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Recommendations for Measurement of Attention Outcomes in Preschoolers With Neurofibromatosis

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Abstract

Children with neurofibromatosis type 1 (NF1) are at increased risk for attention problems. While most research has been conducted with school-aged cohorts, preschool-aged children offer a novel developmental window for clinical studies, with the promise that treatments implemented earlier in the developmental trajectory may most effectively modify risk for later difficulties. Designing research studies around the youngest children with NF1 can result in intervention earlier in the developmental cascade associated with NF1 gene abnormalities. Furthermore, clinical trials for medications targeting physical and psychological aspects of NF1 often include individuals spanning a wide age range, including preschool-aged children. In a prior report, the REiNS Neurocognitive Subcommittee made recommendations regarding performance-based and observer-rated measures of attention for use in clinical trials and highlighted the need for separate consideration of assessment methods for young children. The observer-rated Attention-Deficit/Hyperactivity Disorder Rating Scale–Preschool version is recommended as a primary outcome measure. The NIH Toolbox Flanker, Dimensional Change Card Sort, and List Sort Working Memory tasks and Digits Forward from the Differential Ability Scales–2nd Edition (performance-based measures) are recommended as secondary outcome measures. Specific methodologic recommendations for inclusion of preschoolers in clinical trials research are also offered.

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Children with neurofibromatosis type 1 (NF1) are at increased risk for attention problems.[1,2] While most research has been conducted with school-aged cohorts, preschool-aged children offer a novel developmental window for clinical studies, with the promise that treatments implemented earlier in the developmental trajectory may most effectively modify risk for later difficulties. Designing research studies around the youngest children with NF1 can result in intervention earlier in the developmental cascade associated with NF1 gene abnormalities. Furthermore, clinical trials for medications targeting physical and psychological aspects of NF1 often include individuals spanning a wide age range, including preschool-aged children. In a prior report, the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) Neurocognitive Subcommittee made recommendations regarding performance-based and observer-rated measures of attention for use in clinical trials[3] and highlighted the need for separate consideration of assessment methods for young children. In this article, we report the activities of the REiNS Preschool Group of the REiNS Neurocognitive Subcommittee, including review and recommendations of observer-rated and performance-based measures of attention and related emerging executive functioning for use with young children in clinical trials.

The preschool years are a time of rapid development of a range of cognitive skills, and there is considerable variability among the general population of preschoolers in their attention and related emerging executive functioning skills. For the purposes of this report, attention can be defined as the conscious focus of awareness on certain aspects of the environment/other/self while excluding other stimuli.[4] While separate components of attention and executive functioning are described for older children, adolescents, and adults,[5] these constructs are less well differentiated among preschool-aged children.[6] Across development, however, attention is central to human functioning and is foundational to a range of abilities that are areas of vulnerability for children with NF1, including acquisition of pre-academic and academic skills[7] and perception of social cues to support social functioning.[8]

Research About Attention and Emerging Executive Functioning in Children With NF1

A small body of work examines attention and emerging executive functioning in children with NF1 (table 1 provides a listing of published studies, sample sizes, and related findings). It is notable that the focus on preschool-aged children is new within the NF1 field. While studies before 2010 may have included a few children <6 years of age in their samples, it is only in the last decade that studies focused specifically on younger children have been published. Across these studies, some patterns emerge with respect to measurement approaches and findings. First, the most commonly used observer-reported measures are the Behavior Rating Inventory of Executive Functioning–Preschool (BRIEF-P),[9] Behavior Assessment System for Children–2nd Edition (BASC-2),[10] and the Conners[11] Attention-Deficit/Hyperactivity Disorder (ADHD) Parent Report Short Form (CPRS-R; also referred to as the CADS in some literature). One study used the Achenbach Child Behavior Checklist,[12] without a specific focus on attention.[13]

The findings from the studies focused on preschoolers with NF1 generally converge on a pattern of relatively subtle attention difficulties in the preschool years at the group level. There is variability across studies in the methods used to assess attention difficulties and in the degree of attention difficulties identified among young children with NF1. Very few studies include respondents other than parents, possibly related to variability in school attendance among preschoolers. Furthermore, there is no current published literature on the predictive utility of attention measures for later functioning for children with NF1 or on the stability of identified attention problems from the preschool to later years.

Findings with the BASC-2, which is a broad measure that includes subscales assessing attention and hyperactivity, are variable. Sangster et al.[14] and Lorenzo et al.[15,16] did not find evidence for difficulties with attention. Brei et al.[17] found greater attention problems in the NF1 group compared to normative data, while Klein-Tasman et al.[18] (with an overlapping sample seen at a different longitudinal data point) found a medium effect size that did not reach statistical significance compared to an unaffected participant group.

Findings with the CPRS-R, the parent-report measure used most to assess attention difficulties within the NF1 literature, also are not consistent across studies. Sangster et al.[14] did not identify elevations in either inattention or broader ADHD symptoms using this measure. In contrast, with overlapping samples of participants, Brei et al.[17] and Casnar et al.[19] identified elevated scores relative to the normative mean on many indices of this measure, with some evidence suggesting that inattentive symptomatology may be more discrepant from the normative mean than the hyperactivity symptomatology in the preschool years. On the BRIEF-P, a measure of emerging everyday executive functioning that includes attention-related behaviors, overall composite scores are generally not indicative of difficulties among preschoolers with NF1.[14,16,20] However, the BRIEF-P Working Memory scale emerges as one that appears to be particularly effective at identifying difficulties compared to population means or unaffected contrast groups[14,20] according to both parent and teacher report.[20] This is the scale with the most overlap with attention problems in the behaviors assessed.

The use of performance-based measures has much less consistency in the literature, with individual laboratories using

Table 1 Literature Including Attention and Emerging Executive Functioning in Young Children With NF1

Study	Measures	NF1 Sample	Age	Findings
Sangster et al.[14]	K-CPT, CADS (CPRS-R), BRIEF-P, BASC	26 with NF1 for K-CPT 20 with NF1 for CADS and BRIEF-P	4–5 y	NF1 group with significantly poorer Omissions, Hit RT SE, and Variability than control group. Only significant group difference on questionnaire measures was on BRIEF-P WM (no significant group difference for CADS or BASC attention-related scales).
Lorenzo et al.[17]	BASC-2 BRIEF-P	NF1 (n = 33) Unaffected (n = 38)	30 mo	No significant group differences.
Lorenzo et al.,[16]	BRIEF-P, Shape School, NEPSY Visual Attention, Tower of Hanoi, Delayed Alternation	NF (n = 43), Unaffected (n = 43)	40 mo	NF group with significantly poorer Shape School performance but no difference on NEPSY Visual Attention, Tower of Hanoi, Delayed Alternation. No significant group differences for BASC-II, BRIEF-P composite, Conners ADHD/DSM-IV Scales Parent
Brei et al.,[17]	CPRS-R Short Form BASC-2 Attention Preschool	n = 27–30 with NF1 depending on the analysis	4–6 y	Elevations compared to the normative mean on CPRS-R CPI, ADHD index, and trend for Hy index, and BASC-2 Attention. Few significant relations with language functioning.
Casnar et al.,[18]	CPRS-R Short Form	NF1 (n = 38) Unaffected (n = 23)	4–6 y	Elevations in comparison to normative mean on CPRS-R CPI, Hy, and ADHD index; largest effect size for CPI. No significant correlations between fine motor and attention.
Klein-Tasman, et al.[18]	BASC-2 DAS-II DF	NF1 (n = 40) Unaffected (n = 37)	3–6 y	No significant group different in attention; medium effect size observed. Verbal cluster a significant predictor of attention problems.
Casnar and Klein-Tasman[20]	BRIEF-P DAS-II DF	NF1 (n = 26) Unaffected (n = 37)	3–5 y	Mild elevations based on parent report with elevated WM and EMI scores. Teachers with elevated WM, PO, EMI, and GEC scores. Difference from unaffected group on WM scale. Significant correlation of teacher WM and DAS-II DF.
Rietman et al.[13]	CBCL	Age 4.5 y: n = 61; age 7 y; 11: n = 38; n = 23 followed up over time	4–16 y	No change in externalizing problems over time.
Arnold et al.[45]	CPT-2/K-CPT Omissions, CADS ADHD Index	NF1 (n = 42) Unaffected (n = 37)	5–6 y	NF1 group with significantly poorer performance on CPT-II/K-CPT. Large effect size for Omissions. Children with NF1 with significantly more symptoms of ADHD, with large effect size.
Garg et al.[53]	CPRS-R Short Form	NF1 n = 106 parents, n = 53 teachers	4–16 y	Elevated T scores (>65) based on parent (38%–57%) and teacher (12%–19%) report

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-P = ADHD Rating Scale-Preschool; BASC-2 = Behavior Assessment Scale for Children–2nd Edition; BRIEF-P = Behavior Rating Inventory of Executive Functioning-Preschool; CBCL = Child Behavior Checklist; CPRS/CADS = Conners Parent Rating Scale-Short Form; DAS-II DF = Differential Ability Scales–2nd Edition Digits Forward; EMI = emergent metacognition index; GEC = global executive composite; K-CPT = Kiddie Continuous Performance Test; NF1 = neurofibromatosis type 1; PO = plan/organize; RT = reaction time; SE = standard error; WM = working memory; YABCL = Achenbach Young Adult Behavior Checklist.

different measures (table 1). Studies using performance-based measures are sometimes indicative of challenges at the group level (e.g., on the Shape School,[21] Kiddie Continuous Performance Test [K-CPT],[22] and Differential Ability Scales–2 nd Edition [DAS-II] Recall of Digits Forward)[23] but sometimes not (e.g., NEPSY Visual Attention,[24] Tower of Hanoi,[25] Delayed Alternation[26]).

Little is known about the natural history of attention from preschool to school-age years in children with NF1. There are few cross-sectional developmental studies including children with NF1 in both the preschool and school-age years and none that report specific preschool-to school-age effects on attention. There is also very little longitudinal work tracking attention in the same children with NF1 over time from preschool to school age. One notable exception is the work by Rietman et al.,[27] who found no significant change in externalizing symptomatology on the Child Behavior Checklist over time in their longitudinal investigation.

Clinical Trials Related to Attention in Preschoolers

The REiNS Neurocognitive Preschool Group examined the current clinical trials literature related to attention in preschoolers more broadly to assist in identifying measures that may be useful for this purpose in children with NF1. We began by conducting a search of trials on ClinicalTrials.gov (including search terms of ADHD, attention, preschool, early childhood) followed by a parallel systematic literature search using PubMed to identify related published data. We made note of measures that had been used in at least 2 clinical trials. Several interventional trials focused specifically on improving attention in the preschool years. The vast majority used observer-

Table 2 Attention-Related Measures That Did Not Receive Full Review

Performance-Based Measures	Observer-Rated Measures
A-not-B, Delayed Alternation Task	Abbreviated Symptoms Questionnaire
Auditory Continuous Performance Test for Preschoolers	ADD-H Comprehensive rating scale
Child Continuous Performance Test	Attention-Deficit/Hyperactivity Disorder Test–2nd Edition
Continuous Performance Task for Preschoolers	Behavior Intervention Monitoring Assessment System
Executive Function Battery	Burks Behavior Rating Scales, 2nd Edition
Flanker and Reverse Flanker (Adele Diamond version)	Cognitive Assessment System 2: Rating Scale
Gordon Diagnostic System	Comprehensive Executive Function Interview
Hearts and Flowers	Disruptive Behavior Rating
Kaufman Assessment Battery for Children, 2nd Edition–Number Recall	Early Childhood Attention Deficit Disorders Evaluation Scale
Kaufman Assessment Battery for Children, 2nd Edition–Planning subtests	Health Dynamics Inventory
Leiter-3 Forward Memory, Attention Sustained, Attention Divided	Home Situations Questionnaire Revised
Leiter-3 Nonverbal Stroop	Multidimensional Everyday Memory Ratings for Youth
Leiter-3 Reverse Memory	Psychological Processing Checklist-Revised
NEPSY Visual Attention	SNAP-IV ADHD Rating Scale
NEPSY-II Statue, Auditory Attention	Social Skills Rating System–Teacher
Noisy Book, Nebraska Barnyard	Devereux Early Childhood Assessment Clinical Form
Picture Deletion Test for Preschoolers	
Preschool Continuous Performance Test	
Shape School	
Six Boxes, Nine Boxes	
Stanford-Binet for Early Childhood, Fifth Edition WM subtests	
Stanford-Binet, Fifth Edition Working Memory subtests	
Stroop Color and Word Test: Children's Version	
Trails-P	
Visual Search Task	
Zoo Runner	

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; SNAP-IV = Swanson, Nolan, and Pelham Rating Scale version IV; WM = working memory.

rated measures, including the BRIEF-P[28] (NCT01675869; NCT02225236), Achenbach Child Behavior Checklist[29] (NCT01795040), ADHD–Rating Scale (ADHD-RS-P[30] or ADHD-RS[31]; NCT00254462; NCT02642666; NCT01684644; NCT01918436; NCT02677519), Swanson, Nolan, and Pelham Rating Scale version IV[32] (NCT02433145; NCT00856063), Children's Global Assessment Scale[33] (NCT00031395; NCT00517647), Conners Parent/Teacher Rating Scale[33,34] (NCT00517647; NCT00018863; NCT01320098), BASC-2[35] (NCT01919073), Eyberg Child Behavior Inventory[35,36] (NCT01919073; NCT03967509), Conners Early Childhood (EC)[37,38] (NCT02677519), and Pediatric Quality of Life Inventory[39] (NCT01547702; NCT03806946). Most of these studies reported improvements in ADHD-related symptoms in response to intervention, which includes both psychopharmacologic and psychosocial approaches.

More recently, clinical trials have begun including computerized measures of attention and executive ability, including the KiTAP[40,41] (NCT02642666), CPT[42] (NCT02807870), and Minnesota Executive Function Scale[43] (NCT03383172). There are currently very few clinical trials that have published data using computerized measures. It should be noted that many registered studies on ClinicalTrials.gov did not yet have published data available. It is also notable that there were very few trials for attention that spanned a wider age range but included preschoolers. Most studies that included preschoolers focused specifically on the preschool years. In sum,

Table 3 Age Range, Evaluation, and Ratings of Observer-Rated Measures That Received Full Review

Measure	Age Range	Pros	Cons	Cog-RATE Group Rating[a]
CBCL 11/2-5[12]	1 1/2–5 y (additional forms: CBCL 6–18 y; YABCL 18+ y)	Availability in many languages, widely used in developmental studies	Participant burden; small number of questions assessing attention within a broad measure; may not be as sensitive to attention in NF1 as a more targeted measure	2.58
BASC-3[54]	2–5 y (additional forms: 6–11 y; 12–21 y	Used in NF1 literature, and broadly in the literature	Participant burden; small number of questions assessing attention within a broad measure; may not be as sensitive to attention in NF1 as a more targeted measure, most published data on BASC-2 (32% of items changed)	2.75
BRIEF-P[9]	2–5 y (additional forms: 5–18 y	Used in NF1 in preschoolers (with published data)	Not a pure attention measure; more broadly reflects emerging executive functioning, which includes attention Unclear if sensitive to change in clinical trials	2.78
CPRS/CADS[11]	3–17 y	Widely used in descriptive and clinical trials Good continuity across development	No longer in print; last norms in 1997	2.83
ADHD-RS-P[30]	3–5 y (additional forms: 5–17 y)	Widely used in descriptive and clinical trials Good continuity across development, available in Spanish, good normative data, strong reflection of DSM	Raw scores, mean and SD available, but not standard scores	2.83

Abbreviations: ADHD-RS-P = ADHD Rating Scale–Preschool; BASC-3 = Behavior Assessment Scale for Children-3rd Edition; BRIEF-P = Behavior Rating Inventory of Executive Functioning-Preschool; CBCL = Child Behavior Checklist; CPRS/CADS = Conners Parent Rating Scale-Short Form; NF1 = neurofibromatosis type 1; YABCL = Achenbach Young Adult Behavior Checklist.
Specific sample characteristics and psychometric data are available in the respective technical manuals.
[a] Higher scores reflect stronger ratings.

most clinical trials that include preschoolers use observer-rated measures of attention problems based on DSM criteria for ADHD. The most commonly used measure is a version of the ADHD-RS. The number of studies currently using computerized measures is small, but a review of registered trials suggests that it is possible that their use is on the rise.

The aims of this work were to detail the strengths and weaknesses of candidate attention outcome measures based on currently published data to arrive at recommendations for NF1 clinical trial endpoints and to discuss special considerations when assessing attention in young children with NF1, with the goal of providing practical guidelines for clinical trials procedures.

Methods

The REiNS Neurocognitive Preschool Group reviewed a targeted set of performance-based and observer-rated measures of attention and emerging executive functions for consideration for use in clinical trials that include preschoolers with NF1. We reviewed measures that were deemed promising from the review of the intervention literature with preschoolers without NF1, measures that are commonly used to measure attention in preschool-aged children with NF1, and additional measures of attention as nominated by members of the group on the basis of their experience and expertise. Some measures were excluded from further consideration because they did not meet basic threshold for review (table 2). Group consensus was that these tools were used in very few studies, offered no continuity with measures for older children, were accompanied by outdated psychometric data, were experimental measures without normative data, or were not feasible to administer within a clinical trials context (except with specialized personnel). Notably, researchers might find some of these measures useful as ancillary outcomes should they have personnel with sufficient expertise or if the focus of the clinical trial is restricted to preschool-aged children.

Measures that met the basic threshold underwent a full review and were rated by the full group. These are listed in tables 3 and 4. To systematically evaluate these measures, we used the same rating form used in prior work from the REiNS Neurocognitive Subcommittee.[3] Each measure was rated on 6 criteria: (1) patient characteristics (age range, use with specific populations); (2) use in published studies (descriptive and clinical trials); (3) domains assessed; (4) availability of standard scores; (5) psychometric properties; and (6) feasibility for use in clinical trials. The same procedures as those outlined by Walsh et al.[3] in table 3 were used here, with a conclusion about each measure based largely on the Patient Characteristics, Psychometrics, and Feasibility category ratings.

Results

Table 3 lists ratings of the observer-rated measures evaluated, including central strengths and weaknesses of each observer-rated measure. Table 4 lists ratings of the performance-based measures evaluated by the group, including central strengths and weaknesses of each measure.

Table 4 Age Range, Evaluation, and Ratings of Performance-Based Measures That Received Full Review

Measure	Age Range	Pros	Cons	Cog-RATE Group Rating[a]
K-CPT[22,55]	K-CPT: 4–5 y K-CPT-2: 4–7 y	Psychometrics good, used in published research (including NF1)	Only English, no published studies using current version (K-CPT-II) No data on continuity with CPT-3	2.33
NIH Toolbox (Flanker, DCCS, LSWM)[56,57]	3 y–adulthood	Easy administration, good psychometrics, covers wide age range	Costly, somewhat limited use with preschoolers in current published literature	2.44
CogState (Identification and One Back)[58]	4 y–adulthood	Developed for repeated use	Only small amount of work with preschoolers; normative data for preschoolers weak	1.38
TOVA[59]	Preschool test: 4–5 y 6 mo (additional version: 5 y 6 mo–adult)	Psychometrics strong in older children, 1 clinical trial showing short-term effect of medication	Long, only small amount of work in preschoolers	1.94
DAS-II Digits Forward[25]	2 y 6 mo–17 y 11 mo	Psychometrics strong, used in published descriptive research in NF1	Not used in clinical trials, sites may not have the DAS-II	2.45

Abbreviations: DAS-II = Differential Ability Scales-2nd Edition; DCCS = Dimensional Change Card Sort; K-CPT = Kiddie Continuous Performance Test; LSWM = List Sort Working Memory; NF1 = neurofibromatosis type 1; TOVA = Test of Variables of Attention.
Specific sample characteristics and psychometric data are available in the respective technical manuals.
[a] Higher scores reflect stronger ratings.

Discussion

On the basis of the systematic review of performance-based and observer-rated measures of attention for use in the preschool years, the REiNS Neurocognitive Preschool Group converged on several recommendations for specific measure choices and consensus regarding the status of the current literature and suggested methodologic and practical processes (the figure gives a summary of the main points).

Consensus About Measures

In the assessment of observer-rated measures, the group discussed a range of theoretical and practical considerations. For example, there was discussion of the degree to which separate indices of attention and hyperactivity are needed on questionnaire measures. There was consensus that, especially because clinical trials might be targeting different aspects of ADHD-related symptomatology, ideally observer-rated measures would provide separate indications of hyperactivity and inattention. A related consideration was whether the measure needed to map onto diagnostic criteria for ADHD. There was consensus that this might not be critical given that we are expecting dimensional rather than categorical changes in symptomatology with intervention; in other words, it is not necessarily expected that attention problems would normalize (i.e., no longer meeting diagnostic criteria for ADHD) but rather that treatment will result in improvement in ADHD-related symptomatology.

The CPRS-R and the ADHD-RS-P were rated highest for the assessment of ADHD-related symptomatology. The CPRS-R has been used in research with preschool-aged children with NF1.[14,17,19] The main limitation was that this measure is no longer supported by the publisher and therefore updated norms are not being collected. The Conners EC, while sharing a similar name, is a substantially different measure. It combines both attention and hyperactivity items into 1 scale, and rather than having 1 outcome appropriate for children ages 4 through 18 years (as in the case of the CPRS-R), there is a need to change from the Conners EC to the Conners-3 at 6 years of age. Group consensus was to recommend the ADHD-RS-P. The measure was recommended for several reasons: (1) it is commonly used in clinical trials research related to attention problems; (2) it is very similar to the CPRS-R (which is the measure most widely used in NF1) in its close alignment with diagnostic criteria for ADHD; and (3) the preschool version uses largely the same items as the version for older children (ADHD-RS) with only slight alterations in the language used to make it developmentally appropriate,[30] allowing consistent assessment into the school-age years. The ADHD-RS-P is therefore recommended as a primary outcome measure for clinical trials including preschoolers.

In the assessment of performance-based measures, the NIH Toolbox tasks (Flanker, Dimensional Change Card Sort, List Sort Working Memory) and the K-CPT-2 emerged as the most promising tools for use as attention endpoints in NF1 clinical trials research. The NIH Toolbox is heavily grounded in empirical research about the nature of attention and emerging executive function, has strong normative groups, has been used in large samples of clinical groups, and is increasingly used in research, including clinical trials.[44] Limitations discussed regarding the NIH Toolbox measures included that while the Flanker and Dimensional Change Card Sort tasks are considered central to attention and emerging executive functioning by developmental and experimental literature,[45] the NIH Toolbox does not include a traditional Continuous Performance Test, a more commonly used clinical measure of attention and impulsivity, and there is

Figure Summary of Main Points

Summary of Main Points:

- Measurement of attention in preschool is important because:
  - Attention difficulties are a core vulnerability of individuals with NF1
  - Preschoolers are increasingly included in clinical trials
  - Early intervention may set the stage for optimal development
- Choosing appropriate preschool measures of attention for clinical trials is challenging because:
  - Attention abilities are more variable among preschoolers generally, than among older children
  - There are developmental changes in the manifestations of attention
  - Some preschool measures show continuity with school-age measures, but at other times, a change in measures is needed to accommodate children of different ages. This contributes to challenges with interpreting stability and change.
- Multiple indicators of attention are important
  - The group recommends the ADHD-RS-EC as the observer-rated measure as a primary outcome for use in clinical trials including preschoolers
  - The group recommends the performance-based Recall of Digits Forward from the DAS-II and the NIH Toolbox tasks (Flanker, DCCS. LSWM) as secondary outcomes for us in clinical trials including preschoolers
- For longitudinal research measuring attention:
  - Use age-appropriate measures
  - When a change in measure is needed due to study participants getting older, a control group is critical to interpretation of any observed change in scores
  - Developmentally appropriate standardized administration is important
  - Specialized training and experience in working with young children is needed

ADHD-RS-EC = Attention-Deficit/Hyperactivity Disorder Rating Scale for Early Childhood; DAS-II = Differential Ability Scales–2nd Edition; DCCS = Dimensional Change Card Sort; LSWM = List Sort Working Memory; NF1 = neurofibromatosis type 1.

no current published literature using these measures with children with NF1. Strengths of the K-CPT-2 include that its predecessor, the K-CPT, has been used widely to characterize attention in preschoolers and has also captured attention problems in preschoolers with NF1. Limitations discussed regarding the K-CPT-2 included that the published literature uses a prior version of this measure (K-CPT) and that there are limited published data on the concurrence between scores on the K-CPT and the corresponding measure to be used in older children (CPT-3[42]). Changes from the prior version include an expansion of the appropriate age range (from 4 to 5 for the K-CPT to 4 to 7 for the K-CPT-2) and an expansion of the kinds of scores available to include additional dependent variables. For the K-CPT, the group also recommended that the Commissions and Omissions scores from the K-CPT-2 are used as the main endpoints, which appear to be the most valid and reliable outcomes of this measure. It is notable and important, however, that there is often a tradeoff between these 2 scores: as Commissions score increases, Omissions score decreases and vice versa.[46] An additional approach would be to use reaction time variability,[47] although there is little literature on the validity of this dependent measure for use with young children. Overall, the group consensus was to recommend the NIH Toolbox measures as secondary outcomes for clinical trials including preschoolers because there is little published literature using the KCPT-2 or about the correspondence between the KCPT and the KCPT-2 and because the NIH Toolbox has the advantages of continuity across a wide age range and increasing use with individuals with neurodevelopmental disorders and in clinical trials. Further research into the psychometrics properties of both of these measures with young children with NF1 is needed.

In the work of the REiNS Neurocognitive Subcommittee, a digit span measure was recommended as a secondary endpoint. For conceptual continuity, DAS–II Recall of Digits Forward, a forward digit span task appropriate for use in the preschool years,[23] was also reviewed and is recommended. Unlike many other digit span measures, digits are presented 2 per second, more closely approximating the speed of speech. This measure has shown relations to parent ratings of Working Memory from the BRIEF-P in young children with NF1.[20] The main drawbacks of this measure include cost (in that that it is available only as part of the whole DAS-II) and that training is required to ensure accurate administration.

These recommendations differ somewhat from those for measurement of attention in older children with NF1.[3] Here, the ADHD-RS-P is recommended (rather than a Conners scale) because the Conners EC includes only a combined attention and hyperactivity score. In contrast, the ADHD-RS (for school-age children) and ADHD-RS-P (for preschool-aged children) are largely parallel. Here, the DAS-II Digits Forward was recommended rather than a Wechsler Scale digit span because the preschool Wechsler does not include a digit span, and the DAS-II Digits Forward task can be used into the school-age years with norms until 17 years 11 months. Hence, our recommendation is that if a clinical trial plans to include preschool-aged children, investigators should use these measures so that they can remain consistent into the school-age years. The recommendations remain as earlier proposed for trials that do not include preschool-aged children.[3]

Methodologic and Practical Considerations for Clinical Trials Including Preschoolers With NF1

It is not clear how best to measure attention longitudinally when participants span preschool and school ages during the course of a clinical trial. There was discussion about how centrally to consider continuity of preschool measures with those used in the school-aged years in our recommendations. For clinical trials research, children are seen more than once, and in the case of NF1, they may be seen over a lengthy period (e.g., 2 years in the case of the MEK inhibitor study [NCT02096471]). This is different from traditional ADHD medication trials, which typically span a much shorter treatment period.[48] For many observer-rated measures, there are different forms normed for the preschool years than for the school-age years (e.g., BASC-2 and BASC-3, BRIEF-P/BRIEF-2). Similarly, some of the performance-based tasks reviewed change versions with age. This makes sense because there are different relevant behaviors and functions at different ages. However, it presents challenges for longitudinal work because, when children are followed up over time, they may move from

1 normative group to another. There was consensus that this is a critical consideration and that there are very few relevant data that address anticipated stability or change in scores when a child moves from 1 age range form to another.

There are several approaches when conducting longitudinal work. One approach is to stay with the initial measure so that it is possible to examine change in item or scale endorsement over time with the same item set. For example, if the child entered the study at age 5 years and was given the preschool form or test and then turns 6 by the next scheduled assessment, they could be given the preschool form or test again even if that is not the one that is suggested for their age because raw score change could be examined. When a study has a shorter timeline, this can be a feasible approach because arguably even the normative data may be appropriate to use from a slightly younger chronologic age. Another approach is to administer the age-appropriate form and to examine change based on analogous scales. When there is a longer time period between assessments, this may be especially appropriate because, for example, administering a preschool measure to an 8-year-old is likely not appropriate from a content validity standpoint. This creates some interpretive challenges, however, because there may not be sufficient data to conclude that the analogous scales are fully comparable. If there is a control group, however, this is less of a problem because it will be possible to examine whether the amount of change observed for the intervention group is different from the amount of change seen across forms for a group who did not receive intervention. Hence, when clinical trial participants are expected to span 2 age-appropriate measures, a control group will be essential to gauge the meaning of change in the scores on these measures. Furthermore, it is imperative that the questionnaire respondent remains consistent across time for each participant and that assistance be provided for questionnaire completion for any respondents who do not have at least a middle school education. Consultation with a psychologist regarding outcome choices is recommended to carefully consider the options and to assist in choosing the most appropriate methodology for a given trial.

The members of this group also encourage test developers and validators to consider addressing this question by conorming measures in an overlapping age range to establish relations between scores on the preschool measure and scores on the school-age measure. For example, it would be greatly beneficial to know whether the T score of a late 7-year-old administered the KCPT-2 (appropriate for ages 4–7 years) would be similar to their T score if they were administered the CPT-3 soon after they turned 8 years old.

Some special considerations warrant attention when preschoolers are included in clinical trials. First, it is important to keep in mind the inherent variability in attention in the preschool years. One of the reasons it may be challenging to capture attention problems in young children with NF1 is that the range of attention functioning in the normative population is wide. Therefore, attention problems may emerge in children with NF1 only in the school-aged years, not because the difficulties were not present when they were younger but rather because, when they were younger, these difficulties appeared to be within the broad range of attention that is typically seen in the general population. Furthermore, preschoolers have variable experience with structured classroom settings in which demands for attention are more likely to be present. Some children have not yet had the chance to practice paying attention when they participate in research while others may have. Relatedly, some parents may not have noticed attention problems because there has not been a need for the children to engage in sustained attention, and other caregiver observation may not be available for all children. Furthermore, within the normative developmental literature, there is evidence that the domains of attention may be less differentiated among young children.[6] Working memory and inhibition difficulties may be the first to be evident, while challenges with sustained attention and organization may be harder to capture in the preschool years.[49] This does not necessarily point to the need for different measures across development (because the measures used in the school-age period also assess inhibition), but it may mean that the manifestations of attention problems may vary with age, such that different dependent measures might capture the difficulties at different ages. Studies of the predictive utility of a range of attention measures from the preschool years to the school-age years are needed in case there are subtle or specific attention problem indicators that may be especially predictive of later attention problems in children with NF1, who are at particular risk for attention problems. Last, additional work outlining the domains of cognitive functioning that are most critical to capture for a sense of functioning in preschoolers with NF1 is needed to ensure that the most relevant outcomes for preschoolers are included in clinical trials. Lifespan studies of attention in NF1 are especially needed.

Second, there are practical considerations in the assessment of attention in preschoolers.[50,51] If the outcome measure is not an observer-rated questionnaire measure, researchers will need to be aware that assessment of preschool-aged children requires expertise that may not be as necessary for the assessment of older children. Preschool-aged children may need more explanation and support to fully grasp the task requirements. They may need specific reinforcers and flexibility in testing (e.g., stickers along a path to a larger prize to motivate them; allowing for some movement). An upbeat, engaging interpersonal style may be important to maintain engagement, yet it is critical that the examiner not provide so much structure that they adversely affect the validity of the measure. Specific procedures to address off-task behavior or task challenges should be delineated (e.g., how many times to run through practice trials before deciding that the child cannot complete the task, how many times to provide reminders to attend to the task, what to do if the child gets up from their seat and walks away). Warm but directive statements may be important (e.g., rather than "do you want to sit here?" warmly saying "OK, sit right here!"). Frequent breaks and alternation between more challenging and less challenging tasks may be especially needed. Most critically, clear standardization of these procedures between testers and across multiple sites is important for clinical trials research. To this end, these measures must be administered by professionals experienced with the use of these performance measures among preschoolers.

In summary, was consensus that additional research about attention in the preschool years, including related concepts such as emerging executive functioning, is needed to inform the approach to measurement of attention in children with NF1. Furthermore, additional clarity about the expected developmental trajectory of attention in children with NF1 would be especially helpful. Any change in attention in an intervention study needs to be interpreted against the backdrop of expected developmental trajectory patterns for children with NF1. Questionnaire measures appear to be the most used approach to capturing changes in attention in clinical trials and are likely to be useful for children with NF1 as well. While computerized measures have been used sparsely in the NF1 literature to date, they may be promising for clinical trials research with NF1 because they are often designed with multiple administrations in mind and are relatively easy to administer. It would likely be useful to include both approaches within a clinical trial to effectively capture a child's functioning and intervention-related change. Studies examining the correspondence between these different measurement modalities generally show limited convergence for children with and children without NF1.[50] There is also emerging evidence that the use of multiple measures may result in better reliability of outcomes that may set the stage for greater sensitivity to change.[52] Additional research into the psychometric properties of measures of attention and the relative utility of performance and observer-rated measures in preschoolers with NF1 is needed, especially as new measures are developed and published.

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