cases where there is a statistically significant difference between verbal IQ and performance IQ (.05 level as determined by the WASI-II manual), participants will be eligible if at least one of these quotients is 70 or above
2. Current treatment for intracranial lesions, progressive tumors as per MRI evaluation or treatment with chemotherapy within the past 6 months
3. A motor, visual, or auditory handicap that prevents computer use

Study Intervention: Randomized participants will be trained on one of two home-based computer programs. The first, called *Cogmed*^{RM} targets working memory and is the targeted treatment of the study. The second program is an active control condition called MobyMax, which targets academic skill development (i.e., reading comprehension).

Study Duration: The length of time a participant is enrolled in this study will depend on how quickly each participant completes their at-home training. The training phase of the study will last between 5-9 weeks, after which participants will be asked to return for post-intervention testing within two weeks of completion. Therefore, participation could be as short as slightly over 5 weeks to a maximum of 11 weeks.

Evaluations:

Pre-study: Informed consent, inclusion/exclusion review, and demographics

Study assessments: Physical exam, ADHD-Rating Scale, CogState, Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II), Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V-Integrated), Child Behavior Checklist (CBCL), and Behavior Rating Inventory of Executive Functioning (BRIEF), Test of Word Reading Efficiency- Second Edition (TOWRE-2) and the Test of Everyday Reading Comprehension (TERC).

Statistical Methods:

The primary objective to be addressed statistically is to determine whether *Cogmed*^{RM} improves scores on the CogState One-back subtest when compared to the control intervention MobyMax. The primary analysis approach will be analysis of covariance (ANCOVA) with two factors. One factor is the intervention and the second factor is the stratum. The analysis is on the CogState one-back subtest result at Visit 2, with the baseline result as a covariate.

2. STUDY TEAM

STUDY CHAIR: Kristina Hardy, PhD
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3. ABBREVIATIONS

ADHD: Attention Deficit Hyperactive Disorder

ADHD-RS: Attention Deficit Hyperactive Disorder- Rating Scale

AE: Adverse Event

ANCOVA: Analysis of Covariance

BP: Binding Potential

BRIEF: Behavior Rating Inventory of Executive Functioning

CBCL: Child Behavior Checklist

CI: Confidence Interval

CNHS: Children's National Health System

CPT-II: Conners' Continuous Performance Test, Version II

CT: Cognitive Training

DOD: Department of Defense

DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition

eCRF: electronic Case Report Form

EDC: Electronic Data Capture

GCP: Good Clinical Practice

HIPAA: Health Insurance Portability and Accountability Act

IRB: Institutional Review Board

ICF: Informed Consent Form

ICH: International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IQ: Intelligence Quotient

MPH: Methylphenidate

MRI: Magnetic Resonance Imaging

MTA: Multimodal Treatment of ADHD

NF1: Neurofibromatosis Type 1

NIH: National Institutes of Health

OPG: Optic Pathway Glioma

PET: Positron-Emission Tomography

PI: Principal Investigator

rCBF: regional Cerebral Blood Flow

REDCap: Research Electronic Data Capture

SD: Standard Deviation

SAE: Serious Adverse Event

SWM: Spatial Working Memory

TERC: Test of Everyday Reading Comprehension

TOWRE-2: Test of Word Reading Efficiency—Second Edition

VMAT2/DAT: Vesicular Monoamine Transporter Type 2; Dopamine Transporter

WASI-II: Wechsler Abbreviated Scale of Intelligence—Second Edition

WISC-V-Integrated: Wechsler Intelligence Scale for Children—Fifth Edition

WM: Working Memory

4. BACKGROUND AND SIGNIFICANCE

4.1. Overview of Disease

NF1, cognitive dysfunction, and ADHD

NF1 is a common autosomal dominant disorder with an incidence of 1 in 3,000 characterized by diverse cutaneous, neurological, skeletal and neoplastic manifestations (Ferner, Huson et al. 2007). Improvements in the short and long term prognosis of patients with a diagnosis of NF1 have increased awareness that the most important factors in long term prognoses are cognitive deficits (North, Hyman et al. 2002). Knowledge of the cognitive profile of patients with NF1 has dramatically increased over the past 15 years (Lehtonen, et al., 2012). While general intellectual functioning is only moderately affected, the impact of NF1 cognitive deficits is greatest on academic achievement, with up to 70% of school-aged children with NF1 underachieving (Brewer, Moore et al. 1997) and learning disabilities estimated in 30-65% of children with NF1 (North, Riccardi et al. 1997). In a recent Dutch study, 75% of the NF1 children performed more than one standard deviation below same-grade peers in at least one academic domain (Krab, Aarsen et al. 2008; Coude, Mignot et al. 2007). In addition, they had a four-fold increased risk for requiring special education and a six-fold increased risk for receiving remedial teaching for learning, behavior, speech, or motor problems. Only 10% of children with NF1 did not show any school-functioning problems (Krab, Aarsen et al. 2008). Given that general intellectual deficiency is unlikely to sufficiently explain the pattern of observed academic failure, discovering specific neurocognitive deficits that contribute to the academic difficulties of children with NF1 is a high priority, as such deficits have potential negative consequences for daily living skills, employment opportunities and quality of life (Graf, Landolt et al. 2006).

In terms of specific cognitive deficits, several studies report deficits in visual spatial function (Hyman, Shores et al. 2005; Levine, Materek et al. 2006) and attention difficulties including problems with sustained attention and divided attention (Gilboa et al., 2011; Isenberg et al., 2012; Hyman, Shores et al. 2005). In addition, children with NF1 exhibit extensive compromise in executive function in terms of reduced cognitive flexibility, working memory capacity, inhibition and planning; all functions thought to be mediated by the prefrontal cortex (Payne, Hyman, Shores et al., 2011; Hyman, Shores et al. 2005). Multiple research groups have noted the high incidence of attention deficit hyperactivity disorder (ADHD) in association with NF1 (Mautner, Kluwe et al. 2002). ADHD is defined as a neurodevelopmental disorder manifested by elevated levels of inattention and/or impulsivity and hyperactivity compared with other individuals of the same age (DSM-5, 2013). In the NF1 population, ADHD diagnosis has been prevalent in several studies, with the incidence as high as 70%. Beyond the implications on learning, the presence of ADHD has been found to be a major risk factor for poor social

functioning (Barton and North 2004), as well as general intellectual functioning (Lidzba et al., 2012; Koth, Cutting et al. 2000). Although there is evidence that cognitive control deficits are not limited to NF1 patients with comorbid ADHD (Huijbregts, Swaab et al. 2010; Roy, Roulin et al. 2010), children with both disorders are acknowledged to be among the most severely affected in terms of academic performance.

Importantly, difficulties with working memory are also prevalent in both children with ADHD (Castellanos, Sonuga-Barke et al., 2006; Faraone and Biederman, 1998; Martinussen et al., 2005) and in children with NF1 (Payne, Arnold, et al., 2012). Specifically, children with developmental ADHD experience difficulties with verbal and visual working memory skills (Barnett, Maruff et al., 2001; Martinussen et al., 2005) of medium to large effect size. In a recent meta-analytic review, Kasper and colleagues (2012) analyzed the results of 45 trials with respect to differences in phonological and visuospatial working memory skills between children with ADHD and typically-developing children. Effects sizes (Hedges *g*) were reported of 0.69 (95% CI = 0.53-0.84) for phonological working memory tasks and 0.74 (95% CI = 0.53-0.95) for visuospatial working memory tasks; moreover, these differences were larger for studies using tasks with higher cognitive "load". Similar difficulties in spatial working memory were recently reported by Payne and colleagues (2012) in a sample of children with NF1, both with and without comorbid ADHD.

Working memory (WM) is a particularly compelling target for intervention, given its critical role in the development of other cognitive and academic outcomes. In healthy children, Fry and Hale (1996) found that almost half of developmental increases in IQ could be attributed to age-related improvements in WM and processing speed. Because WM capacity increases two- to three- fold from ages 4 to 16 (Gathercole et al., 1999), disruption to the development of these processes can significantly curtail a wide range of a child's abilities over time. This may take the form of diminished IQ or difficulty with other aspects of executive functioning and academic performance. For example, children with reading difficulties frequently have deficits in WM which appear to contribute to problems with phonological memory (Swanson and Beebe-Frankenberger, 2004). Math skills are also strongly linked to WM capacity in typically-developing children, accounting for between 20 -57% of the variance in math performance (Swanson et al., 2004; Hutton and Towse, 2001). ***Thus, improving WM in children with NF1 may help to offset problems with IQ, executive functioning, and academic performance over time.***

4.2. Research on Interventions to address Attention in NF1

Despite the significant negative impact of cognitive and behavioral deficits, few intervention studies have been conducted in patients with NF1 and attention problems. Given the observed similarities between patients with developmental ADHD and

children with NF1, interventions for ADHD are often employed clinically to treat the behavioral symptoms of children with NF1. Yet, aside from a single study showing efficacy of stimulant medication in children with NF1, such interventions have not been evaluated empirically in the NF1 population, and we are unaware of any published studies using non-pharmacological approaches.

In children with ADHD, the most-well-studied approach for remediating attention difficulties is the use of the stimulant medications, particularly methylphenidate (MPH). MPH is a piperidine derivative most commonly used to treat individuals with neurodevelopmental attention ADHD. It functions to increase the availability of dopamine in the prefrontal cortex and other subcortical connections considered critical for regulation of attentional processes (Volkow et al., 2005).

In children with NF1, Mautner and colleagues (2002) published the only known study of stimulant medication in children with NF1 and ADHD. In this study, a small sample of children with NF1 and ADHD (n = 20) were compared with a group of non-NF1 ADHD participants (n = 26) in terms of response to stimulant medication. In an open label design, researchers used a daily titration of short acting MPH until patients reached a 15 mg dose or test performance reached normal levels on a task of sustained visual attention and inhibition (i.e., Test of Variables of Attention). Children in both groups showed statistically significant improvements in commission and omission errors on the Test of Variables of Attention, and the ADHD control group only showed statistically significant improvements in response time. In addition, at one-year follow-up, parent and teacher ratings of symptoms indicated significant improvements in the NF1+ADHD group for symptoms of inattention and impulse control. There were a number of notable limitations of the study, including the use of a short-acting MPH formula rather than a modern extended-release formula. In addition, there was no assessment of other relevant cognitive domains (e.g., executive functions including working memory), nor was efficacy determined over a range of performance-based and rating scale outcomes.

There is biologically-based evidence that stimulant medications may impact dopaminergic alterations associated with deficits in neurofibromin (Brown et al 2010, Brown et al 2011). Recent studies using Nf1+/- mice with homozygous inactivation of the Nf1 gene in GFAP+ cells (known as Nf1 OPG mice) have established a mechanistic connection between Nf1 gene expression, attention system function, and dopaminergic pathway integrity (Brown, Emnett et al. 2010). These mice exhibit marked defects in non-selective and selective attention without an accompanying hyperactivity phenotype. Reverse-phase high performance liquid chromatography measurements demonstrated a marked reduction in dopamine levels in the striatum in Nf1 OPG mice (compared to control littermates). Crucially, attention defects were rescued following treatment with MPH and levodopa. This was accompanied by normalization of dopamine levels in the

striatum (Brown, Emnett et al. 2010). Further extending these findings, the investigators found evidence of presynaptic dopamine deficits consisting of reduced striatal DARPP32 phosphorylation, reduced VMAT2/DAT (vesicular monoamine transporter type 2; dopamine transporter) expression in striatal tissue and reduced [11C]-raclopride positron-emission tomography (PET) binding in intact Nf1 OPG mice. They also showed that treatment with MPH or l-deprenyl, an irreversible MAO-B inhibitor that increases dopamine levels, reversed the cognitive and behavioral effects as well as the abnormal [11C]-raclopride binding (Brown, Emnett et al. 2010). These findings suggest that reduced dopamine levels underlie the inattention phenotype in Nf1 OPG mice. By extension, it is reasonable to hypothesize that MPH may improve cognitive deficits in children with NF1 by enhancing striatal dopamine levels. PET studies with adults have shown that treatment-naïve adults with ADHD have similar deficits in presynaptic striatal dopamine levels (Volkow, Wang et al. 2007). Based on these biological observations, it is possible to hypothesize that, if deficits in neurofibromin are related to alterations in dopaminergic pathways, clinical improvements or effects obtained using stimulant medications in NF1 patients may be similar to children with developmental ADHD.

In children with ADHD, stimulants are most effective in reducing core symptoms of the disorder as delineated by the DSM-IV-TR (2000). Despite this, there is also evidence that stimulant treatment is less effective in reducing functional impairment related to symptoms, particularly with regard to problems related to executive dysfunction (Abikoff, Nissley-Tsiopinis et al. 2009). Moreover, there is also data from the longitudinal Multimodal Treatment of ADHD (MTA) study that the effects of stimulant medication treatment may not persist over the long term (MTA Group 2004). Additionally, a sizable portion of children (i.e., 20-30%) either cannot tolerate or do not derive significant benefit from stimulant treatment. For these reasons, a number of consensus groups have called for the continued examination of other treatment modalities, under the assumption that a multi-modal treatment approach is likely required for optimal functioning in many patients. Towards this aim, the development of non-pharmacological treatment methods has received increased attention in recent years, particularly for interventions aimed at reducing symptoms that are less well-targeted by psychostimulants (i.e., executive functioning).

4.3. Cognitive training (CT) Programs

Cognitive training (CT) programs have been used for decades to reduce or stabilize neurocognitive deficits in populations of individuals with accidental or disease-related brain injury. Most CT programs emphasize activities designed to improve specific cognitive deficits through repetitive practice of related skills, often with the aid of a trained therapist or “coach” who functions to guide and focus the activities, and to facilitate training with maximum effort and efficiency.

CT has been associated with improved functioning in several child and adult populations including those with traumatic brain-injury (Cicerone 2002; Cicerone 2002; Tiersky, Anselmi et al. 2005; Tiersky, Anselmi et al. 2005), dementia (Moore 2001; Cahn-Weiner, Malloy et al. 2003; Hofmann, Rosler et al. 2003; Cipriani, Bianchetti et al. 2006), schizophrenia (Bell, Fiszdon et al. 2004; Fiszdon, Bryson et al. 2004), mild cognitive impairment (Cipriani, Bianchetti et al. 2006) and ADHD (Klingberg, Forssberg et al. 2002; Klingberg, Fernell et al. 2005). A meta-analytic review of over 85 CT studies concluded that individuals receiving such treatment receive significantly more benefit than those in control/placebo conditions (Cicerone, Dahlberg et al. 2005).

In the past several years, many *computerized* CT programs have been developed specifically to target attention and WM problems, primarily in children and adolescents diagnosed with Attention-Deficit Hyperactivity Disorder (ADHD). Most consist of a series of attention/short-term memory tasks of increasing complexity, and there is emerging support for their efficacy with the ADHD population (Slate, Meyer et al. 1998; Kerns, Eso et al. 1999; Klingberg, Forssberg et al. 2002; Klingberg, Fernell et al. 2005).

Several lines of research indicate that dopamine plays an important role not only in WM function but also for improving WM capacity. In addition, one of the mouse models of NF1 provides compelling evidence supporting dopaminergic modulation as a treatment of inattention in NF1. ***Pharmacological interventions acting on the dopaminergic system, such as methylphenidate, improve WM performance. Cognitive training programs for improving WM performance have also recently been associated with changes in dopamine receptor density***. These two different means of improving WM performance--pharmacological and behavioral--are thus associated with similar biological mechanisms in the brain involving dopaminergic systems.

4.3.1. Cogmed*RM*

Klingberg and colleagues developed a computerized CT program targeted at reducing deficits in working memory (Klingberg, Forssberg et al. 2002; Klingberg, Fernell et al. 2005). The program, called *Cogmed*^{RM}, consists of game-like exercises that involve repeated practice of simple visual-spatial and verbal span tasks. *Cogmed*^{RM} has been assessed in several studies in children with ADHD and other cognitive deficits associated with WM problems. This program lends itself particularly well to randomized, controlled studies given the fixed training "dose" (i.e., 25 training sessions). *Cogmed*^{RM} consists of exercises that are continuously adapted to the child's skill level on a trial-by-trial basis.

Participants who complete *Cogmed*^{RM} typically show immediate gains in objective and subjective attention and WM skills, and there is evidence to suggest that children maintain gains over time (Beck, Hansen et al., 2010;

Bernards, Snijders et al. 1993; Klingberg, Forssberg et al. 2002; Klingberg, Fernell et al. 2005; Holmes, Gathercole et al. 2010) and also progress academically (Holmes, Gathercole et al. 2010). (Holmes, Gathercole et al. 2010). In controlled trials, effect sizes for parent-rated inattention and executive functioning have been moderate to large, averaging at approximately Cohen's d = 0.80 (standardized mean difference; Cohen, 1988). In terms of performance-based measures, effect sizes are largest for near-transfer tasks, particularly visual-spatial tasks (d = .80 – 1.0). Importantly, gains on near-transfer tasks have been largely maintained at 3-month (Klingberg, Fernell et al. 2005) and 6-month (Holmes, Gathercole et al. 2009) follow-up assessments. Moreover, when Holmes and colleagues (2009) evaluated the academic achievement of children with low working memory scores (with or without comorbid ADHD) 6 months following *Cogmed*^{RM} training, math achievement scores were shown to have improved approximately 0.5 SD.

Although it remains unclear both the extent to which training-related gains transfer to everyday functioning, and the exact mechanisms by which training-related gains take place (Gibson, Gondoli et al. 2011; Gibson, Kronenberger et al. 2012), computerized CT is an emerging intervention approach with the potential to benefit children with NF1 and working memory difficulties. Of importance, a recent trial comparing use of stimulant medication to participation in *Cogmed*^{RM} training (Holmes, Gathercole et al. 2009) resulted in significant WM gains following both interventions. However, children on stimulant medication made gains in visuo-spatial WM only, whereas those completing CT made broad gains in several types of WM. Results thus suggest that WM training may have complementary benefits to medication, especially for WM skills (Holmes, Gathercole et al. 2009). Thus, while stimulant medication is highly effective in improving core aspects of attention, WM training targets a broader range of skills related specifically to working memory.

In addition, cognitive training may also impact the dopaminergic pathways and produce changes in neuronal plasticity. McNab and colleagues (2009) showed changes in dopamine receptors using a WM training program. Thirteen volunteers (healthy males 20 to 28 years old) performed the 5-week WM training, resulting in significant gains on performance-based WM tasks. In addition, measurements of the binding potential (BP) of D1 and D2 receptors measured with PET using the radioligands [^{11}C]SCH23390 and [^{11}C] Raclopride, before and after training, showed that increases in WM after training inversely correlated with the D1 dopamine receptor BP in the regions involved in WM performance. The present study shows that practice-induced changes in WM correlate with changes in the D1 receptor BP.

A potential synergistic effect may be observed combining MPH and WM training. Research in experimental animals strongly suggests that stimulation of dopamine receptors in the prefrontal cortex can ameliorate spatial working memory (SWM) related cognitive deficits, and may even enhance cognitive function in healthy animals. Research in humans has not been able to clearly replicate these findings, partly due to the lack of available agents that can safely be used. MPH can enhance cognitive performance in adults and children diagnosed with ADHD (Kempton et al., 1999; Riordan et al., 1999) and also in normal human volunteers on tasks sensitive to frontal lobe damage, including aspects of spatial working memory performance (Elliott et al., 1997). Mehta et al, 2000, investigated changes in regional cerebral blood flow (rCBF) induced by MPH during performance of a SWM task to define the neuroanatomical loci of the beneficial effect of the drug. The results show that the MPH-induced improvements in WM performance occur with task-related reductions in rCBF in the dorsolateral prefrontal cortex and posterior parietal cortex. The beneficial effects of MPH on WM were greatest in the subjects with lower baseline WM capacity (Mehta, et all 2000). Although a randomized clinical trial to investigate a synergistic effect of *Cogmed*^{RM} training and MPH use has not been conducted with any clinical population, Beck and colleagues (2010) conducted a randomized trial of children with ADHD (n = 52), many of whom were also receiving stimulant treatment during the study. Although there were no differences in cognitive training outcomes between those receiving or not receiving stimulant treatment, it is important to note that the authors did not require that participants taking stimulant medication complete their cognitive training sessions during the therapeutic window of the drug. Rather, they merely specified that children complete their training sessions at a consistent time of day; thus, any synergistic effect may have been obscured.

4.3.2. MobyMax

MobyMax (Willett & Willett, 2016) is an adaptive online educational program that targets academic skills across a range of subject areas (e.g., reading fluency, reading comprehension, math computation, etc.). It is designed to be completed by children aged 5+ on a desktop or laptop computer or tablet device with minimal parental supervision. The adaptive format is designed to keep a child practicing exercises within a range of difficulty appropriate to his or her level of performance. MobyMax was selected as an active control for this study because it mirrors *Cogmed*^{RM} in its adaptive qualities; however, target content area in each program differs. *Cogmed*^{RM} is focused on training working memory skill whereas MobyMax is focused on reading comprehension. Although training sessions are defined by the number of trials, as with *Cogmed*^{RM}, participants

assigned to MobyMax will be asked to complete 25 training sessions, each between 30-45 minutes each, which will be automatically tracked by the MobyMax program. Thus, the time spent on MobyMax activities and the time spent on *Cogmed*^{RM} training will be equivalent across groups.

5. STUDY OBJECTIVES

5.1. Specific Aim 1

To assess the efficacy of *Cogmed*^{RM}, a home-based, computerized cognitive training (CT) program in children with NF1, ADHD, and working memory difficulties as compared to a control CT program.

***Hypothesis 1*:** Participants receiving the *Cogmed*^{RM} intervention will show a larger improvement in their CogState One-back scores from baseline than participants receiving the MobyMax intervention.

Sub-Hypothesis 1a: Participants who are identified as ON Stimulants and receiving the *Cogmed*^{RM} intervention will perform better compared to those participants ON stimulants who completed MobyMax with respect to their scores on the CogState One-Back after completion of the intervention.

5.2. Exploratory Aim

To assess the efficacy of cognitive training on other outcomes of interest, including both performance-based and questionnaire measures of working memory.

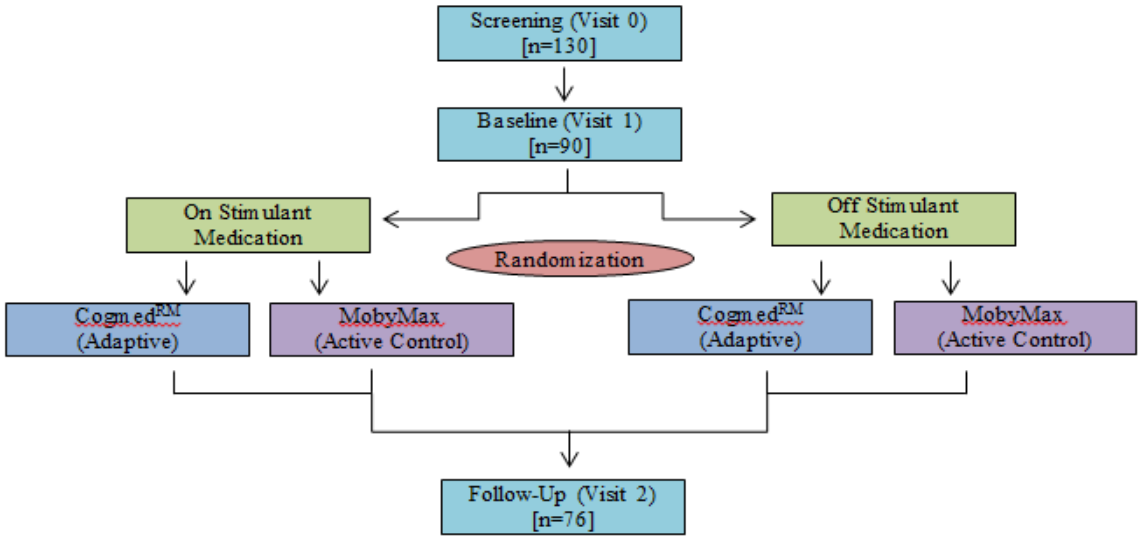
Exploratory Hypothesis:

Participants who complete the adaptive version of *Cogmed*^{RM} will show significantly greater improvements than those who complete MobyMax on performance-based and questionnaire measures of WM and executive functioning. Participants who complete MobyMax are expected to show greater improvements on performance-based measures of reading than those who complete *Cogmed*^{RM}.

6. STUDY DESIGN AND METHODS

6.1. Study Design

Figure 1: Study design



6.2. Stratification and Randomization

All patients will be registered in a centralized participant registry system administered through the Children's National Health System. Eligible participants will subsequently be stratified by medication use and randomized equally between the two interventions using a HIPAA-compliant password-protected web site. This web site will incorporate randomization lists created by the study biostatisticians using a permuted block design with stratification according to stimulant medication status (ON vs. OFF).

7. STUDY POPULATION AND SELECTION

Approximately 90 patients with NF1 will be enrolled at 2 U.S. sites and 2 international sites. Potential participants will include children diagnosed with NF1 aged 8 to 16 who show signs of cognitive deficits related to NF1. No exclusions will be made based on gender, race, or ethnicity. To reach this goal, we anticipate needing to screen approximately 130 participants, though enrollment will end when, or continue until 90 eligible participants are identified. Based on conservative estimates, approximately two-thirds of those screened should meet all eligibility criteria for the intervention phase.

Those who are enrolled in the intervention (n = 90) will be determined by the criteria listed in the inclusion and exclusion section of this document.

7.1. Inclusion Criteria

- 8-16 years old at time of screening
- NF1 Diagnosis based on NIH criteria
- Has an identified caregiver who is willing and able to oversee the training practice during the intervention period
- Has access to a telephone and phone number where they can be reached
- Both patient and caregiver have speaking, and listening comprehension of English. Caregivers must be able to read English with enough proficiency to complete study questionnaires (approximately 5th grade reading level).
- Treated with a stable dose of stimulant medication for at least the last 30 days and not planning to change the dose during study participation *or* receiving no stimulant medications for at least the last 30 days and not planning to initiate a trial of stimulant medications for the duration of the study.
- Score ≥1 SD below the mean on either the WISC-V-Integrated Spatial Span Forward or Backwards tasks or Digit Span Forward or Backwards tasks *or* score ≥1 SD below the participant's estimated IQ on either Spatial Span Forward or Backwards or Digit Span Forward or Backwards.

7.2. Exclusion Criteria

- Full scale IQ ≤ 70, as estimated by WASI-II (Block Design, Vocabulary, Matrix Reasoning, Similarities).
    - Note: In cases where there is a statistically significant difference between verbal IQ and performance IQ. (0.05 level as determined by the WASI-II manual), participants will be eligible if at least one of the these quotients is 70 or above
- Current treatment for intracranial lesions, progressive tumors as per MRI evaluation or treatment with chemotherapy within the past 6 months
- A motor, visual, or auditory handicap that prevents computer use

7.3. Early Termination or Withdrawal

A participant (or the legal guardian acting on behalf of the participant) is free to withdraw consent and discontinue participation in the study at any time, without prejudice to further treatment according to standard clinical practice. Study participation may be discontinued at any time at the discretion of the site PI. The following may be justifiable reasons for removing a participant:

- The participant is uncooperative/noncompliant and will not adhere to study responsibilities, including failure to appear at study visits.
- The participant experiences an unmanageable AE.
- The participant (or the legal guardian action on behalf of the participant) wishes to enroll in any other study which involves a different study intervention.

For participants who discontinue early from the study or if the study is prematurely terminated, the site Principal Investigator (PI) or designee will contact the participant or the participant's legal guardian **within 30** days after withdrawal or termination to assess any AEs. The site PI will be asked to follow all Severe Adverse Events (SAEs) until the event returns to baseline or until the site PI determines that follow-up is no longer medically necessary.

7.4. Study Duration and Enrollment

7.4.1. Study Enrollment

Children meeting the study eligibility criteria will be invited to participate at each participating site according to specific procedures that have been locally approved by the Institutional Review Board at each institution. Study participation begins (i.e., as the participant is "enrolled") once written informed consent form (ICF) is obtained from the potential participant and their guardian/legal representative before any study-specific procedures are performed. The study will be explained and informed consent will be obtained from caregivers by a member of the study team at each institution. Unique study IDs will be assigned to each participant. Each site principal investigator (PI) will keep a study number log relating the names of the participants to their study numbers to permit efficient verification of participant files, when required.

7.4.2. Study Duration

The length of time a participant is enrolled in this study will depend on how quickly each participant completes their at-home training. At a minimum, participants will be enrolled for 5 weeks and may extend to 11 weeks.

8. STUDY INTERVENTION

8.1. Product Details

8.1.1. Cogmed[RM]

Cogmed [RM] is a computer program installable either as a direct download or from a CD-ROM, and compatible with any Windows-based or Apple personal computer. The program is commercially available to qualified practitioners through *Cogmed, Inc*., currently owned by Pearson. The program consists of twelve visually-engaging and interesting exercises that target skills involving visuo-spatial and verbal WM. Difficulty of the tasks is automatically adjusted on a trial-by-trial basis throughout each training session to match a child's current working memory span, such that as the child becomes more proficient, the exercises become more difficult. *Cogmed [RM]* is designed for children aged 8 to 16. Exercises have space and robot themes with names such as "Decoder," "Space Whack," and "Visual Data Link." For example, "Asteroids," a visuo-spatial WM exercise, consists of a number of asteroids floating through space. The asteroids light up in a random order, after which the child is asked to click on the asteroids in the order in which they just were highlighted. When done correctly, the highlighted asteroids explode. In "Stabilizer," a verbal memory exercise, children hear a series of letters while lights illuminate with each letter. Then, when the letter appears on the screen, the child must select the correct light that was originally paired with that letter. *Cogmed [RM]* also contains a game, "Robo Racing," that children can play as a reward for completing their session. Children are encouraged to complete training tasks correctly to earn more "energy" that can later be used during the reward game.

During the intervention, children complete 25 training sessions. Children are asked to complete between 3 and 5 sessions per week, so the total treatment time to complete 25 sessions may range from 5 to 9 weeks. For children completing *Cogmed[RM]*, sessions typically last between 25 and 45 minutes, depending on the child's working memory span. Parents are asked to support their child's training in developmentally appropriate ways. For younger children, this typically involves helping children to turn on the computer and launch the program, as well as providing frequent feedback and encouragement during sessions. Older children usually require less supervision, though parents may be asked by coaches to help their children follow through with coaching suggestions (e.g., taking a break after challenging activities). Prior to beginning training, all families are asked to identify specific days, times, and settings during which training sessions will take place (on average) so that a quiet, distraction-free

environment can be selected for training, at a time when the child has adequate energy and no competing demands.

8.1.2. Control Program – MobyMax

MobyMax's "Reading Stories" program is an adaptive activity that mirrors *Cogmed*^{RM} on a learning level. The participant's reading comprehension as determined by the baseline testing session, will determine the grade placement within the Reading Stories activity of the MobyMax program. Each grade contains 30 lessons, in which each lesson contains 3 stories that are tailored to the participant's grade level. Participants are given questions to answer at the conclusion of each story. Depending on whether the participant passes or fails, the adaptive program will place the participant at the appropriate reading level. Participants randomized to this program, will be asked to spend the same amount of time as the participants randomized to *Cogmed*^{RM} (i.e., 30-45 minutes per session for 25 training sessions over a 5 to 8 week period), and, as with *Cogmed*^{RM}, a training coach from the study team will be assigned to access and track each participant's progress, as well as provide weekly, phone based coaching support.

8.1.3 Ongoing communications with participants for both interventions

For both intervention arms, families will have phone meetings at least once per week with an intervention coach to ensure compliance, record any adverse events (grade 3 or above), track progress, provide feedback and answer any questions that may have arisen during treatment. While the coaching structure is the same for all participants, the coach retains the flexibility to specifically address difficulties according to each child's needs. There may be children who, despite coaching efforts, are not compliant with training. Every effort will be made to obtain follow up data from these participants, and their data will be analyzed on an intent-to-treat basis.

9. STUDY ASSESSMENTS

Table 1 *Schedule of Assessments* outlines the overall study schedule including clinic visits and at home follow-up.

Table 1. *Schedule of Assessments*

STUDY VISIT	VISIT 1	HOME TRAINING	VISIT 2

STUDY INTERVAL	**BASELINE**	**FOLLOW-UP PHONE CALLS**	**FOLLOW UP**
STUDY PROCEDURES	DAY 0	WEEKS 1-9	DAY
Informed Consent	**X**		
Inclusion/Exclusion	**X**		
NF1 Diagnosis Confirmed	**X**		
Demographics	**X**		
Medical/Surgery History	**X**	**X**	**X**
Weight/ Height	**X**		**X**
Vital Signs	**X**		**X**
Concomitant Medication	**X**	**X**	**X**
Physical Exam	**X**		**X**
ADHD-RS	**X**		
Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II)	**X**		
Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V-Integrated)-select tests	**X**		**X**
Child Behavior Checklist (CBCL) *	**X**		
CogState	**X**		**X**
Behavior Rating Inventory of Executive Functioning (BRIEF)*	**X**		**X**

Test of Word Reading Efficiency Second Edition (TOWRE-2)	**X**		**X**
Test of Everyday Reading Comprehension (TERC)	**X**		**X**
Intervention Compliance Assessment		**X**	**X**
Adverse Event		**X**	**X**

**Parent completed measure*

9.1. Screening and Baseline Assessments (Visit 1)

Below are the neuropsychological measures that will be administered at Visit 1 by a neuropsychologist or a Clinical Research Assistant supervised by the neuropsychologist. Of note, parents and members of the study team collecting outcome data will be blinded to participants' treatment status throughout the study, such that they will not be given information on whether the child was randomized to *Cogmed*^{RM} or MobyMax (i.e., therapeutic intervention versus control condition). In addition, members of the research team collecting neurocognitive outcome data will also be blinded to each participant's stimulant medication use. Training coaches, by definition, cannot be blind to the treatment arm, as they utilize feedback about the child's daily training progress to make suggestions to the child and parents as to how training motivation and efficiency can be maximized. As such, at least three site-specific personnel are required at the screening/baseline assessment: a medical provider who will perform the medical examination (e.g., nurse practitioner, physician, nurse, etc.), a psychologist/ neuropsychologist who either performs the neurocognitive evaluation or supervises a mid-level provider or testing technician who does so, and a clinical research assistant who is able to provide the intervention training to the participants who qualify for randomization.

9.1.1. CogState

(Maruff, Thomas et al., 2009) CogState is a computerized package that offers a range of semi-automated assessment modules for individuals aged 6-90. We will use tasks of processing speed, visual attention, visual and verbal learning and memory, and working memory. Reliability is 0.77 with no practice effects after initial training (Falleti, Maruff, Collie, & Darby, 2006). Age-based standard scores (mean = 100, SD 10) are computed for each task based on a normative sample of several hundred individuals. CogState tasks have been used successfully in

trials of populations relevant to NF1. Specifically, the battery has been used with children with ADHD, for which CogState tasks discriminate between those with and without the diagnosis, and those on and off medication, as well as typically-developing children. Of importance, tasks in the CogState battery were also used in our pilot trial of *Cogmed*^{RM} with an NF1 sample. CogState will be administered at baseline (Visit 1) and follow-up (Visit 2) assessments. We will use the One-back working memory task as the primary outcome measure of the study, and will also use the One-Card Learning and Groton Maze Learning tasks as supplemental working memory and executive functioning measures.

9.1.2. ADHD-RS

(DuPaul, Power, Anastopoulos, & Reid 1998). ADHD-RS consists of the 18 DSM-IV ADHD symptoms. Each item is scored for frequency on a four-point Likert scale (0–3: 0 = never or rarely; 3 = very often). Summary T scores for Inattentive, Hyperactive-Impulsive, and Total symptoms are calculated based on norms for age and gender. This assessment will be completed by the parent or guardian of the participant during the baseline (Visit 1).

9.1.3. Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II)

(WASI-II; Wechsler 2011). The WASI-II is an abbreviated measure of intelligence that can be administered to individuals aged 6 and older. The WASI-II will be used at the screening visit (Visit 1) to estimated IQ based on the scaled scores from four tasks: Block Design, Similarities, Vocabulary, and Matrix Reasoning.

9.1.4. Child Behavior Checklist (CBCL)

(Achenbach 1991) is a parent-completed measure of the emotional/behavioral functioning of children aged 4-18 across home and school domains. CBCL scores will be calculated during the baseline (Visit 1) in the assessment of participants' psychological functioning. Population mean scores are 50 with an SD of 10. Values on any subscale or overall scale that are 70 or higher indicate a concern in that domain.

9.1.5. Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V-Integrated)

(Wechsler, 2015) Subtests from the WISC-V-Integrated will be administered at baseline and follow up, including verbal (Digit Span) and visual (Spatial Span) working memory subtests. This test will be administered at baseline (Visit 1) and

follow-up (Visit 2). For both subtests, scaled scores have a population mean of 10 and SD of 3.

9.1.6. Behavior Rating Inventory of Executive Functioning (BRIEF) (Gioia, Isquith et al. 2002) is a parent-completed measure of behavioral executive functioning. For this study, the Metacognition subscale will be used. The Working Memory score of the BRIEF will be administered at baseline and at follow-up as a secondary outcome measure for Exploratory Aim 1. T-scores are calculated with a mean of 50 and a standard deviation of 10.

9.1.7. Test of Word Reading Efficiency – Second Edition (TOWRE-2)

(Torgesen, Wagner, & Rashotte 2012) The TOWRE-2 is a common test for children and young adults aged 6-24 that assesses fluency in word reading. This test will be administered at baseline (Visit 1) and follow-up (Visit 2). Standard scores are calculated with a mean of 100 and a standard deviation of 15.

9.1.8. Test of Everyday Reading Comprehension (TERC)

(McArthur, Jones et al. 2013) The TERC is a screening test composed of 10 items that is used to examine the reading comprehension of a child aged 6-12. This test will be administered at baseline (Visit 1) and follow-up (Visit 2). Standard scores are calculated with a mean of 100 and a standard deviation of 15.

9.1.9. Intervention training

During Visit 1, a research participant will be randomized to receive one of two computer based training programs (either *Cogmed*^{RM}, or MobyMax). During Visit 1the neuropsychologist or designee will train the study participant on how to open the assigned computer program and use it.

9.2. Cognitive Training Follow-up (Visit 2)

Participants will return to clinic within two weeks of completing cognitive training for brief medical and neuropsychological assessment. In addition to a medical exam recording participants' weight, vital signs, and side effects, children will also undergo re-evaluation of neuropsychological outcomes of interest. The entire visit is expected to last 1 to 1 ½ hours.

Table 2. *Timeline of Neurocognitive Measures*

Study Variable	Measure	Format/Subscales	Respondent	Time Required	Time Points

Attention Ratings	ADHD-RS	Symptom questionnaire of DSM-5 TR ADHD Symptoms	Parent & Teacher (during the school year)	5 minutes	Visit 1 (Baseline Only)
Intelligence	WASI-II	Block Design, Vocabulary, Matrix Reasoning, Similarities	Child	20-30 minutes	Visit 1 (Baseline) only
Psychological Functioning	Achenbach Child Behavior Checklist (CBCL)	Questionnaire of child's emotional & behavioral functioning	Parent	10 minutes	Visit 1 (Baseline) only
Verbal Working Memory	WISC-V-Integrated	Digit Span (Backward)	Child	5 minutes	Visits 1,2
Visual Working Memory	WISC-V-Integrated	Spatial Span	Child	5 minutes	Visits 1,2
Working Memory	CogState	CogState- One-back	Child	5 minutes	Visits 1,2
Short-term Memory	CogState	CogState One-Card Learning	Child	5 minutes	Visits 1,2
Executive Functioning	CogState	CogState- Groton Maze Learning	Child	10-12 minutes	Visits 1,2
Executive Function	BRIEF	Questionnaire measure of everyday executive function	Parent & Teacher (during the school year)	10 minutes	Visits 1,2
Reading fluency	TOWRE -2	All	Child	5 minutes	Visit 1,2

Reading comprehension	TERC	All	Child	5 minutes	Visit 1,2

9.3. Other Assessments

9.3.1. Demographics

Demographics will be collected during the baseline assessments. The following information will be collected: date of birth, gender, race, and ethnicity and captured in the relevant eCRF (electronic Case Report Form).

9.3.2. Medical/Surgery History

Participant medical and surgical history will be collected during the baseline assessments. A qualified member of each participating clinical center will obtain detailed information regarding all past medical and surgical events. The dates and descriptions of past events will be captured in the relevant eCRF.

9.3.3. Weight/Height

Standing height in centimeters (cm) and weight in kilograms (kg) will be collected at both the baseline visits and the follow-up visit. Height and weight should take approximately 2 minutes and are not associated with any risks. These measurements are routinely performed during standard clinical examinations.

9.3.4. Vitals

The following vital signs will be collected: systolic and diastolic blood pressure (millimeters of mercury [mmHg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). Vitals will be captured in the relevant eCRF.

9.3.5. Concomitant Medication

All known prescribed medications, not including topical skin preparations, supplements, and other over the counter medications, used by the participant within 4 weeks before signing the ICF will be collected by a qualified member of each participating clinical center. The following information will be collected: the medication name, dose, unit, frequency, route, indication, start and stop dates. Prior medications will be captured in the relevant eCRF.

10. SAFETY

10.1. Adverse Event and Serious Event Reporting

There have not been any documented cases of an adverse event (AE) occurring with this intervention in any of the past published studies. However, we will define an AE as any unfavorable and unintended diagnosis, symptom, or disease temporarily associated with the study intervention, which may or may not be related to the intervention. AEs include any new events not present during the pre-intervention period or events that were present during the pre-intervention period, which have increased in severity. Because this is a minimal risk study for which no serious events are expected, we will only collect information on adverse events of at least moderate severity. In addition, any pre-planned hospitalization will not be considered as a Serious Adverse Event, but any non-planned hospital admissions will be regarded as a Serious Adverse Event.

Adverse Event and Serious Adverse events should be documented in the provided CRF with a full description including the nature, date and time of onset and resolution, determination of seriousness, severity, causality, corrective treatment, and outcome. Serious Adverse Events should be verbally notified to Project Manager and a Serious Adverse Event form should be fax within 24 hours to project manager. Follow-up information regarding the event must be reported to the Project Manager within 15 days of the initial event. SAEs will be followed by the site investigator until resolution.

Additionally, the Ethical Committee must be notified in writing of any expedited SAEs. All unexpected SAEs associated with the use of the study treatment will be immediately reported to appropriate regulatory agencies by the sponsor.

11. STATISTICAL PLAN

11.1 General

The primary objective to be addressed statistically is to determine whether *Cogmed*^{RM} improves scores on the CogState One-back subtest when compared to the adaptive MobyMax control. All analyses will be based on an intention to treat (ITT) approach, i.e., if a participant is randomized, they will be included in analyses, regardless of the number of sessions that they actually did in the assigned intervention.

This is a Phase II study with two hypotheses within the primary aim. Each will be tested at a two-sided alpha=0.025. All other analyses will be considered exploratory.

11.2 Baseline characteristics

We will use descriptive and summary statistics to detail the total number of patients screened, determine rates and reasons for non-eligibility and patient refusal for randomization. The baseline neuropsychological assessments will also be summarized descriptively by intervention group, within stratum, across both strata, and overall.

11.3 Analyses of Specific Aim 1

Specific Aim 1: To assess the efficacy of a home-based, computerized cognitive training (CT) program in children with NF1, ADHD, and working memory difficulties.

***Hypothesis 1*:** CogState One-back score errors in WM results will be lower in the Cogmed^{RM} group than in the MobyMax group.

The primary analysis will be a two-way analysis of covariance (ANCOVA), analyzing the in post-intervention in the CogState One Back errors in WM. One factor in the analysis will be the intervention group (*Cogmed^{RM}* vs MobyMax), and the second factor will be the stratification group (on vs. off stimulant medication). The model will use baseline CogState errors as the covariate and the model will not include an interaction effect, in due to the moderate sample size. *Cogmed^{RM}* will be considered effective if the error rate is significantly lower than the error rate on MobyMax in this analysis.

Sub-Hypothesis 1a: Participants who are identified as ON Stimulants and who have completed *Cogmed^{RM}* will perform better on the CogState One-Back subtest for working memory than those participants who completed the MobyMax training.

In order to address this hypothesis, we will perform an ANCOVA within the ON Stimulants stratum. This analysis will have one factor for treatment group, and the baseline CogState result as a covariate.

In addition, a linear regression model will be fit using the performance-based (CogState One-back) 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. In addition, we will also calculate standardized regression-based change (RBC) scores for each participant in order to determine whether or not any observed changes are clinically meaningful.

Exploratory Aim: 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.

Exploratory Hypothesis: We will again use linear regression models (with alpha set at .05) to analyze the change in performance-based and questionnaire ratings scores

between the Baseline (Visit 1) and Cognitive Training Follow-Up (Visit 2). Specifically, the following performance-based measures will be included in the exploratory analyses: ADHD-RS, WISC-V-Integrated Digit Span Backward, Letter-Number Sequencing, and Spatial Span, CogState One-card Learning and Groton Maze Learning. In addition, the following questionnaire variables will be included in the exploratory analyses: BRIEF Working Memory Index, Behavioral Regulation Index, and Metacognition Index. Finally, in order to examine whether participants reading level is improved as a function of completing either the treatment or control conditions, we will examine the TOWRE-2 and TERC scores. Treatment group (i.e., *Cogmed*^{RM} *vs.* MobyMax) will be included as the independent variable. These exploratory analyses will be used primarily to generate hypotheses for subsequent studies using these intervention approaches.

11.4 Sample size justification:

The target sample of 80 randomized subjects has 80% power to detect a mean difference of 5 in the CogState WM performance result between participants in the *Cogmed*^{RM} and the MobyMax interventions assuming a standard deviation of 10, and that the baseline CogState result will explain 50% of the variability in the results of the Visit 2 CogState.

11.5 Other Summaries

Other summaries for this study will include summaries of compliance with the interventions and comparison of compliance rates overall between the interventions and within each stratum. In addition, adverse events will be summarized as well as concomitant medications. Since this study is about behavioral interventions and not medications, these analyses are for completeness of review of the data in this clinical trial and are not expected to show any differences between the intervention groups, either overall or within stratum, nor to show any difference of adverse events from the background rates of children with NF1.

12. DATA COLLECTION, QUALITY ASSURANCE AND MANAGEMENT

12.1. Data Collection

12.1.1. Electronic Data Capture (EDC) System

Study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies. REDCap provides user-friendly web-based case report forms, real-time data entry with branching logic and validation procedures for importing data from external sources, and advanced features such as a data

quality check module. It can export data to common statistical packages like SPSS, SAS, Stata, and R. The system was developed by a multi-institutional consortium initiated at Vanderbilt University (http://project-redcap.org/).

Electronic CRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored, and records retention for the study data will be consistent with standard operating procedures (SOPs).

12.1.2. Data Entry

All reported data from the enrolled treating-physician's site will be entered via a secure web-based data entry screens and the data will be transferred via secure (SSL) connections to the study database. Access rights to the EDC system for the site team will need to be requested and every user of the system will be made aware of the fact that user names and passwords should never be shared and their electronic signature constitutes the legally binding equivalent of a handwritten signature. All sites will be fully trained in using the EDC system, including eCRF screen completion guidelines and only trained personnel certified by the Coordinating Center will receive a username and password. All participating sites will only have access to view and enter the data for their own patients.

All data will be directly entered or collected on a source document and then entered into REDCap. The Coordinating Center's data management team will monitor the eCRFs for completeness and acceptability throughout the course of the study. The Coordinating Center will be allowed access to all source documents in order to verify eCRF entries.

12.2. Quality Assurance

At its discretion, the Department of Defense (sponsor of this study) or its designee may conduct a quality assurance audit of this study. Auditing procedures of the Sponsor and/or its designee will be followed in order to comply with GCP guidelines. If such an audit occurs, the Investigator will give the auditor direct access to all relevant documents, and will allocate his/her time and the time of his/her staff to the auditor as may be required to discuss findings and any relevant issues.

In addition, regulatory authorities and/or the IRB/IEC may conduct an inspection of this study. If such an inspection occurs, the Investigator will allow the inspector direct access to all source documents, eCRFs, and other study documentation for source data check and/or on site audit inspection. The Investigator must allocate his/her time and the time of his/her staff to the inspector to discuss findings of any relevant issues

12.3. Data Management

12.3.1. Source documents

Source documents are defined as original documents, data, and records. These documents may include hospital records, clinical and office charts, participant diaries or evaluation checklists, and other records. Data can be directly entered into REDCap however when data is collected on source documents the source documents must be filed with the participant study documents..

A participant screening/enrollment log is to be completed at each investigative site. Data recorded on the screening/enrollment log are to include a subject identifier, the date of screening, and the reason the participant was not entered (if applicable). All patients initially screened are to be recorded in this log.

12.2.3 Data Processing

To ensure accuracy the data will go through validity checks (i.e. invalid values, outliers, missing data) at the time of entry. The Coordinating Center will also run monthly data query reports to check for higher level and longitudinal discrepancies. Clarification of data will be requested from the study site. The database will be quality assured in accordance to the data management plan and will be available for statistical analysis according to the methods outlined in 11. Statistical Analysis and the Statistical Analysis Plan.

13. SPECIAL REQUIREMENTS AND PROCEDURES

13.1. Protocol Deviations

A protocol deviation occurs when there is a variance between the procedures described in the protocol and the procedures performed. Protocol deviations may be minor or major. Minor protocol deviations, such as a site not recording a data point on a CRF, do not affect the participant's rights, safety, and/or well-being. Major protocol deviations include any actions that jeopardize a participant's rights, safety, and well-being, such as a breach of confidentiality.

Major deviations must be reported to the site's local ethics committee within the timelines defined by the site local ethics committee guideline or within 10 business days, whichever is first. All other minor deviations must be reported in writing to the local ethics committee as part of the annual report or when requested, whichever is first. The site PI must follow local regulations for reporting of protocol deviations and must

report deviations to the Coordinating Center as soon as possible or when reported to the site's local ethics committee.

13.2. Access to Source Data/ Documents

Each participating site (both U.S. and international) will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the Coordinating Center and regulatory agencies including the DOD to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. The investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data documents

13.3. Investigator Responsibilities

13.3.1. Institutional Review Board/Ethics committee

Each study site Principal investigator (PI) will be responsible for obtaining local ethics committee approval for the protocol and informed consent. Sites are responsible for providing the Coordinating Center with copies of the initial local ethics committee approval and any continuing review approvals. During the entire period of the study, each site will be responsible for providing their local ethics committee with any new protocol information and for submitting annual renewals.

The investigator will notify the IRB of violations from the protocol and serious adverse events.

13.3.2. Protocol Compliance

Each site PI will also be responsible for conducting the study according to the procedures described in this protocol and any supplemental study-specific manuals or guidelines. In addition, each site PI will be responsible for assuring that only qualified individuals perform each aspect of the study.

13.3.3. Informed Consent and Assent

All parent(s)/legal guardians acting on behalf of the participant in the study will be given the consent form that describes the study and provides sufficient information for the parent(s)/legal guardian to make an informed decision about whether to provide permission for the child to participate in this study. The formal consent, using the local ethics committee-approved consent form, will be

obtained before any study procedure. The consent form will describe the study intervention, the chance each participant has at receiving each intervention and any risk due to participation in the research study. The participant and their family will have an opportunity to have all questions answered before signatures are added to the consent forms. This consent form must be signed by the participant and/or legal guardian, and the site investigator-designated research professional obtaining consent. A copy of the consent form will be given to the participant's parent/ legal guardian, and this will be documented in the participant's record. A copy of the signed consent form will be retained in the participant's medical record. The participants may withdraw consent at any time throughout the course of the study. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.3.4. Participant Confidentiality

The rights and privacy of participants who participate in this study will be protected at all times. The data obtained by the study will be kept confidential. All neuropsychological evaluation forms, and other data will contain only the participant's identification number, respondent role (e.g., mother or father) and date of the study evaluation. The computerized information will be password protected and if printed, the records will be filed in a locked cabinet in the office of the site investigator or study coordinator. Participants will not be identified in any publicly released reports of this study.

Clinical information will not be released without written permission of the participant, except as necessary for monitoring by an ethics committee, the study monitor, or other government agency.

13.4. Participant Compliance and Compensation

The *Cogmed*^{RM} program automatically tracks the number and length of children's sessions, along with their progress through program levels. Specifically, training data is uploaded into a secure server every time the child logs into the program. In the event that internet access is not available during a particular session, participants can still complete training, but will be required to upload training data at least every 3rd session. When *Cogmed*^{RM} is administered in typical clinical practice, coaches work with parents and children to identify external reinforcers to promote adherence to the training schedule. In other words, caregivers typically provide tangible incentives (i.e., prizes) and/or enhanced privileges as their children complete *Cogmed*^{RM} sessions in order to help children maintain motivation and effort over the course of the training period. Accordingly, to provide a consistent incentive for participants in the proposed study,

children will earn gift cards following completion of each segment (session 8, session 17, session 20, & session 25) of cognitive training. As an additional reinforcer, each participant will be provided with a chart and stickers to visually track their progress through the program.

The control condition, MobyMax, also automatically tracks the number and length of children's sessions, along with their success with each training activity. To be consistent with the incentives provided for participants training with *Cogmed*^{RM}, participants completing MobyMax will also be provided with gift cards following the completion of sessions 8, 17, 20, and 25, and will be provided with a chart and stickers to visually track their progress through the program.

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