

Composite Score Selection in Pre-AD

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Abstract

- Small decline in standard scales – some items do not change
- Companies are creating composites from existing items – ADAS-cog, CDR-sb, MMSE – to improve sensitivity to change
- Method: Identify item combinations sensitive to change over time or conversion to AD or both -- with optimal weighting
- Best combinations include ADAS-cog, MMSE and CDR items; NTB and ADL items are excluded
- New combination score improves sensitivity, reducing the required sample sizes by 41% in MCI and 31% in CSF ABeta positive patients over CDR-sb and by 89% and 91% over ADAS-cog*

* NOTE: Enriched is only available for ADNI which had great sensitivity for CDR-sb and not for ADAS-cog (opposite of ADCS study)

Criteria for Evaluating Composites

- Responsiveness to Progression (MSDR or CV)
- Responsiveness / Sensitivity to Treatment Effects
- Cross-validated with multiple data sets & resampling or bootstrapping

Comparison of Results Using Time and Diagnosis

			Time Only	Diagnosis Only	Time + Diagnosis
Scale	Item	score	11 items	14 items	11 items
ADAS-cog	Word Recall	10	5.5%	5.2%	6.0%
	Delayed Word Recall	10	5.5%	3.7%	5.0%
	Orientation	8	6.4%	6.2%	7.1%
	Word Recognition	12		2.1%	
	Word Finding Comprehension	5	4.4%		
		5		6.1%	
MMSE	Orientation Time	5	8.2%	5.5%	7.4%
	Orientation Place	5		4.0%	
	Attention	5		3.6%	3.3%
	Constructional Praxis	1			
CDR-sb	Personal Care	3	6.5%	7.3%	7.9%
	Community Affairs	3	16.1%	10.9%	14.5%
	Home and Hobbies	3	13.0%	9.9%	12.4%
	Judgment /Problem Solving	3	10.4%	11.8%	12.7%
	Memory	3	11.6%	14.1%	14.9%
	Orientation	3	12.4%	9.6%	12.0%
MSDR in Pooled MCI sample (unadjusted)			0.5391	0.4875	0.5134

- Items selected using time are similar to items selected with diagnosis. Combination of time and diagnosis may be best.
- Although MSDR is lower for diagnosis, bias may also be smaller

MSDR for Each Item Set

Combination	Mean to Standard Deviation Ratio			
	MCI (ADNI and ADCS)	Prodromal AD (CSF+)	MCI APOE4+	Mild (3 studies)
ADAS-cog & MMSE	0.4709	0.6731	0.6188	0.6845
ADAS-cog, MMSE & NTB	0.4807	0.7006	0.6445	0.6845
CDR & ADL	0.5123	0.7704	0.6370	0.8241
ADAS-cog, MMSE & CDR	0.5391	0.8749	0.6948	0.8227
ADAS-cog, MMSE, NTB, CDR & ADL	0.5632	0.8535	0.7260	0.9083

Best Combination: Items and Relative Contributions

Test	Item	Percentage
ADAS-cog	Word Recall	5.3%
ADAS-cog	Delayed Word Recall	5.3%
ADAS-cog	Orientation	6.2%
ADAS-cog	Word Finding Difficulty	4.3%
MMSE	Orientation	11.1%
CDR-sb	Personal Care	6.2%
CDR-sb	Community Affairs	15.6%
CDR-sb	Home and Hobbies	12.6%
CDR-sb	Judgment and Problem Solving	10.0%
CDR-sb	Memory	11.3%
CDR-sb	Orientation	12.0%
Total		100.0%

MSDR for this combination is 0.539 in MCI and 0.875 in MCI CSFAB+

Sample Sizes Per Arm -MCI over 12 months 80% power, alpha=0.05

25% effect	Overall MCI	CSF AB+	APOEe4+
ADAScog	7971	3608	4152
CDRsb	1464	477	729
Composite	866	329	522

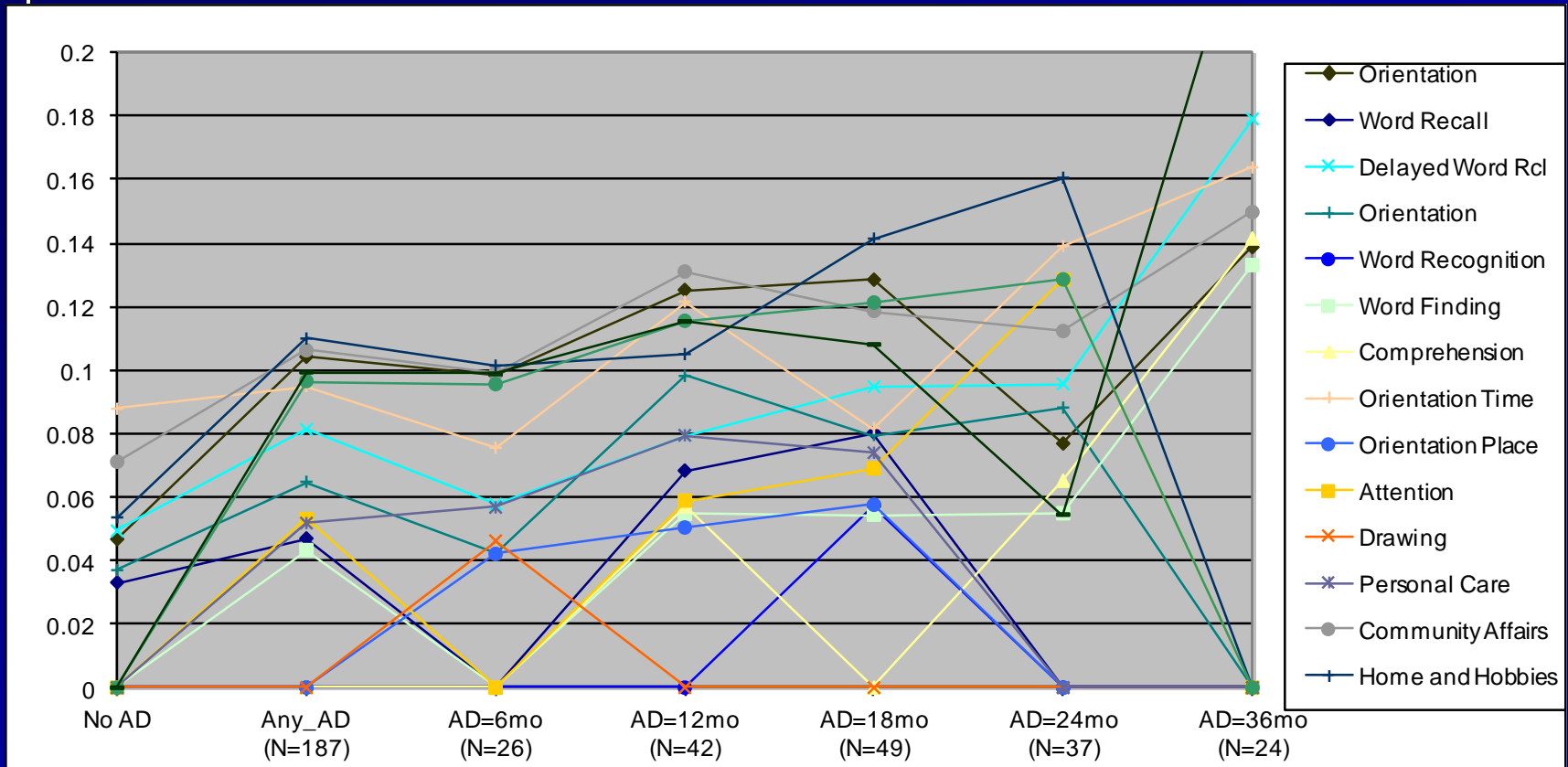
50% effect	Overall MCI	CSF AB+	APOEe4+
ADAScog	1993	902	1038
CDRsb	366	120	183
Composite	217	83	131

- 41% improvement compared to CDR-SB in non-enriched MCI population
- 31% improvement compared to CDR-SB in enriched (CSF A β 42+) MCI population

Responsiveness to Treatment Effect

		T-Statistic (p-value) for Comparison vs Placebo			
Study	Treatment	ADAS-cog	CDR-sb	MMSE	Composite
ADCS-MCI	10 mg Donepezil	-1.70 (0.0893)	-1.71 (0.0911)	-2.46* (0.0145)	-2.43* (0.0153)
	2000 IU Vitamin E	-0.98 (0.3320)	-0.53 (0.6182)	-0.50 (0.6107)	-0.24 (0.8103)

Item Contribution by Time to AD Diagnosis



■ CDR-sb items and cognitive items show a different pattern

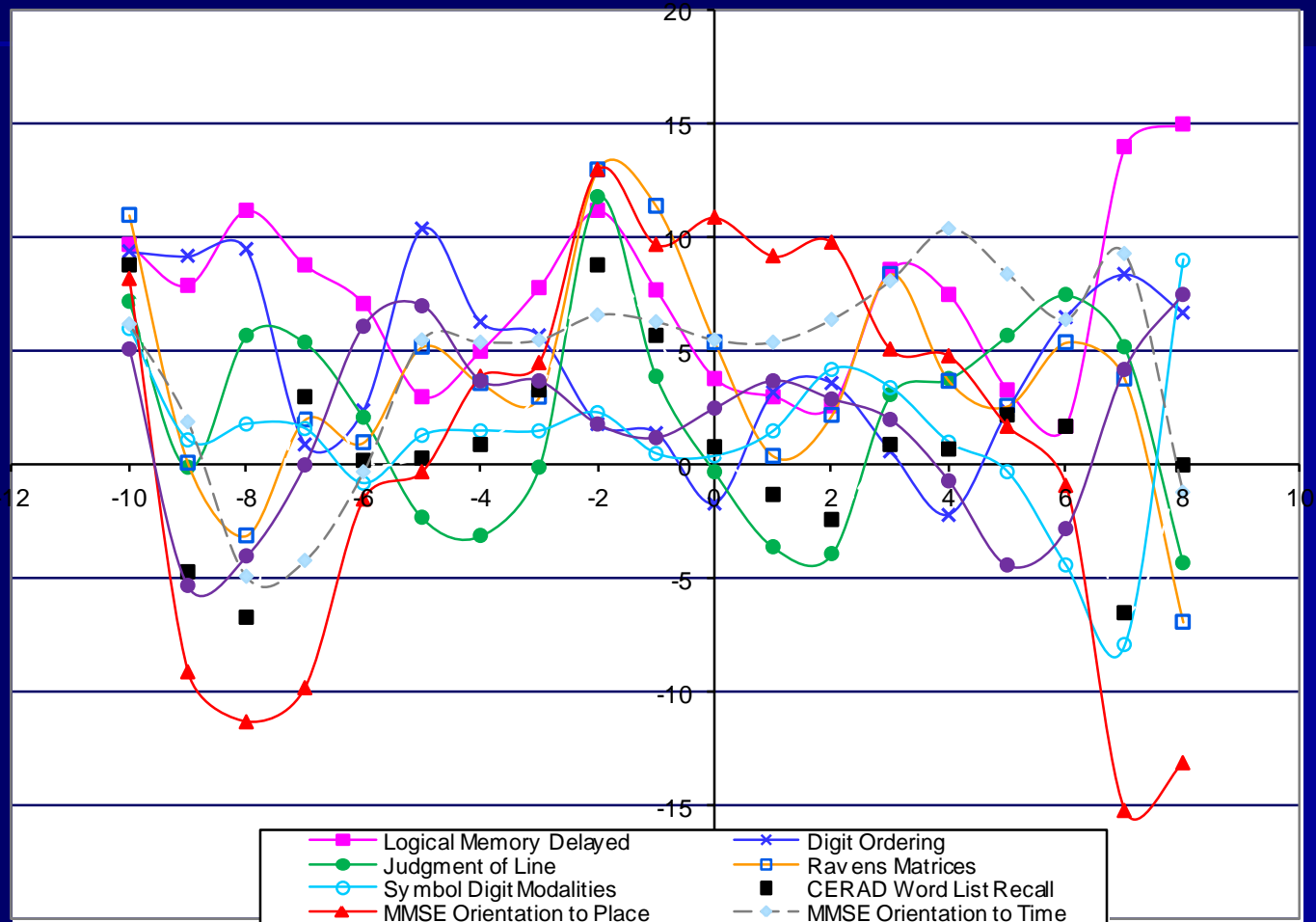
Use of Composite

- Composite needs validation for use as a primary endpoint in a pivotal study
- Composite could be used for internal decision making at the end of phase 2 (go/no go decision)
- If validated, composite could be used as co-primary with biomarker for a pivotal study

Summary and Conclusions

- A composite score from ADAS-cog, MMSE, & CDR-sb items improves sensitivity over standard scores
- Composite is sensitive to treatment effects
- Cross-validation results show minimal bias but additional datasets would help

Rush Data – API Composite



Preliminary Results – Subject to Changes