

Critical Evaluation of Vineland™-II and Vineland™-3 as Outcome Measures for ASD Clinical Trials

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Objectives

- Identification of reliable and valid measures of social communication challenges that are sensitive to change is critical for assessing the efficacy of new behavioural and pharmaceutical interventions for autism spectrum disorder (ASD)
- The aim of this research was to evaluate the Vineland Adaptive Behavior Scales, 2nd Edition (Vineland™-II) and Vineland™-3 Adaptive Behavior Scales as outcome measures for ASD clinical trials

Methods

- To support decision-making around the selection of tools for future clinical research, we reviewed the content, outputs and other clinical study data available for Vineland™-II and Vineland™-3 and evaluated the advantages and disadvantages of each with respect to provision of valid and sensitive measures of social communication in ASD

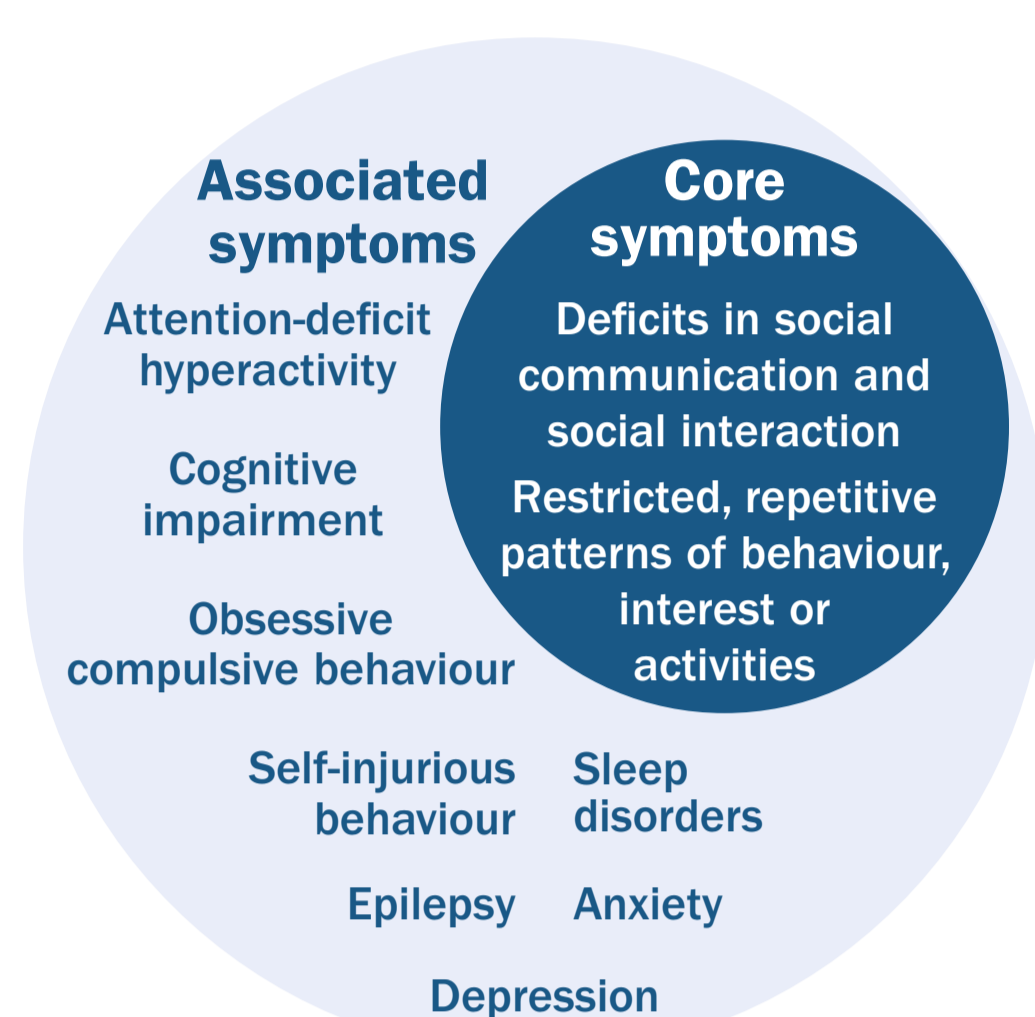
Conclusions

- **Vineland™-II, Vineland™-II 2-Domain Composite (2DC; a composite of the socialization and communication domains of Vineland™-II) and Vineland™-3 appear to be fit-for-purpose measures for assessing social communication in ASD**
 - **Vineland™-3, along with Vineland™-II and Vineland™-II 2DC, has shown good to excellent reliability and strong validity**
- **While Vineland™-3 is an updated and potentially improved scale, the absence of large-scale validation and evidence of sensitivity to change in ASD populations indicate that Vineland™-II is still a valuable measure for clinical development programmes**

Background

Social Communication Challenges Are Part of the Core Symptoms of ASD

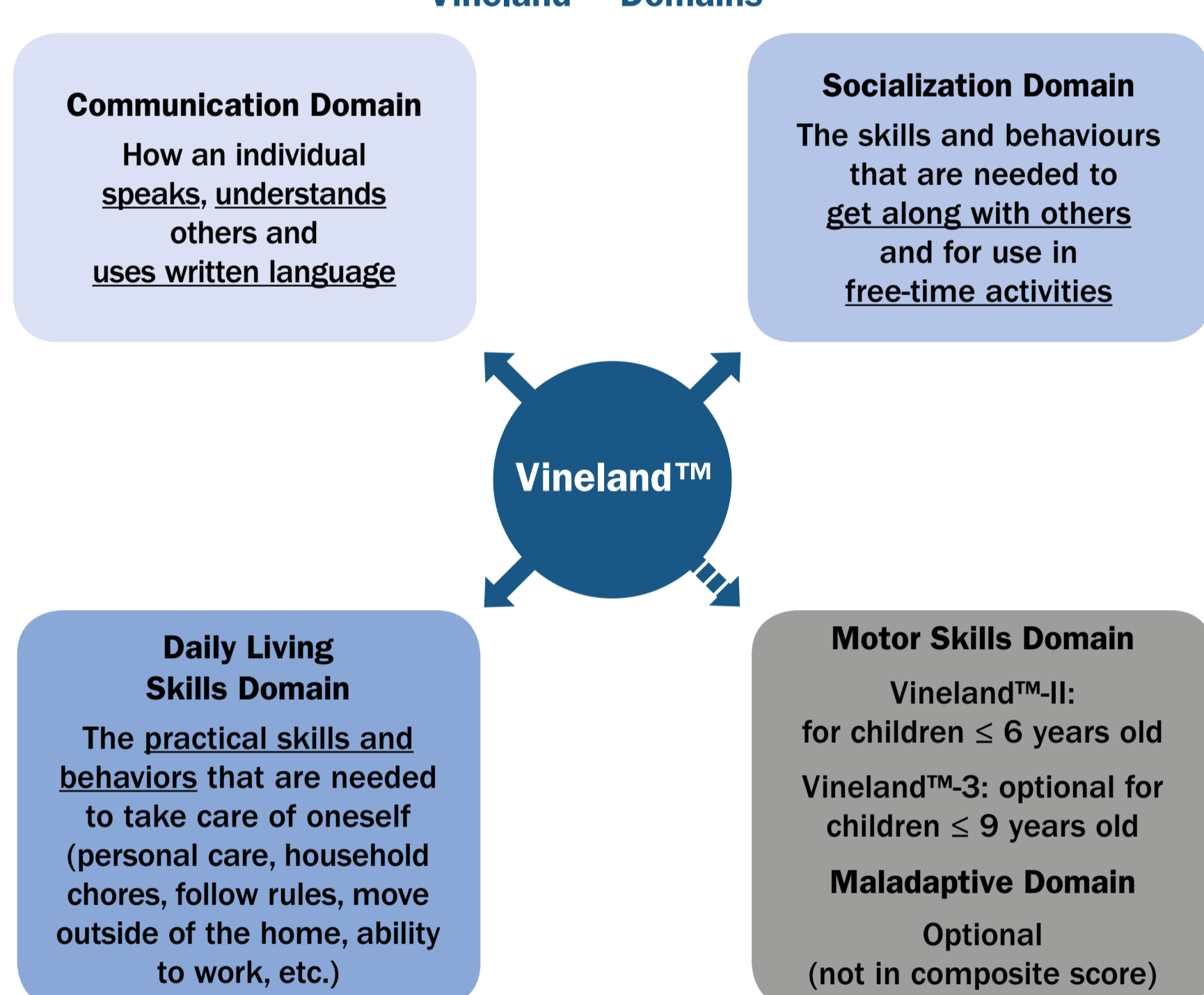
Core and Associated Symptoms of ASD



- ASD is a complex, heterogeneous neurodevelopmental disorder characterized by impairments in social communication and interaction, as well as repetitive behaviours and restricted interests¹
- Adaptive functioning, including social communication abilities, is an important factor in predicting long-term outcomes for people with ASD^{2,3} and therefore improving adaptive abilities is a desirable treatment goal

The Vineland™ Adaptive Behaviour Scales Are Designed to Measure Adaptive Behaviour Ability in Daily Settings From Birth Through Adulthood

Vineland™ Domains^{5,6}



- Both Vineland™-II and Vineland™-3 measure **adaptive behaviour**: skills that people need to function independently at home, at school and in the community^{5,6}
- They include three core domains of adaptive behaviour: communication, socialization and daily living skills^{5,6}
- Importantly, both scores measure adaptive behaviour abilities rather than deficits

- Vineland™-II is one of six measures of social communication recommended by an expert panel engaged by Autism Speaks to assess measures for their utility in ASD clinical trials⁴
- Vineland™-II has been used in multiple clinical trials, including those evaluating balovaptan (e.g. VANILLA [NCT01793441], V1aduct [NCT03504917] and aV1ation [NCT02901431])
- A Vineland™-II 2DC score comprising the communication and socialization domains of Vineland™-II is also being used as a primary endpoint in balovaptan clinical trials (V1aduct [NCT03504917] and aV1ation [NCT02901431])
- Vineland™-3 is an updated version of the scale that has recently been used in some ASD trials, including the ongoing arbaclofen trial (NCT03682978)
- Vineland™-3 has updated content that reflects changes in skills related to everyday life (e.g. new technologies such as smartphones), and updated norms capturing changes in population-level adaptive behaviour skills⁶

Results

Vineland™-II and Vineland™-3 Have Good to Excellent Reliability

- Vineland™-II and Vineland™-3 have similar, good to excellent reliability across several methods of evaluation^{5,6}
- Vineland™-II 2DC also has good test-retest reliability (0.83)⁷

Reliability Across Vineland™ Scores

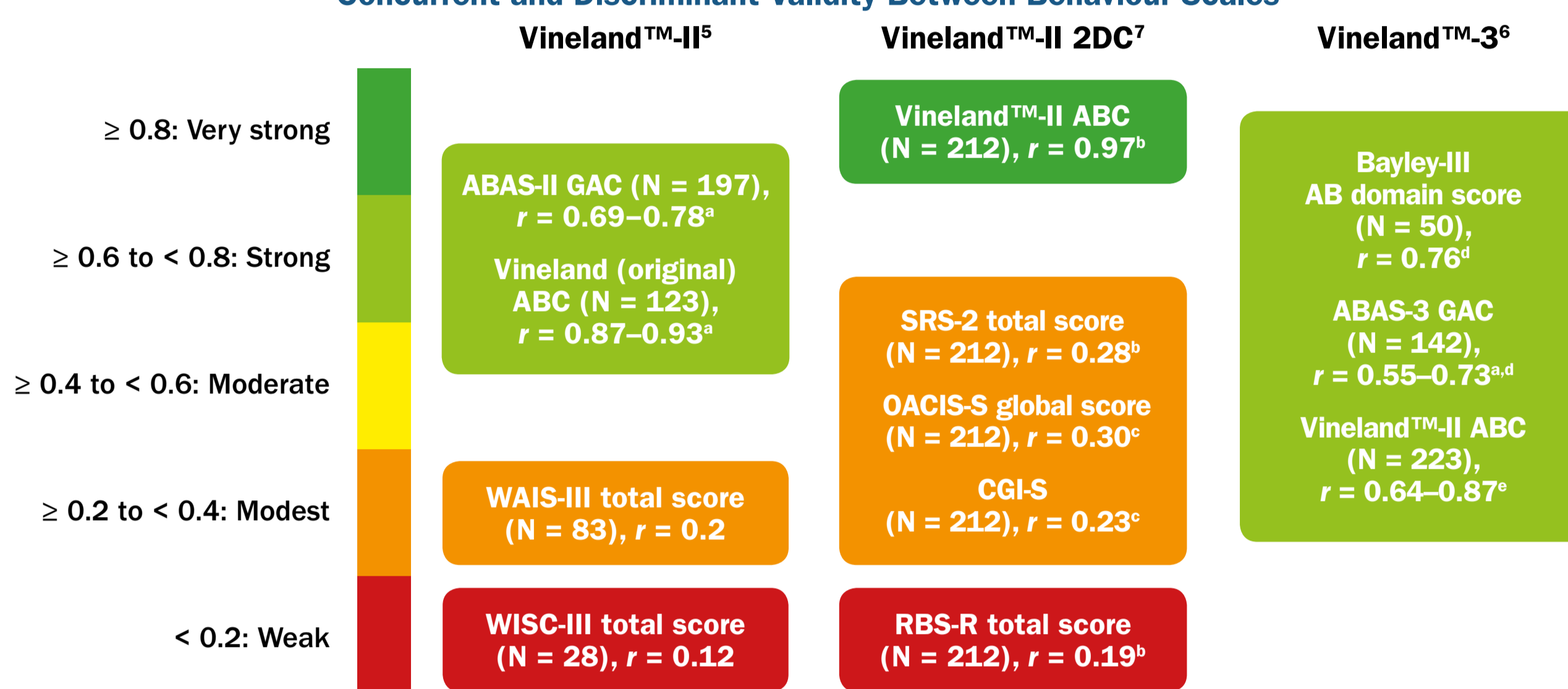
	Vineland™-II ⁵	Vineland™-3 ⁶
Internal consistency		
ABC score	0.93–0.97 ^b	0.98
Across domains ^a	0.77–0.93 ^b	0.90–0.96
Test-retest reliability		
ABC score	0.83–0.96 (N = 414) ^{b,c}	0.80–0.92 (N = 248) ^{b,e}
Across domains ^a	0.74–0.96 (N = 414) ^{b,d}	0.73–0.92 (N = 248) ^{b,e}
Inter-interviewer reliability		
ABC score	0.78 (N = 112)	0.79 (N = 96)
Across domains ^a	0.68–0.80 (N = 112)	0.70–0.81 (N = 96)
Inter-rater reliability		
ABC score	0.82 (N = 152)	0.69–0.87 ^b (N = 148)
Across domains ^a	0.71–0.83 (N = 152)	0.67–0.85 ^b (N = 148)

^a Excludes maladaptive behaviour domains. ^b Across age groups. ^c 0.83 for Vineland™-II 2DC based on socialization and communication domains only and assessed at 84 days post first administration. ^d Assessed between 13 and 34 days from the first administration. ^e Assessed within 12 to 35 days of each other. ABC, Adaptive Behavior Composite.

Vineland™-II, Vineland™-II 2DC and Vineland™-3 Have Demonstrated Strong Validity With Other Concurrent Measures

- Vineland™-II and Vineland™-3 correlated strongly with each other and other behavioural measures, including Adaptive Behavior Assessment System-II/-3 (ABAS-II/-3) and Bayley-III^{5,6}
- For Vineland™-II and Vineland™-II 2DC, only modest/weak correlations were observed with scales that measure different attributes, such as intelligence quotient (IQ) and repetitive behaviours^{6,7}

Concurrent and Discriminant Validity Between Behaviour Scales



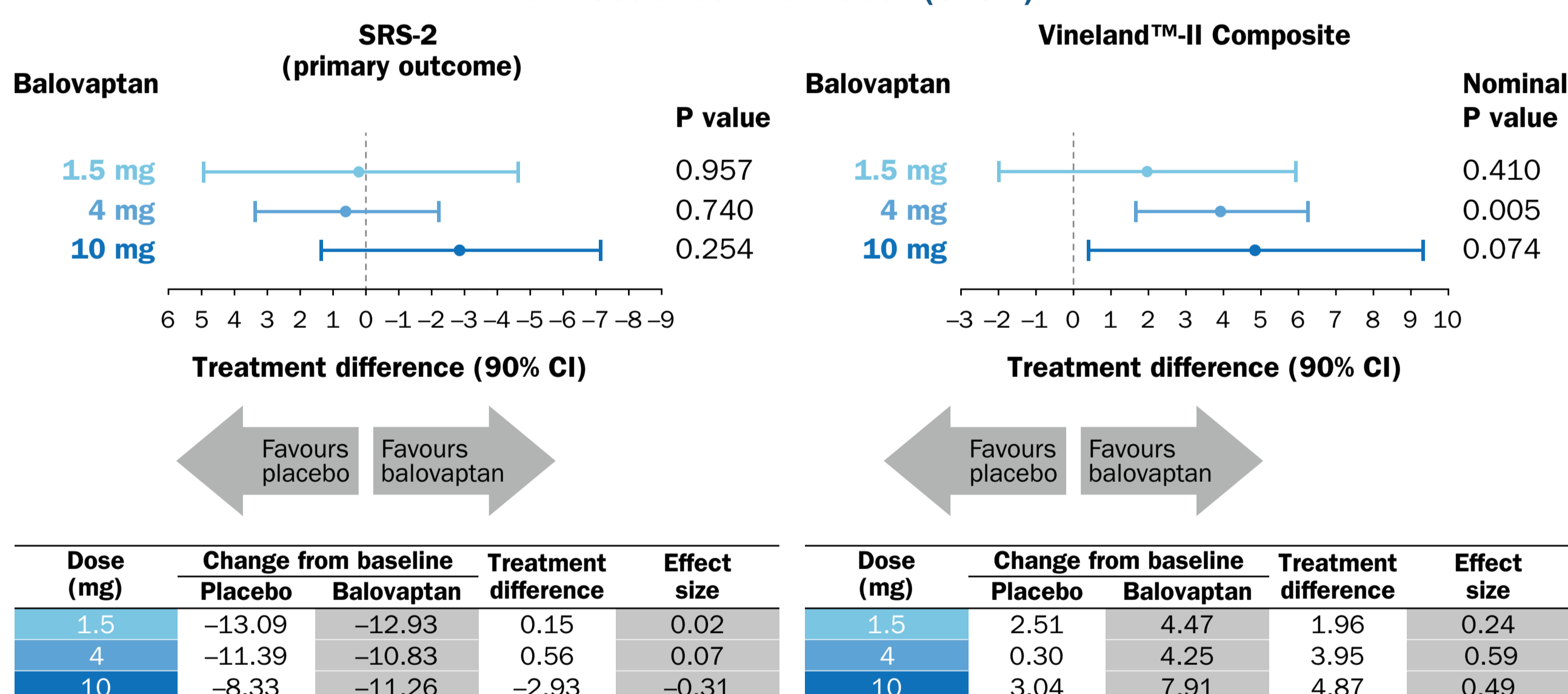
^a Across age groups. ^b Pearson's rank correlation coefficient. ^c Spearman rank correlation coefficient. ^d Correlation with ABC score of the parent/caregiver comprehensive forms. ^e Correlation across domains and ABC scores of the interview form. AB, adaptive behaviour; ABAS, Adaptive Behavior Assessment System; Bayley, Bayley Scales of Infant and Toddler Development; CGI-S, Clinical Global Impression-Severity; GAC, General Adaptive Composite; OACIS-S, Ohio Autism Clinical Impressions Scale-Severity; RBS-R, Repetitive Behaviors Scale-Revised; SRS-2, Social Responsiveness Scale, 2nd Edition; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale for Children.

Vineland™-II and Vineland™-II 2DC Have Been Shown to Be Sensitive to Detecting Changes in Symptoms in Clinical Trials

- The original Vineland™ score has been demonstrated to be sensitive to changes in adaptive behaviours in children with ASD treated with risperidone^{8,9} and the Early Start Denver Model¹⁰
- However, large-scale data on the psychometric properties of Vineland™-3 in ASD trials are pending

- In VANILLA, a phase 2 study of balovaptan in adult men with ASD and IQ ≥ 70 , Vineland™-II was shown to be sensitive to detecting changes in symptoms, while being less prone than other measures, including SRS-2, to placebo effects¹¹
- Using the same data set, Vineland™-II 2DC has also been shown to be sensitive to change, with a mean treatment difference of 4.57 (nominal P value < 0.05) between individuals achieving 'minimally improved or better' or 'no change or worse' on the Clinical Global Impression-Improvement (CGI-I) score⁷

VANILLA: Changes From Baseline at Week 12 in Adapted Behaviour (Vineland™-II) and Social Communication (SRS-2)¹¹



MCIDs Have Been Determined for Vineland™-II Enabling Researchers to Interpret the Clinical Significance of Results; However, MCID Estimates for Vineland™-3 Have not yet Been Determined

- Using Vineland™-II scores of 9067 individuals with ASD collated from several consortia and registries, a recent study estimated the minimum clinically important difference (MCID) for the composite score and domains using distribution and anchor-based methods¹²
 - For the composite score, anchor-based estimates ranged from 2.44 to 3.76 and distribution-based estimates correlated well with these
 - In general, the weighted MCID estimates tended to increase with IQ (Wilcoxon signed-rank test P < 0.0001), with scores ranging from 2.4 to 2.8 in those with IQ < 70 and from 2.9 to 3.8 in those with IQ ≥ 70
 - MCID estimates also tended to increase with age (Wilcoxon signed-rank test P = 0.02), with scores in children aged 0 to 13 years ranging from 2.5 to 2.9 and scores in adults ranging from 2.8 to 3.8

In the VANILLA trial, the balovaptan 4 mg and 10 mg dose treatment groups exceeded MCID thresholds with mean improvements from baseline of 4.25 and 7.91, respectively (estimated MCID in this population = 3.4–3.8)^{11,12}

- MCID estimates for Vineland™-3 have not been determined

Practical Considerations for the Use of Vineland™ Measures

Comparison of Practical Considerations for the Use of Vineland™ Measures

	Vineland™-II ⁵	Vineland™-3 ⁶
Clinician-administered interview form	✓	✓
Parent/caregiver self-report form	✓	✓ Language simplified in this version
Teacher rating form	✓	✓
Time for completion of clinician-administered interview	20–60 minutes	20–50 minutes (shorter domain-level forms are also available)
Domain-level forms available	✗	✓
Languages	Available in 27 languages ¹³	Validated in English and Spanish
Online version available	✗	✓

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