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Outcome Measures for Clinical Trials in Down Syndrome

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Abstract

Increasingly individuals with intellectual and developmental disabilities, including Down syndrome, are being targeted for clinical trials. However, a challenge exists in effectively evaluating the outcomes of these new pharmacological interventions. Few empirically evaluated, psychometrically sound outcome measures appropriate for use in clinical trials with individuals with Down syndrome have been identified. To address this challenge, the NIH assembled leading clinicians and scientists to review existing measures and identify those that currently are appropriate for trials; those that may be appropriate after expansion of age range addition of easier

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items, and/or downward extension of psychometric norms; and areas where new measures need to be developed. This paper focuses on measures in the areas of cognition and behavior.

Keywords

Down syndrome; intellectual disability; assessment; cognition; behavior; clinical trials

Basic and behavioral scientists continue to identify new targets for treating the developmental challenges, along with declines that have been associated with aging, in the population of individuals with intellectual and developmental disabilities (IDD). These findings have spurred an increase in the number of clinical trials targeting IDD-specific conditions and have led to the identification of effective pharmaceutical treatments (Arnold et al., 2012; Scharf, Jaeschke, Wettstein, & Lindemann, 2015) and evidence for intervention-related phenotypic modifiability (Dawson et al., 2012; Rogers et al., 2014). Clinical trials of targeted methods of treatment that have proven to be promising using specific animal models, for conditions such as Down syndrome (DS), are currently underway with human participants. The targets of treatment are based on condition-specific aspects of neurobiology, neurochemistry, and neuroplasticity or connectivity within the brain and vary widely across conditions. To be successful, clinical trials must provide substantial evidence that a treatment has the effect that it purports to have. If a treatment is being developed for a specific condition the trial must demonstrate that the treatment is reaching its intended target within the population and must also demonstrate outcomes that are clinically meaningful to the patient. Early clinical trials in identifiable IDD conditions (such as DS and fragile X syndrome) have brought to light a major hurdle that exists in clinical trials involving individuals with IDD: identifying appropriate and meaningful outcome measures (Berry-Kravis et al., 2013).

Outcome measures are used to evaluate the potential benefit or harm to an individual receiving an intervention. In general, outcome measures must be: 1) developmentally appropriate for the intended population; 2) reliable, not only with respect to internal consistency but also to temporal stability; 3) valid for content and criterion-related standards; 4) able to detect change, including developmental differences; 5) interpretable; and 6) feasible to administer and without substantial floor or ceiling effects. Selecting appropriate outcome measures for clinical trials involving individuals in the general population is challenging in itself; selecting measures for use in the IDD population is even more so. Psychometrically sound outcome measures that are sensitive indicators of change for clinical trials and that are specifically tailored or appropriate for individuals with IDD of specific etiologies are few and far between.

Trisomy 21 (aka Down syndrome) is the most common chromosomal cause of intellectual disability and was identified over 150 years ago (Down, 1887). However, there is still much to be learned regarding the nuances of the condition in the context of a clinical trial. The past decade has brought renewed calls for improving quality of life outcomes for individuals with DS and new demands for translational research that will yield effective treatment outcomes (Gardiner et al., 2010; McCabe, Hickey, & McCabe, 2011). DS predisposes individuals to a

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fairly distinct cognitive phenotype across the lifespan that results in varying degrees of impairment across various domains of development including social-emotional functioning, behavior and self-regulation, motor development, cognition, attention, and language (Silverman, 2007). DS is associated with intellectual disability, with relative strengths in visual processing, visuospatial short-term memory, and imitation (Gathercole & Alloway, 2006; Klein & Mervis, 1999). Relative weaknesses are often identified in the verbal domain, with grammar, especially in the expressive modality, as the area of greatest difficulty (Hodapp & Dykens, 2004). In addition, individuals with DS generally have difficulty with working and long-term memory (Fidler, Most, & Philofsky, 2008). Individuals with DS evidence relative strengths in the area of social behavior, including better social skills (eye gaze, facial displays, social interactions) and less significant behavior problems in comparison to their peers with other etiologies of IDDs (Fidler & Nadel, 2007). The low muscle tone and wide gait common in DS contribute to difficulties with motor development and skill acquisition. These difficulties can include challenges with balance, fine-motor control, gross motor planning, and muscle strength (Frank & Esbensen, 2015; Winders, 2013).

Although there is a general phenotype of DS that differentiates it from other conditions, there is great variability within the population in the areas of cognition, behavior, and genetics (trisomy 21, mosaic DS, Robertsonian translocation) that warrants attention when considering outcome measures. DS is associated with intellectual abilities that range from low average for the general population to severe/profound disability (Carr, 2012). The expressive language abilities of older children and adults with DS vary from syntactically complex utterances to single words or even a lack of expressive language (Finestack & Abbeduto, 2010; Klein & Mervis, 1999). Comorbid psychiatric conditions, such as autism spectrum disorders and attention deficit hyperactivity disorders, can influence measurement of outcomes, particularly as they can impact inhibitory control and executive functioning capabilities (Capone, Grados, Kaufmann, Bernad-Ripoll, & Jewell, 2005; Ekstein, Glick, Weill, Kay, & Berger, 2011). Common comorbid health conditions such as congenital heart defects and sleep apnea affect approximately half of individuals with DS (Shott, 2006). These health conditions have been shown to be important sources of within-syndrome variability in developmental outcomes and adaptation in this population (Breslin et al., 2014; Visootsak et al., 2011). Further, similar to individuals in the general population without IDD, individuals with DS are experiencing a dramatic extension of life expectancy (Yang, Rasmussen, & Friedman, 2002). Life expectancy for individuals with DS is currently greater than 60 years. As a result, aging adults with DS are also experiencing many of the same age-associated health problems as older adults in the general population (Esbensen, 2010). Approximately half of individuals with DS will develop clinical dementia during middle adulthood (Tyrrell et al., 2001), although there is considerable variability in age of onset (Zigman, 2013). Smaller percentages of individuals with DS demonstrate gastro-intestinal conditions, hypothyroidism, leukemia, and other conditions (Bull & Genetics, 2011; McCarron, Gill, McCallion, & Begley, 2005), which may also confound measurement of clinical outcomes. As such, appropriate measurement tools for treatment studies in DS must be sensitive to a wide range of presentations and developmental levels in order to capture the range of functioning in this diagnostic group. Clinical trials also warrant attending to

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subpopulations of individuals with mosaic DS as they may react differently in a clinical trial in comparison to individuals with full trisomy 21.

Several clinical trials have been conducted in recent years examining pharmaceutical compounds aimed at improving cognition in individuals with DS. To date, these studies have included early-phase 1 (small-sample trials to evaluate safety, dosing, and side effects) and phase 2 (larger-sample trials to evaluate efficacy and further evaluate safety) trials with adolescents and adults with DS, to evaluate the efficacy and safety of these compounds. Although these trials are early phase studies, they illustrate the promising efforts in bringing novel compounds to trials designed to improve outcomes for individuals with DS and the need for sensitive and validated outcome measures that will reflect clinical efficacy.

Given the variability in the behavioral and cognitive phenotype associated with DS, assessment and measurement in this population pose a complex set of challenges. Measures considered for clinical trials need to be evaluated for their psychometric properties, as well as for their demands on attention, language abilities, and motor skills of individuals with DS. Chronological age and developmental level also need to be taken into account. To address this growing need, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) assembled a group of leading clinicians and basic and behavioral scientists in DS research, experts in clinical trials and measurement development, and representatives from DS advocacy groups (including the National Down Syndrome Society, National Down Syndrome Congress, LuMind Research Down Syndrome Foundation, and Global Down Syndrome Foundation), federal agencies, and pharmaceutical companies. The goal of this group was to identify outcome measures suitable for use in pharmacological and behavioral clinical trials with individuals with DS, outcome measures in need of further refinement, and gap areas for which measures need to be developed.

In this report, we describe the steps taken by the members of the NIH Outcome Measures for Clinical Trials in Down Syndrome working groups when considering, evaluating, and identifying potential outcome measures for use in clinical trials with individuals with DS. The overarching goals for this paper are twofold: (1) to identify measures potentially appropriate for use in clinical trials and (2) to examine the reliability and validity of these measures for individuals with DS, especially in the context of clinical trials. For the first goal, it is important to note that although there are a number of measures that can be used with a wide range of individuals with IDD, including DS, we have focused on tools that could be used in clinical trials specific for individuals with DS. For the second goal, the intent was not to examine targeted tests with respect to their general reliability and validity estimates but, rather, to examine the psychometric properties of the tests with respect to their use in clinical trials for individuals with DS. These observations reflect the current state of developmental and measurement science in the field of DS research and can inform the process of measurement selection in future clinical trials in this population.

Method

Following a framework that was structured using a modified version of the Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to

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Support Labeling Claims (FDA 2009), two working groups were established. The working groups were comprised of individuals with specific clinical or research expertise in individuals with DS, expertise in assessment development, and experience with clinical trials. The first group focused on issues related to cognition and the second on issues related to behavior.

Both the cognitive and behavior working groups were first tasked with identifying domains relevant specifically to DS that could potentially benefit from intervention. The domains chosen were intended to serve as likely targets for potential DS-specific treatment trials, with a particular focus on “core” deficits and/or areas that would contribute to improving the quality of life for individuals with DS. Working groups were asked to generate domains based on a review of the literature on the behavioral and cognitive phenotype in DS, treatment targets in clinical trials, and expert opinion.

The second task the groups were given involved identifying existing measures relevant to the chosen domains that were psychometrically sound and appropriate for individuals with DS. Groups were tasked with surveying assessment measures that have been employed in clinical trials in individuals with DS or with other IDDs. The measures were evaluated using the following criteria: reliability, validity, evidence that they could detect change during the time frame of a clinical trial, interpretability, and administrative burden. The groups defined the context of use and the type of measure (e.g., performance observation, clinician report, parent/caregiver report). The measures were then classified by the working groups as appropriate in their current form for clinical trials with individuals with DS, likely appropriate based on their performance among individuals with other types of IDD, or promising but needing modification or further evaluation. The groups were also asked to identify gaps where measures were needed but no appropriate measures were available.

Groups interacted via teleconferences and email during a 3-month preparation period. A two-day face-to-face meeting was held in Washington, DC in April 2015 at which both groups presented their findings and participated in additional discussion and refinement of the initial work. Input was obtained from members of the NIH, FDA, pharmaceutical companies, advocacy organizations, and a medical outcomes working group. A final overview of the current status of outcome measures was developed by each working group and is presented in the following sections.

Results

In this section, we present the overview of domains generated by the two working groups collectively before and during the NIH-sponsored meeting on Outcomes Measures for Clinical Trials in Down syndrome. Members of the working groups independently generated possible domains through expert opinion and a thorough review of the literature related to DS. These domains were later refined in group discussion. Groups identified domains based on areas targeted in basic science that are the focus of outcome measures in current clinical trials and that are common problems in DS which could serve as foci for outcome measures in future clinical trials. Issues raised during the tasks of identifying core areas of challenge and evaluating measures of these concepts are delineated below.

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Cognition Domains

When identifying core domains, the Cognitive Working Group noted that due to the potential confound of pronounced deficits in language development (especially in expressive grammar and speech articulation) for individuals with DS, candidate measures should minimize expressive language demands unless expressive language is the target outcome. Given the pervasive cognitive impairments that are inherent to DS, this group gave careful consideration to measures of cognition that might be used in a treatment trial with this population to directly or indirectly improve cognitive functioning. Domains identified by the Working Groups include language, executive functioning, memory and learning, social cognition, attention, processing speed, and mild cognitive impairment associated with dementia. Proposed measures and their associated domains are listed in Tables 1 and 2.

Language—Several aspects of language pose significant difficulty for individuals with DS. Grammar and narrative language expression are most challenging, whereas vocabulary is relatively stronger and closer to expectations based on cognitive developmental level (Klein & Mervis, 1999; Singer Harris, Bellugi, Bates, Jones, & Rossen, 1997). Speech articulation is also significantly impacted (Barnes et al., 2009). Insofar as language skills are crucial to independent functioning, they will certainly be targeted in pharmaceutical trials.

The working group identified several language measures that either have been validated for individuals with IDD or that may be useful but likely need modification for use with individuals with DS (Table 1). No language measures have been completely validated for individuals with DS. The measures that were considered most promising, although still in need of evaluation with individuals with DS are the Peabody Picture Vocabulary Test – Fourth Edition (PPVT-4) for measuring receptive vocabulary, the Expressive Vocabulary Test – Second Edition (EVT-2) for expressive vocabulary, and the Social Responsiveness Scale – Second Edition (SRS-2) for measuring some aspects of language pragmatics (Constantino & Gruber, 2002; Dunn & Dunn, 2007; Williams, 2007). The PPVT-4 and EVT-2 are direct, individually-administered measures, and the SRS-2 is a parent report measure. All are normed and accommodate a wide range of age and ability. The PPVT-4 and EVT-2 provide growth scale values in the form of W-ability scores based on the Rasch ability scale, making these assessments potentially useful for tracking change over time. However, additional data regarding the psychometric properties of the PPVT-4 and EVT-2 specifically for individuals with DS are needed.

Among the measures identified by the working group that need modification and further testing with individuals with DS are several that are embedded within comprehensive language assessment measures; namely, the MacArthur-Bates Communicative Development Inventories (CDI), the Clinical Evaluation of Language Fundamentals – Fifth Edition (CELF-5), and CELF Preschool – Second Edition (CELF-P2) (Fenson, 2007; Wiig, Secord, & Semel, 2004; Wiig, Semel, & Secord, 2013). The CDI, which has two versions, is a parent report measure. The CDI: Words and Gestures measures both receptive and expressive vocabulary and also communicative gesture use (early gestures, late gestures, total gestures). The CDI: Words and Sentences measures expressive vocabulary, morphology, and syntax. The CDI also provides dissociation norms addressing the relations between different

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components of language (e.g., expressive vocabulary size relative to receptive vocabulary size; gesture ability relative to receptive vocabulary size; gesture ability relative to expressive vocabulary size; sentence complexity relative to expressive vocabulary size). The CELF-5 and/or CELF-P2 contain subtests that measure expressive grammar (Word Structure, Sentence Recall, Formulated Sentences), receptive grammar (Sentence Comprehension), and pragmatics (Pragmatics Scale). These are direct measures that require oral responses (expressive language) or pointing responses (receptive language) by examinees. For use with individuals with DS, the CDI would need norms over a broader age range and standard scores and/or Rasch ability scores for the entire age range. For the CELF-5 and CELF-P2, expanded norms would be needed that cover a broader age range and lower levels of functioning over the entire age range; Rasch ability scores would be very helpful in tracking change over the course of a clinical trial.

Also identified as promising but needing modification are the Test for Reception of Grammar – Second Edition (TROG-2), the Children's Communication Checklist – Second Edition (CCC-2) for measuring language pragmatics, and the Goldman-Fristoe Test of Articulation – Third Edition (GFTA-3) (Bishop, 2003, 2006; Goldman & Fristoe, 2015). The TROG-2 has norms for adults, and an adult version of the CCC-2, the Communication Checklist – Adult (CC-A), is available (Whitehouse & Bishop, 2009). For all of these measures, standard scores need to be expanded downward to accommodate lower performing individuals, and the measures need to be evaluated specifically for individuals with DS in terms of their psychometric properties.

Finally, measures of expressive language sampling were identified as needing modification and extension. Experimental procedures exist that collect, for example, narrative samples and then transcribe and analyze them using computerized systems (e.g., Systematic Analysis of Language Transcripts, SALT) (Miller & Iglesias, 2015). The analysis produces measures of expressive grammar, lexical diversity, intelligibility, dysfluency, and talkativeness; many other measures also could be derived. Typically, language is elicited by asking participants to tell the story from a wordless picture book. Norms need to be developed for a wide age and ability range. Experimental procedures addressing language sampling during conversation and play are also being developed to provide a comprehensive characterization of language change. There is considerable evidence that these procedures distinguish individuals with DS from typically developing individuals and from those with other IDD provided that appropriate scripting and standardization procedures are followed (Abbeduto, Kover, & McDuffie, 2012). There also is ample evidence of excellent psychometric properties for these procedures when used in typically developing children or children with, or at risk for, language impairments. Preliminary evidence has even emerged for individuals with IDD (Berry-Kravis et al., 2013). The psychometric properties of these procedures when used in individuals with DS need to be established. The NIH is currently funding research that will provide these data.

Executive functioning—Executive control is an important domain for cognitive and behavioral rehabilitation in DS. According to models of executive function (EF) described by Miyake and colleagues (Miyake et al., 2000), executive control involves several cognitive components that are associated with prefrontal lobe function, including attention regulation,

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inhibition, working memory, and set-shifting (i.e., high level cognitive control and flexibility). Other conceptualizations of the domain of executive function include cognitive fluency, or the rapid and creative generation of verbal responses in a category (e.g., verbal fluency). Several studies in young individuals with DS have reported EF deficits when employing individually administered assessments, including deficits in working memory (Rowe, Lavender, & Turk, 2006; Vicari, Carlesimo, & Caltagirone, 1995) and cognitive flexibility (Lanfranchi, Jerman, Dal Pont, Alberti, & Vianello, 2010). Parent and caregiver report measures have demonstrated a consistent profile of EF strengths and weaknesses on the Behavior Rating Inventory of Executive Function – Preschool version (BRIEF–P) in children with DS, including deficits in working memory and planning, but not in inhibition or emotional control (Daunhauer et al., 2014; Gioia, Espy, & Isquith, 2003; Lee et al., 2011). A thorough consideration of this domain is also important for tracking markers of cognitive decline in DS, as there is evidence to suggest decline in EF in early to mid-adulthood may precede the onset of Alzheimer disease (Ball et al., 2006; Ball, Holland, Treppner, Watson, & Huppert, 2008).

There are a number of challenges for assessment in this domain. First, the mental age of most individuals with DS falls in a critical age-range for prefrontal development (i.e., between ages 3 years to late childhood). As such, tests tailored to very young children or late childhood [e.g., A-not-B (Diamond & Goldman-Rakic, 1989) or Wisconsin Card Sorting Test (Heaton, 1993)] are not appropriate across the full range of ability in DS. In general, only recently have EF assessments been developed that can be administered across a wide range of ages (Gershon et al., 2010), although most of these have not been specifically validated in individuals with DS. A second concern is that EF measures are often plagued with practice effects, as a number of these tests include phases that are easily re-learned if a participant has completed the test once during the baseline assessment. For instance, the final phases of the Cambridge Neuropsychological Test Automated Battery (CANTAB) Intra-dimensional/ Extra-dimensional set-shifting (IDED) task require the participant to shift responses to a non-obvious rule. Once the “trick” to the test is learned, the test will not be as difficult in a second sitting, although the enduring nature of this learning is not known in individuals with DS; thus, highlighting the temporal stability of such findings for a clinical trial.

Despite these limitations, the working group identified some EF measures that could be implemented in the context of a clinical trial in DS. Working memory and attention assessments are described below in those respective sections. Most batteries containing memory measures (e.g., the CANTAB, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Children’s Memory Scale (CMS)) include tests of verbal and spatial working memory, and recent reports suggest good psychometric validation of spatial span assessments, including the CANTAB Spatial Span (forward) (Cohen, 1997; D’Ardhuy et al., 2015; Randolph, 2012). Measures of Verbal Fluency have been successfully utilized in studies of aging in DS, showing low floor effects (3.6% in Ball et al., 2008). Parent reports using the BRIEF-P and BRIEF-School-Age forms have been examined in previous test validation studies (Gioia, 2000). Results of these studies show correlations between the BRIEF scales and laboratory assessments of EF, minimal floor performance, and adequate test-retest reliability in DS (D’Ardhuy et al., 2015; Edgin et al., 2010).

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However, the BRIEF-Preschool resulted in ceiling effects in adults with DS and some researchers have suggested the use of the BRIEF-School-age form after childhood (D'Ardhuy et al., 2015). One potentially useful approach for generating meaningful outcome measure data using the BRIEF involves selecting the version that is appropriate for an individual's overall functioning level, and then calculating standardized scores using an individual's mental age, rather than their chronological age (Daunhauer et al., 2014; Lee et al., 2011). This approach accounts for an individual's overall level of developmental delay, and makes it possible to compare BRIEF performance relative to children at similar mental ages, rather than children with similar chronological ages. Though papers using this approach have been accepted for publication in peer-reviewed outlets, this approach would require more rigorous evaluation to determine its psychometric soundness for use in outcome measures research (e.g., what other factors might influence this administration modification?).

Other EF measures are promising based on their use and validation in typically developing children, but we are lacking psychometric investigations in DS. Primarily, the NIH toolbox assessments showed good test-retest reliability in young children (Weintraub et al., 2013), but these measures have not been formally validated in DS to date. As of the writing of this article, a funded NIH study examining the psychometric properties of the NIH Toolbox measures in DS and fragile X syndrome is underway (PI David Hessl) and should yield critical information pertaining to the appropriateness of the Toolbox tasks for individuals with IDD. In total, data are emerging to help guide the choice of measures of EF in this population. However, few EF measures have been subjected to formal validation studies replicating the clinical trials context (as in d'Ardhuy et al., 2015), and the field lacks validated measures that are appropriate across a wide range of ages.

Memory and learning—Consistent with the presence of intellectual disability, memory and new learning demands pose significant challenges for individuals with DS. There is clear evidence that not only are verbal short-term memory deficits present, but they are not secondary to slow speech, mode of presentation, or hearing loss—i.e., these deficits represent core cognitive deficiencies in DS (Jarrold, Baddeley, & Phillips, 2002; Klein & Mervis, 1999; Numminen, Service, Ahonen, & Ruoppila, 2001; Seung & Chapman, 2004). Delayed recall, or long-term memory, in individuals with DS also has been described as variable, with a dissociation being reported for implicit and explicit types of long-term memory, in favor of the former (Carlesimo, Marotta, & Vicari, 1997). Consequently, a targeted clinical trial assessment strategy for memory appears to point to short- and long-term explicit memory functions across both verbal and nonverbal domains (Lee, Pennington, & Keenan, 2010).

The working group identified several potential explicit memory tasks that mapped well onto the DS memory phenotype and that have been used in clinical trials for this population. These included select subscales of the CANTAB (e.g., Paired Associate Learning, Spatial Recognition, Spatial Span), RBANS (e.g., List Learning, List Recall, List Recognition, Story Memory), and the CMS (e.g., Dot Locations, Word Pairs). Specifically, the CANTAB is a battery of computerized assessments with touch screen technology, designed for individuals aged 4 to 90 years, that is standardized, normed, and has alternate forms.

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Memory tasks include Paired Associate Learning, Pattern Recognition Memory, Spatial Recognition Memory, Verbal Recognition Memory, Delayed Matching to Sample, Spatial Span, and Spatial Working Memory. Prior research suggests that the Paired Associate Learning, Spatial Recognition and Spatial Span (forward) subtests work best for individuals with DS (Boada et al., 2012; D'Ardhuy et al., 2015; de Sola et al., 2015; Edgin et al., 2010). On the RBANS, the List Learning subtest has also worked well with individuals with DS, and the other subtests evaluated are demonstrating promising performance regarding ceiling and floor performance (D'Ardhuy et al., 2015). Given their already proven utility, several subscales of these tasks would appear ready for use for individuals within the mental age range for these tasks.

Another promising measure for use in clinical trials for individuals with DS is the Woodcock-Johnson IV (WJ IV) Tests of Cognitive Abilities (Schrank, Mather, & McGrew, 2014). This is well-standardized and normed battery that was designed for ages 2 through 90 years that contains multiple subtests and has been used in populations of individuals with IDD. Memory tasks span auditory and visual modalities, immediate and delayed aspects of explicit recall, and learning. Tests include Story Recall, Numbers Reversed, Nonword Repetition, Visual-Auditory Learning, Picture Recognition, Memory for Words, and Sentence Repetition. The WJ IV provides an array of scores including a W-score, which will permit an accurate tracking of change over time. These memory tasks have many positive qualities, but have not yet been used in clinical trials.

Measures of memory also may be extracted from tests of intelligence or memory batteries (e.g., Wide Range Assessment of Memory and Learning-2) (Sheslow & Adams, 2003). If such tasks are employed, then it is important for issues of subtest specificity to be considered. For example, specific memory subtests could be extracted from the Stanford-Binet 5 or the Leiter International Performance Scale-3 (Roid, 2003; Roid, Miller, Pomplun, & Koch, 2013). These assessments are well standardized and normed on a wide age range from preschool to geriatric, and they have been used extensively in a variety of populations with IDD. Both tests also provide an array of scores including metrics that are based on Rasch modeling that will permit an accurate tracking of change. These measures would be deemed promising. Other notable possibilities for consideration that might need ongoing study and/or modification include the NIH Toolbox, the DAS-II subtests of Recall of Digits-Forward, Recall of Digits-Backward, Recall of Objects, and Recall of Objects-Delayed, and the Observer Memory Questionnaire (Parent/Caregiver rated). The DAS-II subtests yield a variety of scores, including ability scores based on Rasch analysis, offering accurate tracking of change over time. Additionally, the working group considered several tasks that could provide an opportunity to examine learning in a clinical trial with this population: CMS Dot Locations and Word Pairs, NEPSY-II List Learning (there are a variety of other list learning tasks, but many are inappropriate for use for most individuals with DS), Learning Propensity Assessment Device (Positional Learning Task, Associative Recall 16 Word Memory Test), Camping Trip/Visit to Doctor's Office, with these tasks being, at best, promising for use in a clinical trial (Cohen, 1997; Feuerstein, 2002; Korkman, Kirk, & Kemp, 2007).

Social cognition—Social cognition comprises the mental operations that underlie social functions and is multidimensional, including theory of mind, social perception, social

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knowledge, attributional style, and emotional processing (Green et al., 2008). These components facilitate recognizing, attending to, and prioritizing social cues; interpreting emotions from facial expressions, voice qualities, and situational cues; understanding other people's beliefs, intentions—especially when different from the individual's; and recognizing and adhering to social conventions (e.g., politeness). Individuals with DS show delays in their social cognitive development relative to chronological age expectations, variable delays relative to other developmental anchors (e.g., mental age), and symptom overlap with autism (Cebula & Wishart, 2008).

Measurement of social cognition in clinical trials remains problematic due to either poor or limited psychometric data for many tasks, especially in relation to DS. Despite several tasks being available for the general population (Social Cognition Psychometric Evaluation project), the applicability of these tasks for individuals with DS remains to be determined (Pinkham, Penn, Green, & Harvey, 2015).

Several social cognition tasks do show promise for use in clinical trials for individuals with DS. A predecessor of the SRS-2 was used with individuals with DS between the ages of 10 and 21 years; mean T-scores were in the clinically significant range for Social Cognition and Autistic Mannerisms (Channell et al., 2015). As such, this test may be among the most promising for current or near-term clinical trials for DS.

Two other measures have promise but require ongoing development or modifications to be useful for clinical trials involving individuals with DS. The Emotional Judgment Test (Channell, Conners, & Barth, 2014), which presents brief video vignettes that vary facial and contextual cues with character emotion, has demonstrated satisfactory internal consistency with adolescents with DS, but few differences in performance have been reported between individuals with DS and nonverbal mental age-matched typically developing controls (Channell et al., 2014). Psychometric properties important for clinical trials, such as test-retest and sensitivity to change, have yet to be addressed, and the ease of administration will need to be examined.

The Social Resolution Task, which utilizes drawings of appropriate and inappropriate social interactions (e.g., helping with household chores, not sharing), has normative data for children, ages 4 to 12 years, but has been used with individuals with DS ages 18 to 42 years (Hippolyte, Iglesias, Van der Linden, & Barisnikov, 2010). There are expressive language demands to complete this test, and performance has been shown to correlate with attention, inhibitory control, and language; consequently, these factors would need to be taken into consideration with respect to its use in a clinical trial with individuals with DS.

Attention—This domain forms the foundation for all other types of cognitive processes. As with each of the cognitive domains reviewed in this paper, attention is a multidimensional construct that changes with advancing age (Anderson, 2008) and is vulnerable to pathological conditions (e.g., dementia). There are a number of models of attention and its subcomponents, with some overlap with executive functions, but most models of attention describe four types: selective, sustained, divided, and alternating/shifting. A number of studies have examined attention-related functions in the DS population. Difficulties in

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several aspects of attention have been described, but particularly selective attention, focused attention, and higher-order forms of attention such as divided, shifting, and attentional control (Faught, Conners, & Himmelberger, 2016; Krinsky-McHale, Devenny, Kittler, & Silverman, 2008; Rowe et al., 2006). However, their measurement in clinical trials for individuals with DS has been relatively untested.

Despite this observation, there are a number of tasks that would have promise for use in clinical trials for this population. For selective attention, there are a variety of cancellation tasks that have been used with individuals with DS. For example, the Cancellation Task (Diller et al., 1974) requires the individual to cross-out each occurrence of a target item in an array of black and white line drawings. This test is easy to understand and yields an overall score for hits, errors, and false alarms (cancellation of targets from prior trials). Similarly, the Ruff 2 & 7 Selective Attention Test (Ruff & Allen, 1996) measures selective attention for individuals ages 18 to 80 years. On the Ruff, there are 20 15-second trials where the individual is required to draw a line through specific targets (always the numbers 2 and 7) while ignoring other letters or numbers. This task requires minimal language skills; however, the individual must be able to recognize numbers and use a pencil. Another cancellation task variant comes from the Alzheimer's Disease Assessment Scale-Cognitive Behavioral Section (ADAS-Cog) where a Numbers Cancellation Test is used (Mohs et al., 1997). This task requires participant to "cross-out" two numbers on a page that are mixed with other numbers.

Sustained attention typically is assessed using continuous performance tests. These measures are computerized, with commercially available tasks requiring anywhere from 7 minutes (Vigil) to 22 minutes (Test of Variables of Attention) (Greenberg & Waldman, 1993; Pearson, 1998). In general, these tasks utilize a signal detection paradigm wherein an individual watches the screen and pushes a button when he/she sees the target or the target sequence. Laboratory variants of these programs also are available. The applicability of these types of tasks to individuals with DS is relatively unknown, and their possible utility in clinical trials will require ongoing exploration.

For the divided and alternating/shift types of attention, there are a few measures that hold promise. For example, the Stroop Color and Word Interference Test (Golden & Freshooter, 2002) provides a measure of the alternating/shift type of attention. Here, the individual is required to name colors, simple words, and then the color of the ink in which the words are written. Versions of the Stroop also are available where the reading component is eliminated and replaced by shapes (e.g., Happy/Sad Stroop). For divided attention, the Brief Test of Attention (Schretlen, 1996) has been employed. This test consists of two lists of alpha-numeric strings (e.g. M-6-3-R-2) presented on audiotape that increase in length from 4 to 18 characters. In the first list, the task is to disregard the letters and count how many numbers are presented. In the second list, the task is to disregard the numbers and count the number of letters. Other measures of the alternating/shift type of attention, such as the Wisconsin Card Sorting Test (Grant & Berg, 1981) and the Contingency Naming Test (From & Taylor, 2005) are too difficult and are typically not appropriate to use in repeated measure settings such as in clinical trials.

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Finally, there are omnibus measures that provide estimates for the subcomponents of attention. For example, the Test of Everyday Attention (TEA), and its child variant (Test of Everyday Attention for Children, TEA-Ch), measure selective, sustained, alternating/shift, and divided attention (Manly, Robertson, Anderson, & Nimmo-Smith, 1998; Robertson, Nimmo-Smith, Ward, & Ridgeway, 1994). However, their applicability to individuals with DS or their appropriateness for use in clinical trials remains unknown.

Processing speed—Closely related to attention and executive functions is the construct of processing speed. Simply defined, processing speed refers to how quickly an individual can react to a stimulus via verbal or motor output modalities. As such, this is a construct that cuts across nearly every cognitive and behavioral function with respect to efficiency of functioning. It also is a construct whose measurement can quickly become confounded by a variety of difficulties such as poor receptive language, disorganization, and task complexity. For individuals with DS, there have been few studies that have examined this construct directly, but some have noted that individuals with DS produce inconsistent deficits on simple reaction time measures (Silverman, 2007). Consequently, processing speed tasks may provide useful tools for exploration in a clinical trial, particularly given that many pharmaceutical agents may hold the potential to improve information processing speed via a variety of different mechanisms. In that regard, there are several measures that hold good promise for their inclusion in a clinical trial for individuals with DS.

For example, the Simple Reaction Time task from the CANTAB has minimal language involvement, satisfactory test-retest reliability and no reported practice effects (Anand et al., 2015). Thus, this task appears ready for use in a clinical trial. For individuals with significant motor involvement, however, this task could prove difficult to administer and the field would benefit from a simple reaction task that requires little to no fine-motor involvement.

Additionally, there are a number of other processing speed tasks that hold promise for use in clinical trials for individuals with DS. Specifically, there are several processing speed tasks that can be extracted from child and adult intellectual/cognitive batteries. For example, the DAS-II Rapid Naming subtest and the WJ-IV Rapid Naming subtest require the individual to label as many pictures as possible within a specified time frame. Both subtests yield a variety of scores, including scores based on Rasch modeling that will yield accurate measurement of change over time. While these types of tasks appear promising, they are confounded by language-related capabilities and are untested for this population in a clinical trial.

Mild Cognitive Impairment/Alzheimer Disease—For adults with DS, dementia occurs more frequently and at earlier ages than in other adults with IDD (Zigman, 2013). Indeed, nearly all adults with DS have the neuropathology of Alzheimer disease (AD) by 35–40 years of age, and more than two-thirds of adults with DS have the clinical signs and symptoms of dementia after age 65 years (Tyrrell et al., 2001). While a combination of factors contributes to the development of AD in this population, it is generally accepted that the location on chromosome 21 of the gene coding for the amyloid precursor protein (APP; a large transmembrane glycoprotein, the breakdown of which can produce the β-amyloid

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fragments forming plaques) is centrally involved (Prasher et al., 1998). Because most individuals with DS have three copies of this gene, it is likely that overexpression of APP contributes to the development of neuropathology consistent with AD seen in this population (Zigman, 2013).

There is a clear need to identify sensitive and valid measures of early AD in adults with DS, as evidenced by other working groups convened to discuss outcome measures for dementia in DS (D. Hartley et al., 2015). AD-related neuropathological changes occur years to decades prior to the clinical presentation of AD both within the general population (e.g., (Aizenstein et al., 2008)) and in adults with DS (e.g., (S. L. Hartley et al., 2014; Lao et al., 2015; Rafii et al., 2015)). The identification of biomarkers of these pre-symptomatic neuropathological changes, such as amyloid plaques and intracellular neurofibrillary tangles composed of the protein tau, is essential for evaluating disease-modifying treatments and several research groups are presently active in this endeavor. A review of the AD biomarker research may be found elsewhere (e.g., (Jack & Holtzman, 2013)). Much like biomarker research, recent research on measures of AD cognitive and functional declines in DS has focused on the early stages of the disease. Growing research suggests that many typical individuals evidence mild cognitive impairment (MCI), defined as cognitive functioning that is more limited than what is expected with normal aging but not associated with clinical impairments in adaptive functioning, prior to the onset of AD (Petersen, 2011). There is a critical need for sensitive and valid neuropsychological measures of MCI in adults with DS (MCI-DS) (Jenkins et al., 2008). Such measures will allow researchers to track individuals with DS prospectively prior to onset of dementia and thus are most likely to be relevant in clinical trials for medications aimed at delaying the onset of and/or preventing AD. Indeed, treatments are likely to be most effective if introduced prior to irreversible losses of critical neural pathways in the later stages of the disease (see (Krinsky-McHale & Silverman, 2013).

The detection of MCI presents clear challenges with adults with DS who have lifelong cognitive impairments and variability of baseline level of functioning. Moreover, there is a lack of data on normative age-related declines in cognition and functioning among healthy adults with DS, making it difficult to determine expected age-related declines from MCI. Despite these difficulties, recent studies have begun to identify direct measures of memory and cognitive functions that are appropriate for use with adults with DS and sensitive to relatively subtle declines that may be indicative of MCI-DS or early AD stages (Ball et al., 2006; Holland, Hon, Huppert, & Stevens, 2000; Krinsky-McHale et al., 2008; Krinsky-McHale & Silverman, 2013).

The DS population will undoubtedly require a unique set of considerations in terms of sensitive and valid assessments of MCI-DS and AD. Baseline assessments of functioning will be important as will be the need for carefully-planned and consistent testing sessions. Some direct neuropsychological measures will likely only be sensitive and valid in verbal or higher functioning adults with DS. Indeed, some researchers have suggested that observer-rated scales may be more informative than direct neuropsychological tests for AD assessment in nonverbal or lower functioning adults with DS (Deb & Braganza, 1999). The earliest declines associated with MCI-DS and early stage AD have generally been found in episodic memory, executive functioning, and visuospatial processing (Devenny, Krinsky-

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McHale, Sersen, & Silverman, 2000; Krinsky-McHale, Devenny, & Silverman, 2002), with some evidence of early psychiatric/behavioral changes (Ball et al., 2006; Urv, Krinsky-McHale, & Zigman, 2007). Early mild declines in motor functioning have been under-studied, but are suggested based on early amyloid-β deposition (Lao et al., 2015). Complete MCI-DS and AD assessment should include memory and learning, executive functioning, psychiatric/ behavioral problems, language, and motor performance. Although these constructs overlap with other cognitive constructs reviewed above, they warrant evaluation for appropriateness for individuals with DS of a different older age range, and for decline rather the growth of skills. Thus, measures judged by the working group to be appropriate for adults with DS or to show promise but to need further evaluation, are listed separately in Table 2. A more detailed review of outcome measures specific to dementia in DS is available (Burt & Aylward, 2000).

Several informant-based dementia screening measures have been developed for adults with DS. The Dementia Scale for Down syndrome (DSDS) and Dementia Questionnaire for People with Learning Disabilities (DLD; formerly the Dementia Questionnaire for Mentally Retarded Persons (DMR)) are two informant-based tools used to assess dementia in individuals with intellectual disabilities with adequate specificity and sensitivity (Evenhuis, Kengen, & Eurlings, 2006; Gedye, 1995). The Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID; (Deb, Hare, Prior, & Bhaumik, 2007) was validated in a large sample of participants with DS and dementia, larger than either the DSDS or DLD and possesses excellent sensitivity and specificity for dementia. The Adaptive Behavior Dementia Questionnaire (Prasher, Farooq, & Holder, 2004) has also been shown to be a valid screening tool for dementia in a DS population. The National Task Group Early Detection Screen for Dementia (Esralew et al., 2013) is a conceptually-strong tool developed by experts in the field but in need of more research. Several direct assessments of mental status have also been shown to be able to distinguish adults with DS with dementia from those without including the Severe Impairment Battery (Panisset, Roudier, Saxton, & Boller, 1991), Modified Haxby Down Syndrome Mental Status Examination (Haxby, 1989; Silverman et al., 2004), and Modified Mini Mental State Examination (Teng, Chui, Schneider, & Metzger, 1987).

In terms of direct neuropsychological measures the Rapid Assessment for Developmental Disabilities (RADD) holds great promise (Walsh et al., 2007). Among individuals with IDD, the RADD allows for statistical analysis of potential treatment effects, has adequate test-retest reliability, and is resistant to confounding factors such as poor motivation and language impairment. Among adults with DS, the RADD exhibited high sensitivity and specificity in discriminating among individuals with DS with and without dementia (Walsh et al., 2015). The Cued Recall Test and Modified Selective Reminding Task may have particular relevance for detecting MCI-DS, as performance on both has been shown to be predictive of which individuals with DS will later develop dementia (Devenny et al., 2000; Krinsky-McHale et al., 2002). Many other measures of memory and learning, language, executive processing, and visuospatial processing show promise for capturing MCI-DS in adults, but are in need of more research (S. L. Hartley et al., 2014; Krinsky-McHale & Silverman, 2013).

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Measures of adaptive behavior that have been broadly used with individuals with IDD (e.g., Vineland Adaptive Behavior Scale – II) (Sparrow, Cicchetti, & Balla, 2005) appear to be appropriate for documenting declines in daily living skills associated with AD. The Adaptive Behavior Dementia Questionnaire (ABDQ; (Prasher et al., 2004)) is a measure of adaptive behavior that was designed especially for AD with good reliability and validity in adults with DS and high accuracy in identifying AD. Other measures of adaptive behavior that have been used in the context of assessing MCI-DS or AD in a DS population that show promise but are in need of more assessment are the Daily Living Skills Questionnaire (NIA, 1989), Adaptive Behavior Assessment System (Harrison & Oakland, 2015), Activities of Daily Living Schedule (Lawton & Brody, 1969), and Bristol Activities of Daily Living Scale (Bucks, Ashworth, Wilcock, & Siegfried, 1996). Relatively little is known about the reliability and validity of measures of AD-related changes in psychiatric symptoms and behavior problems. The Reiss Screen for Maladaptive Behaviors (Reiss, 1994) has been shown to capture the changes in personality and behavior that occur with dementia progression (Urv et al., 2007). There is also evidence that personality and behavior change captured on the Cambridge Examination for Mental Disorders of the Elderly-Down Syndrome (CAMDEX-DS; (Hon, Huppert, Holland, & Watson, 1999)) may be sensitive to early changes in adults with DS (Ball et al., 2006; Holland et al., 2000).

Looking forward, there is an urgent need for more research on the reliability and validity of measures of MCI-DS in adults with DS and ideally the identification of measures appropriate for individuals with a range of ability levels. As shown in Table 2, many measures shown to be reliable and valid are not appropriate for adults with DS with low baseline functioning levels and/or those in the later stages of AD. In part, efforts to find sensitive measures of MCI-DS will require better normative data on age-related declines in cognition and functioning in healthy adults with DS using large samples. Studies should be longitudinal in nature and aimed at identifying measures sensitive to within-person declines in cognition and functioning from baseline to MCI-DS as well as across all stages of AD (early-stage, middle-stage, and late-stage). Finally, it is crucial that research on measures of AD-related cognitive and functional declines occur in conjunction with research on biomarkers of early neuropathological changes.

Behavior Domains

When identifying core domains, the Behavior Working Group noted that the cognitive phenotype in part contributes to a common behavioral profile and made efforts to review the behavioral presentation associated with these core cognitive deficits. Domains identified by the Working Groups include self-regulation, psychopathology, sleep, daily living/adaptive behavior, and maladaptive behavior. When evaluating measures appropriate for assessing these domains, the Behavior Working Group also reviewed the literature on individuals with IDD, as often individuals with DS were not the expressed target population but were included in the scale's development. Proposed measures and their associated domains can be seen in Table 1.

Self-regulation—Many individuals with DS demonstrate difficulties with self-regulation throughout the lifespan (Daunhauer & Fidler, 2013). These patterns begin to emerge in early

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childhood, when toddlers with DS demonstrate poorer performance on measures of planning and goal-directed behavior when compared to developmentally matched children (Fidler, Hepburn, Mankin, & Rogers, 2005). The assessment of self-regulation shows a great degree of overlap with the assessment of executive function, as reviewed in the Cognition section, as executive functioning is conceptualized as the cognitive underpinning of aspects of self-regulation. After much consideration, however, some members of the working groups argued that self-regulation is an important and distinct concept worthy of further investigation among individuals with DS, beyond its cognitive underpinnings.

For this purposes of this paper, the working groups defined self-regulation as including goal-directed planning and motivation, which tend to pose challenges to individuals with DS, particularly during the early part of the lifespan. For applied, everyday manifestations of behavior management and goal-directed behavior, the Planning and Organizing domain of the BRIEF-School Age informant and self-report forms and the BRIEF-P may be useful. The BRIEF-P has demonstrated reproducible findings across samples of individuals with DS during middle childhood (Daunhauer et al., 2014; Lee et al., 2011). The BRIEF assessments also may be useful for assessing emotional control in naturalistic environments.

Though proxy report of self-regulation skills is useful for assessing global outcomes related to self-regulation in DS, this approach may also be subject to some degree of reporter bias. As such, it will likely be useful to identify additional, precisely administered and coded laboratory tasks to quantify outcomes related to self-regulation in DS and other disorders. Though various approaches (impossible puzzle tasks, lock boxes) have been applied to the study of persistence and motivation in DS, the study of early self-regulatory skills in typically developing children may offer more standardized, potentially psychometrically valid assessment techniques. Early planning skills in DS have been assessed in the laboratory using an adaptation of Diamond's Object Retrieval task (Diamond & Goldman-Rakic, 1989; Fidler et al., 2005), wherein a child is required to obtain a desired object through the opening of a clear Plexiglas box across a variety of trials. The overall quality of the reach and retrieval strategies produced by the child is then coded and quantified. Similarly, the quality of early planned behavior can be assessed using laboratory assessments of praxis, wherein a child is asked to perform a variety of planning tasks involving objects (put a necklace in a cup; insert coins in a bank) (Fidler et al., 2005). Again, independent coders are needed to evaluate planning performance based on specific criteria for each task. A different approach to early planning relates to capturing a child's ability to generate a variety of planned actions without any predetermined guidelines or structures (generativity). Assessments of object-related generativity involve characterizing the number of different planned actions and the number of objects utilized during the duration of the assessment period, and have been recently used in studies with school age children (Fidler, Will, Daunhauer, Gerlach-McDonald, & Visootsak, 2014). The use of such assessment strategies in a clinical trial has not yet been attempted.

For assessing aspects of inhibition and delay of gratification, variations on "delay" tasks typically used in studies of normative child development may be a promising approach. One version of this type of laboratory task involves trials wherein a child must wait for a signal (e.g., the ring of a bell) to retrieve a snack from under a clear cup. This approach can involve

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a variable number of trials with variable (5, 10, 20, and 15-second) lengths of delay time (Carlson, 2005). Other approaches involve asking a child to wait to open a present placed in front of him/her (Kochanska, Murray, Jacques, Koenig, & Vandegeest, 1996). These laboratory-based self-regulation measures are easy to administer but require trained coders to code video-recorded data. To date, none of these laboratory-based measures has been validated for use in the population of individuals with DS.

Psychopathology—The phenomenology and expression of psychopathology and related symptomatology in persons with DS/IDD may be characterized in various ways: 1) by age at onset (childhood, adolescent, young adult, elderly adult); 2) by presentation, such as abrupt onset of new symptoms or intensification of pre-existing, low-level symptoms; 3) by functional consequences, such as with/without loss of previously acquired cognitive-executive and social-adaptive skills; or 4) in a somewhat nondescript manner, such as mixed anxiety and mood features, perseveration and repetition with/without other internalizing or externalizing behaviors.

The prevalence of psychopathology in adults with DS is unknown, but according to some estimates affects 20–30% of individuals (Mantry et al., 2008). On the French version of the Reiss Screen for Maladaptive Behavior, adults with DS had significantly lower (better) global scale scores than adults with IDD of unknown etiology; scores for all of the subscales except Autism also were significantly lower for the DS group (Straccia, Tassé, Ghisletta, & Barisnikov, 2013). Clinical diagnoses of depression were more common among adults with DS than among adults with IDD of other etiologies (Collacott, Cooper, & McGrother, 1992). As the mean age of the individuals with DS who had depression was in young adulthood, the authors argued that the elevated rate of depression was not due to dementia or pre-dementia. In contrast, clinical diagnoses of conduct disorder, personality disorder, or schizophrenia/paranoid state were significantly less common among adults with DS than among adults with IDD of other etiologies (Collacott et al., 1992).

Some preschool and young school-age children (5–43%) with DS manifest symptoms of inattention, distractibility and poor impulse control with/without hyperactivity and other disruptive behaviors (Ekstein et al., 2011). Occasionally, school-age children and adolescents (5–39%) will manifest autistic-like behaviors with severe intellectual disability, impairments in social-reciprocity, language and executive function with/without regression in previously acquired developmental skills (Capone et al., 2005; Castillo et al., 2008; Channell et al., 2015; Worley et al., 2014). Similarly, adolescents and young adults will experience intensification or new-onset anxiety, compulsive behaviors, social avoidance, mood disturbance/depression, sleep disturbance and disordered thought processing (Dykens et al., 2015).

The variety and complexity of psychiatric symptomatology, maladaptive behaviors and functional skill impairments seen in persons with DS underscores the challenge of designing and conducting clinical trials of behavioral function. In targeting any particular psychopathology, consideration of confounding factors such as co-morbid features, intellectual and language levels, psychosocial stressors, educational/vocational programming, parent/family factors, pubertal status, and comorbid medical conditions is

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essential. These concerns would be exacerbated in a clinical trial as they may potentially blur the impact of a particular drug agent on a targeted cognitive and/or behavioral outcome.

Currently available instruments, presented in Table 1, include observer-reported and clinician-reported measures that have been developed for either the typical or IDD population with psychiatric symptomatology. Structured psychiatric interviews, such as the K-SADS-PL (Kaufman et al., 1997) and NIMH-DISC-IV (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), represent another option for measuring psychiatric outcome, but the application of these methods to an IDD population in a clinical trial remain relatively unknown. In need of further exploration and development are outcome measures to assess frontal systems, motivation/initiation (Malloy & Grace, 2005), eating/appetite regulation (Russell & Oliver, 2003), self-talk/voices (Chadwick, Lees, & Birchwood, 2000), regression/functional decline, and specific psychopathologies such as psychosis (Hatton et al., 2005).

Sleep—Sleep is a primary concern among individuals with DS. Obstructive sleep apnea (OSA) affects 24–57% of individuals with DS (Maris, Verhulst, Wojciechowski, Van de Heyning, & Boudewyns, 2016). In addition, children and adults with DS also experience behavioral sleep problems that are often missed by polysomnography, such as bedtime resistance, sleep onset delay, sleep anxiety, night waking, and parasomnias (Carter, McCaughey, Annaz, & Hill, 2009; Churchill, Kieckhefer, Bjornson, & Herting, 2014; Esbensen, 2016). Both OSA and behavioral sleep problems are important outcomes to track in clinical trials as they are associated with daytime inattention, difficulties with learning, and maladaptive behaviors (Churchill et al., 2014).

Diagnosing and assessing improvements in sleep apnea are best accomplished with polysomnography, as parent reports generally miss cases of disrupted breathing (Shott et al., 2006). Behavioral sleep problems can be assessed using actigraphy, parent ratings with daily sleep logs, or the Children's Sleep Habits Questionnaire (Breslin et al., 2014). Other parent-rating forms have been developed for assessing sleep in typically developing children, but have not been explored in individuals with DS; e.g., the Behavior Evaluation of Disorders of Sleep (BEDS) and Sleep Disturbances Scale (SDSC) (Bruni et al., 1996; Schreck, Mulick, & Rojahn, 2003).

Adaptive behavior—Adaptive behavior, defined as the social (e.g. interpersonal skills), practical (e.g. activities of daily living), communication (e.g., language use), and motor skills (e.g., gross motor, fine-motor) learned and used by people so they can function in everyday living situations, has been widely studied in individuals with IDD and more specifically in individuals with DS (Dressler, Perelli, Feucht, & Bargagna, 2010; Dykens, Hodapp, & Evans, 2006). As a way of measuring strengths and weaknesses in daily functioning, assessing adaptive behavior in people with DS is critical for determining relations with cognitive abilities, quality of life, or level of independence. The published research studies on individuals with DS have focused primarily on changes in adaptive behavior abilities across the lifespan (Dressler et al., 2010; Dykens et al., 2006; Makary et al., 2014). Very little is known about the usefulness of adaptive behavior scales in clinical trial settings.

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The working group identified four main scales measuring adaptive behavior outcomes. The first is the Vineland Adaptive Behavior Scale II (VABS-II), which has been used in a few DS clinical trials (Sparrow et al., 2005). The VABS-II covers birth to age 90 years, is standardized and normed for the US and Japanese populations, and has both parent questionnaire and survey interview forms available. The Survey Form takes 45 to 60 minutes to complete and needs a well-trained interviewer. The third revision of the Vineland (VABS-3) has just been published (Sparrow, Cicchetti, & Saulnier, 2016). The Diagnostic Adaptive Behavior Scale (DABS) covers ages 4 to 21 years and is also available in a survey interview form (Tassé, Schalock, Balboni, Spreat, & Navas, 2016). The scale is standardized and normed for the US population and takes 60 minutes to complete. The DABS is recommended by the American Association on Intellectual and Developmental Disabilities for diagnostic purposes. The Adaptive Behavior Assessment System (ABAS-3) covers birth to age 89 years. It is in questionnaire form and takes 20 minutes to complete (Harrison & Oakland, 2015). The Scales of Independent Behavior – Revised (SIB-R) covers birth to age 80 years, is available in survey interview form, and takes 45 to 60 minutes to complete (Bruininks, Woodcock, Weatherman, & Hill, 1996). It is standardized and normed for the US population and includes Rash-based scaling (i.e., W-scores) that will allow for accurate measurement of change over time.

In the context of clinical trials in DS, the working group identified the VABS-II, and perhaps the VABS-3 and the SIB-R, as viable options that meet important criteria and could be used to measure potential improvements in adaptive functioning domains. In particular, survey interview forms from these tests were preferred for clinical trials to reduce potential placebo effects. Further, these two scales are suitable for a wide age range, maintain good psychometric properties, and the scales have already been used in trials with people with DS (Boada et al., 2012; Kishnani et al., 2010). In addition, maladaptive domains, which are key in this population (see section on Maladaptive Behavior) can be examined with these two scales. However, in the context of multi-site multi-country trials, cautions are needed when interpreting adaptive behavior standard scores. Since adaptive behavior expectations have a strong cultural component and the norms for these measures were mainly derived from the US population, differences in standard scores between countries (e.g. USA vs. Japan) could be due, in part, to differences in cultural expectations. Thus, country-specific adaptations and norms would be necessary. A Japanese version of the VABS-II is available and a French version is expected to be published in 2016 (Sparrow, Cicchetti, & Balla, 2014).

Maladaptive behavior—Maladaptive behaviors are commonly present in 20–30% of individuals with DS, with rates often highest during childhood and with the onset of dementia in late adulthood (Dykens & Kasari, 1997; Urv, Zigman, & Silverman, 2008). Individuals with DS tend to exhibit problematic behaviors in the form of noncompliance, inattention, hyperactivity, and impulsivity (Cornish, Steele, Monteiro, Karmiloff-Smith, & Scerif, 2012; Dykens & Kasari, 1997). Behavioral difficulties negatively impact the individual's ability to engage in schoolwork, vocational and leisure activities and contribute to stress within the home environment. For example, parents of individuals with DS report significantly higher rates of stress, pessimism and depression in comparison to parents of typically developing individuals (Roach, 1999; Sanders, 1997). Often, maladaptive

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behaviors are more common in reaction to a stressor or life changes, such as the transition out of school and to the work place (Owen et al., 2004). The previously mentioned weaknesses in executive functioning, processing speed, and learning can contribute to challenges coping with stressors and result in the expression of maladaptive behaviors. Similarly, the previously mentioned psychopathology can contribute to increases in rates of maladaptive behavior.

When targeting maladaptive behaviors in a clinical trial, there are subpopulation characteristics to consider. Younger children with DS are more at risk for maladaptive behaviors such as agitation, aggression, sleep problems, inattention, impulsivity, rigid and repetitive behaviors, oppositional behavior, and reciprocal social impairment (Esbensen & MacLean, in press). In contrast, in adulthood mental health concerns such as anxiety, depression, and obsessive-compulsive disorder contribute to the presentation of maladaptive behaviors. Maladaptive behaviors common in adulthood include repetitive, perseverative, compulsive and hoarding behaviors, social withdrawal, sleep problems, inattention and cognitive disorientation, and agitation associated with dementia (McGuire & Chicoine, 2006).

Most current measures of maladaptive behavior include observer-reported outcome measures. These measures have been developed for typically developing individuals or for individuals with IDD more generally; no measures of maladaptive behavior have been developed specifically for individuals with DS. Observational coding of behaviors is an option for assessing parent-child behavior and maladaptive behavior. The observer-reported measures presented in Table 1 meet criteria for measuring maladaptive behaviors in individuals with IDD in regard to psychometric properties, and were not viewed by the working group as functioning differently among individuals with DS.

Outcomes warranting development among children with DS include measures of compliance, self-regulation of behavior and emotion, coping with transitions, eating and appetite behaviors, physical activity, and psychophysiological measures such as eye tracking, cortisol and biomarkers. Outcome measures warranting development among adolescents and young adults also include measures of compliance, coping with transitions, adaptive declines, eating and physical activity, specific psychopathologies, motivation, and quality of life.

Commonalities Identified Across the Working Groups

Both working groups identified developmental change as an important variable to consider in the characterization of the DS cognitive and behavioral phenotypes. For example, some behaviors that are considered problematic in adolescence and adulthood (e.g., difficulties with behavior regulation) may be considered more age-appropriate in early childhood. Similarly, although the cognitive phenotype associated with DS is quite pronounced relative to chronological-age matched peers in adolescence and adulthood, specific cognitive delays are more subtle and difficult to detect during infancy, and findings may vary depending on the component of cognition assessed (Milojevich & Lukowski, 2016; Roberts & Richmond, 2015). In addition, the profile of relative strengths and weaknesses that defines the DS phenotype emerges with age as the result of the complex interplay between the genetic

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condition, characteristics of the individual, and his or her interactions with the environment. These issues are important to consider given that early childhood has been identified as an important time window for future treatments in order to maximize downstream effects of treatment on development (Edgin, Clark, Massand, & Karmiloff-Smith, 2015).

A second insight generated from the working groups was that a particular difficulty often could be conceptualized as both a behavioral problem and a cognitive problem. This issue arose as a function of the range of areas of scientific and clinical expertise represented at the NIH meeting. For example, the behavior group identified difficulties with rigidity and compliance as an area of challenge from a psychiatric perspective for a subset of adults with DS. These types of difficulties were framed from a cognitive perspective as part of the executive function presentation in DS, and in particular, challenges related to cognitive flexibility or shifting. Given the overlapping nature of identified targets for treatment, efforts were made to consider numerous perspectives (psychiatric, developmental, and medical) when identifying targets for treatment.

Discussion

Evaluation of treatment interventions in DS requires the deployment of sound clinical outcome measures. The NIH organized discussion and meetings among clinical and research experts from the field of DS to evaluate current outcome measures, specify relevant outcome targets, and identify areas of need for future clinical trials. Although clinical outcome measures have the most urgent relevance to pharmacological trials targeting cognition (improvement or prevention of decline associated with dementia), the working groups also identified behavioral outcomes that warrant attention given the needs of individuals with DS.

In a large number of areas, both groups reported important gaps in our current overall scientific knowledge base regarding the natural history of DS and the complexity of the DS cognitive and behavioral phenotype. Gaps in our current knowledge base exist in large part due to the observation that the outcome measures used have seldom been consistent across studies. As such, converging information regarding the psychometric properties of candidate measures was not available. Both groups strongly emphasized the importance of future work to characterize the emergence of the DS cognitive and behavioral phenotype across the lifespan with greater precision and an eye toward future treatments of core phenotypic impairments.

Yet another issue raised in the process of identifying candidate measures involved selecting measures that would not only reliably and validly assess cognition and behavior but would also be precise and sensitive to change over time. Some candidate measures that have demonstrated strong psychometric properties for individuals with IDD (e.g., adaptive behavior scales), and perhaps individuals with DS in particular, were noted as covering a wide range of chronological ages, with only a few items capturing functioning at a particular developmental level. Thus, these measures may not be suited to capture change in response to pharmacological treatment over a several-month time window. There are an increasing number of cognitive and behavioral measures that utilize item response theory (e.g., Rasch

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modeling) in their test development, and these types of measures hold promise for tracking change over time more accurately.

The working groups pointed out that in addition to the psychometric properties of an assessment, the measure's administration features are critical for a clinical trial, and these features will be particularly important for individuals with DS. Initially, it will be important to note whether a test is standardized in its administration. The administration format also should be considered. Depending on the test, these formats may stimulate more or less interest for individuals with DS completing the tests. For example, nonverbal administration procedures may facilitate the performance of individuals with DS with severe language impairments, but impede performance of individuals with relatively good language abilities. These features become even more critical to consider when multiple sites are used in a clinical trial. For example, the use of computerized testing provides the opportunity for strong standardization and automatic scoring, but this type of testing might be hindered by the relatively short attention span and the social nature of individuals with DS if the tasks are of less interest or too long. With regard to the time required for administration, shorter is not necessarily better, but for many clinical trials, and particularly for individuals with DS, shorter administration times may produce greater interest in the testing and, ultimately, greater compliance and improved reliability.

A developmental reframing is required to determine if a test will be useful for individuals with DS. For example, a test designed for individuals of a particular age does not mean it can be used successfully for individuals with DS of that age, particularly if their developmental level falls below the youngest age for which the test was normed. Thus, knowledge of the floor/ceiling effects of a test is essential. Moreover, it is necessary for the test instructions and associated materials to align with the developmental level of the individual being assessed. If there is a mismatch, data will be unreliable and any changes in the trial may be masked secondary to this issue. The selection of a single test that would cross over all of the chronological ages and developmental levels represented by DS is likely limited by their availability, although there are a few possibilities (e.g., WJ IV). Nonetheless, having such tasks to assess cognitive and behavioral functions at different developmental time periods would be helpful in reducing the measurement variance that already will be present in this population given their performance difficulties.

Summary of Working Group Observations

The working groups made the following general observations regarding the development, validation, and use of outcome measures in individuals with DS:

1. **Ongoing work is needed to evaluate outcome measures for use in clinical trials with individuals with DS.** Some outcome measures are currently ready for use in DS or may only need minor modifications to increase their appropriateness for use with individuals with DS. However, other areas warrant innovations, particularly in the development and evaluation of new measures. For any clinical trial, it is important that psychometric properties such as test-retest reliability and sensitivity to change be established specifically for the population of individuals with DS given the real possibility of differences between this

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population and the normative samples on which most standardized measures are developed. Consequently, there is a need for new tests and measurement strategies as well as examination of currently available measures with respect to their possible modification for use in clinical trials for individuals with DS.

2. **Outcome measures are needed that have lower performance floors.** Outcome measures warrant development of lower floors, in order to be appropriate for individuals with DS who may be lower functioning. Lower floors allow clinical trials to be accessible to a broader range of individuals with DS increasing the generalizability of findings. Measures appropriate for very young children also warrant development and evaluation, as providing earlier intervention may have downstream effects on academic skills, socialization and cognitive development.

3. **To be useful in clinical trials, measures must accurately assess change over the time period of the trial**. For this purpose, W-scores or ability scores based on Item Response Theory could be a critical characteristic of any measure selected for use in a clinical trial. Further, in an ideal world, individual measures would be applicable across the lifespan of individuals with DS. At present, however, researchers need to be cognizant of the natural development of individuals with DS and select measures appropriate for the developmental level of the research participants.

4. **Outcome measures are needed that cross cultural and linguistic boundaries.** Current clinical trials on specific genetic syndromes, such as DS, are being conducted internationally. In planning these clinical trials, their study designs are limited in what measures could be used across countries and languages. As international studies are the norm for many clinical trials, outcome measures for use in other cultures warrant development, norming and translation. Using tests that are culturally and linguistically sensitive is important; otherwise, the utility of the measures in international sites or in minority cultures within the United States will be limited and potential changes in clinical trials in which the measure was used could be masked. For example, it would be helpful for outcome measures to be normed among Spanish-speaking individuals in the United States; so far, this has only been accomplished for a few of the measures the working groups identified.

5. **A more completely characterized natural history of development in DS is needed to guide the innovations in outcome measures for use in clinical trials.** In addition to developing a battery of measures appropriate for use in clinical trials, there is a need for researchers to document the natural history of development of individuals with DS across the life span as this developmental trajectory will help to highlight areas of need at different developmental epochs. This is a clear area for potential support from both federal and private funding agencies.

6. **Comorbid conditions should be considered when developing outcome measures.** Comorbid conditions common among individuals with DS are important to consider when developing outcome measures and when designing

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clinical trials. Not only are these conditions potential targets for a clinical trial, but their impact on other targeted behaviors or cognitive abilities in a clinical trial must be taken into account in an effort to lessen the confounds of a pharmacological (or behavioral or educational) intervention. As an action item, it will be important for the field to systematically examine specific comorbid or co-occurring conditions with respect to their impact on various types of outcomes.

7. **There may be downstream benefits that should be assessed in any clinical trial for DS.** Behavioral and cognitive outcomes overlap in that the root cause may affect multiple modalities. For example, a treatment trial targeted to address attention or anxiety might also be found to result in a positive change in memory performance, if measures targeting memory were included in the trial. As this example demonstrates, it will be important for clinical trials to include not only primary measures, but also measures addressing related outcomes to assess for downstream effects of an intervention.

8. **Efforts to improve outcome measures will need to be collaborative.** To be able to validate a core set of outcome measures and/or data elements for clinical trials for individuals with DS, research groups will need to agree on a common set of measures to include in their studies. A common set of measures is necessary in order to aggregate data, making it possible to accumulate a large enough sample to accurately characterize the natural history of DS (e.g., cross-sectional differences) and/or to identify differences due to an intervention.

9. **Special attention should be given to the use of technology when assessing outcome measures.** The use of technology, be it individual computerized assessment of reaction time, actigraphy, measurement of galvanic skin responses, or real-time language sampling, is in need of psychometric validation for the population of individuals with DS. Although technology has the potential to provide more accurate measurement, some of these measures may sometimes be less engaging for individuals with DS (computerized assessments). Ongoing evaluation of both ability to complete the measure and the level of engagement of the individual with the task will provide stronger information for evaluating with whom these tasks may be appropriate.

10. **Community education and awareness of clinical trials are needed.** Throughout the discussion of the working groups, it was evident that misperceptions of clinical trials are common among clinicians, researchers, and individuals with DS and their families. These misperceptions and lack of awareness likely contribute to challenges for individuals and family members to obtain accurate information from clinicians about clinical trials, leading to limited research participation. There is a strong need to generate and disseminate information to the DS community about advances that have been made in research, both in support of clinical trials and the preliminary results of these trials. There is also a need for further research collaboration across basic and behavioral sciences to generate appropriate outcome measures. Community education and awareness is needed to increase participation in the development

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and evaluation of outcome measures and conduct of clinical trials and to facilitate more rapid progress.

At present, few evidence-based behavioral and clinical treatments are available for individuals with DS. Without appropriate outcome measures, results of clinical trials will be difficult to interpret and null findings could result from poor or insensitive outcome measures rather than the ineffectiveness of the treatment. Further, without a targeted battery of assessments, this population may experience fatigue effects, which could also cloud the study's results, as has been seen in two recently published clinical trials in this population (Fernandez & Edgin, 2016). With an increasing number of pharmacological targets now derived from basic science, the further validation of outcome measures is a necessary next step for the field of DS (Gardiner, 2015). Although some efforts have been made to evaluate outcome measures appropriate for use in treatment studies and clinical trials in DS (D'Ardhuy et al., 2015; de Sola et al., 2015; Edgin et al., 2010; Lott et al., 2011), yet more evaluations of systematically selected outcome measures are needed in order to maximize the validity of future clinical trials for individuals with DS.

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Table 1

Summary of measures available by domain and appropriateness for use in clinical trials among individuals with DS.

	Appropriate/Validated with DS	Appropriate/Validated with IDD	Needs Modification/ Promising
Language			
Comprehensive	-	-	CDI CELF-5 CELF-P2
Receptive	-	PPVT-4	TROG-2
Expressive	-	EVT-2	Narrative and other expressive language samples
Language Pragmatics	-	SRS-2	CCC-2
Articulation	-	-	GFTA-3
Executive functioning	-	BRIEF-Preschool BRIEF-School-age CANTAB spatial span forward Verbal fluency	NIH Toolbox
Memory & learning	CANTAB paired associate learning CANTAB spatial recognition CANTAB spatial span RBANS list learning	Leiter 3	CMS dot location CMS word pairs DAS-II recall of digits forward DAS-II recall of digits backward DAS-II recognition of pictures NIH Toolbox NEPSY-II list learning OMQ RBANS list recall RBANS list recognition SB5 working memory WJ IV WRAML-2 Learning Propensity Assessment Device Camping Trip/Visit to Doctor's Office
Social cognition	-	SRS-2	Emotional Judgement Test
Attention	-	-	WISC-5 cancellation Ruff Selective Attention Test ADAS-Cog Stroop Color/Word inference test Brief Test of Attention TEA, TEA-Ch
Processing speed	-	-	CANTAB simple reaction time DAS-II rapid naming DAS-II speed of information processing WJ IV

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	Appropriate/Validated with DS	Appropriate/Validated with IDD	Needs Modification/ Promising
			DABS
Self-regulation	-	BRIEF-Preschool BRIEF-School-age	Assessment of Praxis Diamond Object Retrieval Generativity Gift/snack delay
Psychopathology			
Semi-structured Interview	-	PAS-ADD	K-SADS-PL NIMH-DISC-IV
Psychopathology screens	-	ADD DASH-II PIMRA[^] Reiss Scales (Children) Reiss Screen (Adults)	BPRS
Diagnosis specific	-	ADAMS BFCS GDS[^] NCS	CBC C-YBOCS-PDD NPI for Dementia PANSS SANS
Side effects	-	MOSES	
Sleep			
Sleep Apnea	Polysomnography		-
Behavioral Sleep Problems	Actigraphy CSHQ	Daily sleep log BEDS SDSC	-
Adaptive behavior	VABS-II	SIB-R	ABAS 3
Maladaptive behavior	-	ABC BPI-01 Childhood Routines Inventory Conners DBC NCBRF Restricted Behavior Problem Checklist RBS-R SIB-R problem behavior Vanderbilt ADHD VABS-II maladaptive behavior	BASC-3 CBCL

[^]Self-Report option available

ABAS 3 = Adaptive Behavior Assessment System; ABC = Aberrant Behavior Checklist; ADAMS = Anxiety Depression and Mood Scale; ADAS-Cog = Alzheimer's Disease Assessment Scale – Cognition; ADD = Assessment of Dual Diagnosis; BASC-3 = Behavioral and Emotional Screening System – Third edition; BEDS = Behavioral Evaluation of Disorders of Sleep; BFCS = Bush-Francis Catatonia

Am J Intellect Dev Disabil. Author manuscript; available in PMC 2018 May 01.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Scales; BPI-01 = Behavior Problems Inventory; BPRS = Brief Psychiatric Rating Scale; BRIEF = Behavior Rating Inventory of Executive Function; CANTAB = Cambridge Neuropsychological Test Automated Battery; CBC = Compulsive Behavior Checklist; CBCL = Child Behavior Checklist; CCC-2 = Children's Communication Checklist – Second Edition; CDI = MacArthur-Bates Communicative Development Inventories; CELF-5 = Clinical Evaluation of Language Fundamentals – Fifth Edition; CELF-P2 = CELF Preschool – Second edition; CMS = Children's Memory Scale; CSHQ = Children's Sleep Habits Questionnaire; CYBOCS-PDD = Children's Yale-Brown Obsessive Compulsive Scale – Modified for PDD; DABS = Diagnostic Adaptive Behavior Scale; DAS-II = Differential Ability Scales – Second Edition; DASH-II = Diagnostic Assessment for the Severely Handicapped – Second Edition; DBC = Developmental Behaviour Checklist; EVT-2 = Expressive Vocabulary Test – Second Edition; GDS = Glasgow Depression Scales; GFTA-3 = Goldman-Fristoe Test of Articulation – Third Edition; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children; Leiter 3 = Leiter International Performance Scale – Third Edition; MOSES = Monitoring of Side Effects Scale; NCBRF = Nisonger Child Behavior Rating Form; NCS = Northoff Catatonia Scales; NIMH-DISC-IV = NIMH Diagnostic Interview Schedule for Children – Fourth Edition; NPI = Neuropsychiatric Inventory for Dementia; OMQ = Observer Memory Questionnaire; PANSS = Positive and Negative Syndrome Scale; PAS-ADD = Psychiatric Assessment Schedule for Adults with Developmental Disabilities; PIMRA = Psychopathology Inventory for Mentally Retarded Adults; PPVT-4 = Peabody Picture Vocabulary Test – Fourth Edition; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RBS-R = Repetitive Behavior Scale—Revised; SANS = Scale for Assessment of Negative Symptoms; SDSC = Sleep Disturbances Scale for Children; SIB-R = Scales of Independent Behavior, Revised; SB5 = Stanford-Binet – Fifth Edition; SRS-2 = Social Responsiveness Scale – Second Edition; TEA = Test of Everday Attention; TEA-Ch = Test of Everday Attention for Children; TROG-2 = Test for Reception of Grammar – Second Edition; VABS-II = Vineland Adaptive Behavior Scale – Second Edition; WISC-5 = Wechsler Intelligence Scale for Children – 5th Edition; WJ IV = Woodcock-Johnson IV Tests of Cognitive Abilities; WRAML-2 = Wide Range Assessment of Memory and Learning – Second Edition

Am J Intellect Dev Disabil. Author manuscript; available in PMC 2018 May 01.

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Table 2

Measures that have been used among individuals with DS and judged to be 'appropriate' for the assessment of mild cognitive impairment and Alzheimer's disease or 'promising but needs more assessment'.

	Appropriate for DS	Promising; But Need More Assessment
Dementia Status		
Caregiver report	Dementia Screening Questionnaire for Individuals with Intellectual Disabilities Dementia Questionnaire for Learning Disabilities (previously: Dementia Questionnaire for Mentally Retarded Persons) Dementia Scale for Down syndrome	National Task Group Early Detection Screen for Dementia
Caregiver report and Direct assessment	Adaptive Behavior Dementia Questionnaire	Cambridge Examination for Mental Disorders of Older People with Down's syndrome and Others with Intellectual Disorder
Mental Status		
Direct assessment	Modified Haxby Down Syndrome Mental Status Examination [a] Modified Mini Mental State Examination[a] Severe Impairment Battery [a]	Brief Praxis test Test for Severe Impairment
Memory/Learning		
Direct assessment	Corsi Block-Tapping Forward Cued Recall Test [a] Modified Selective Reminding Task [a] Rapid Assessment for Developmental Disabilities[a] Rivermead Behavioural Memory Test for Children - Picture Recognition and Story Recall subtests [a] WISC Coding [a] WISC Digit Span Forward	Alzheimer's Disease Assessment Scale-Cognition Cambridge Neuropsychological Test Automated Battery Wechsler Memory scales
Visuospatial construction		
Direct assessment	Beery Buktenica Developmental Test of Visual Motor Integration Haxby Block Design WISC Block Design [a]	-
Executive processing		
Direct assessment	Cat and Dog Stroop tests [a] Corsi Block-Taping Backward [a] NEPSY Visual Attention Subtest Scrambled Boxes [a] Selective Attention Cancellation Task[a] WISC Digit Span Backward [a] Verbal Fluency tasks [a]	Cambridge Neuropsychological Test Automated Battery NIH Toolbox Dimensional Change Card Sort NIH Toolbox Flanker Inhibitory Control and Attention Test Tower of London Weigl Sorting Test

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	Appropriate for DS	Promising; But Need More Assessment
Caregiver report		BRIEF
Psychiatric symptoms/Behavior problems		
Caregiver report	Reiss Screen for Maladaptive Behaviors	Columbia University Scale for Psychopathology in Alzheimer's disease Neuropsychiatric Inventory
Clinical interview/ Direct assessment	-	Psychiatric Assessment Schedules for Adults with Developmental Disabilities Psychopathology Instrument for Mentally Retarded Adults
Language		
Direct assessment	Boston Naming Test [a] British Picture Vocabulary Scale Categorical Fluency [a] Expressive-One Word Picture Vocabulary Test [a] NEPSY Word Generation Semantic Fluency Subtest [a] Peabody Picture Vocabulary Test	Controlled Oral Word Association Test Rey Auditory Verbal Learning Task
Adaptive behavior		
Caregiver report	Adaptive Behaviour Dementia Questionnaire Vineland Adaptive Behavior Scales	Activities of Daily Living Schedule Adaptive Behavior Assessment System Bristol Activities of Daily Living Scale Daily Living Skills Questionnaire Deficiency Adaptive Behavior Scale
Motor performance		
Direct assessment	-	NIH Toolbox motor measure Purdue Pegboard Tinetti gate test

[a] = may not be appropriate for adults with low baseline language and cognitive functioning. AD = Alzheimer's disease; DS = Down syndrome; IDD = Intellectual and developmental disabilities.

This table reviews measures that the task force felt were most appropriate and promising, but does not provide an exhaustive list of all measures that have been published on.

Citation for measures not reviewed in text: American Association on Mental Deficiency Adaptive Behavior Scale (Nihira, Foster, Shellhaas, & Leland, 1974), Beery Buktenica Developmental Test of Visual Motor Integration (Beery, 2004), Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2001), Brief Praxis Test (Dalton & Crapper-McLachlan, 1986), British Picture Vocabulary Scale (Dunn, Dunn, Styles, & Sewell, 2009), Cambridge Cognitive Examination (Ball et al., 2004), Cambridge Neuropsychological Test Automated Battery (Robbins et al., 1994), Cat and Dog Stroop (modified Day-Night Stroop) (Gerstadt, Hong, & Diamond, 1994), Columbia University Scale for Psychopathology in Alzheimer's disease (Devanand et al., 1992), Controlled Oral Word Association Test (Lezak, Howieson, Loring, Hannay, & Fischer, 2004), Corsi Blocks (Milner, 1971), Dimensional Change Card Sort (Frye, Zelazo, & Palfai, 1995), Expressive-One Word Picture Vocabulary Test (Martin & Brownell, 2010), Haxby Block Design (Haxby, 1989), NEPSY Visual Attention (Korkman et al., 2007), NEPSY Word Generation Semantic Fluency Subtest (Korkman et al., 2007), Neuropsychiatric Inventory (Cummings et al., 1994), Peabody Picture Vocabulary Test (Dunn & Dunn, 2007), Pegboard (E. Strauss, Sherman, & Spreen, 2006), Psychiatric Assessment Schedules for Adults with Developmental Disabilities (Moss et al., 1998), Rey Auditory Verbal Learning Task (Schmidt, 1996), Rivermead Behavioural Memory Test for Children (Wilson, Ivani-Chalian, & Aldrich, 1991), Scrambled Boxes (H. Strauss & Lewin, 1982), Selective Attention Cancellation Task (Krinsky-McHale et al., 2008), Test for Severe Impairment (Albert & Cohen, 1992), Weigl Sorting (H. Strauss & Lewin, 1982), Tower of London (Krikorian, Bartok, & Gay, 1994), WISC Block designs (Wechsler, 2004), WISC Coding (Wechsler, 2004), WISC Digit Span (Wechsler, 2004), Wechsler Memory Scales (Wechsler, 2009).

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