Strategies for assessing cognition in clinical trials for non-CNS disorders

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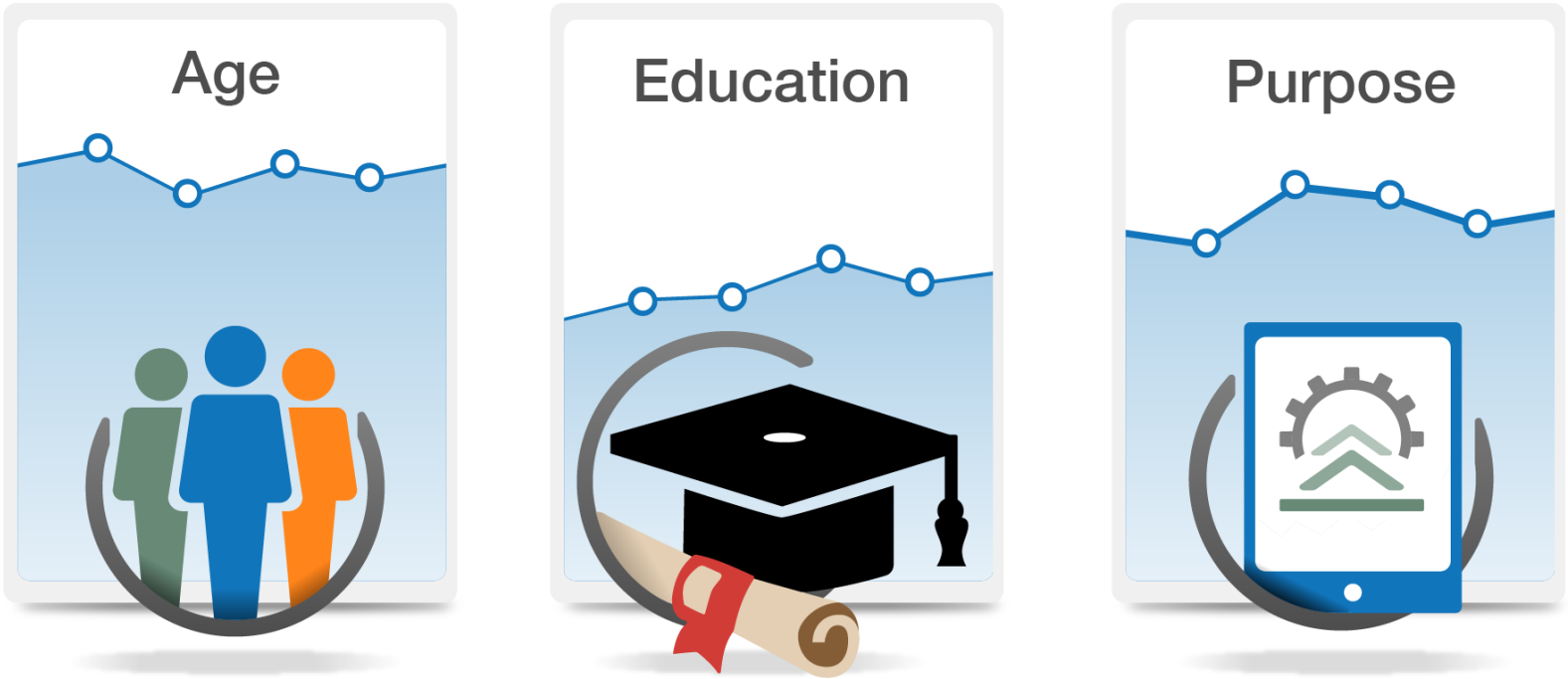
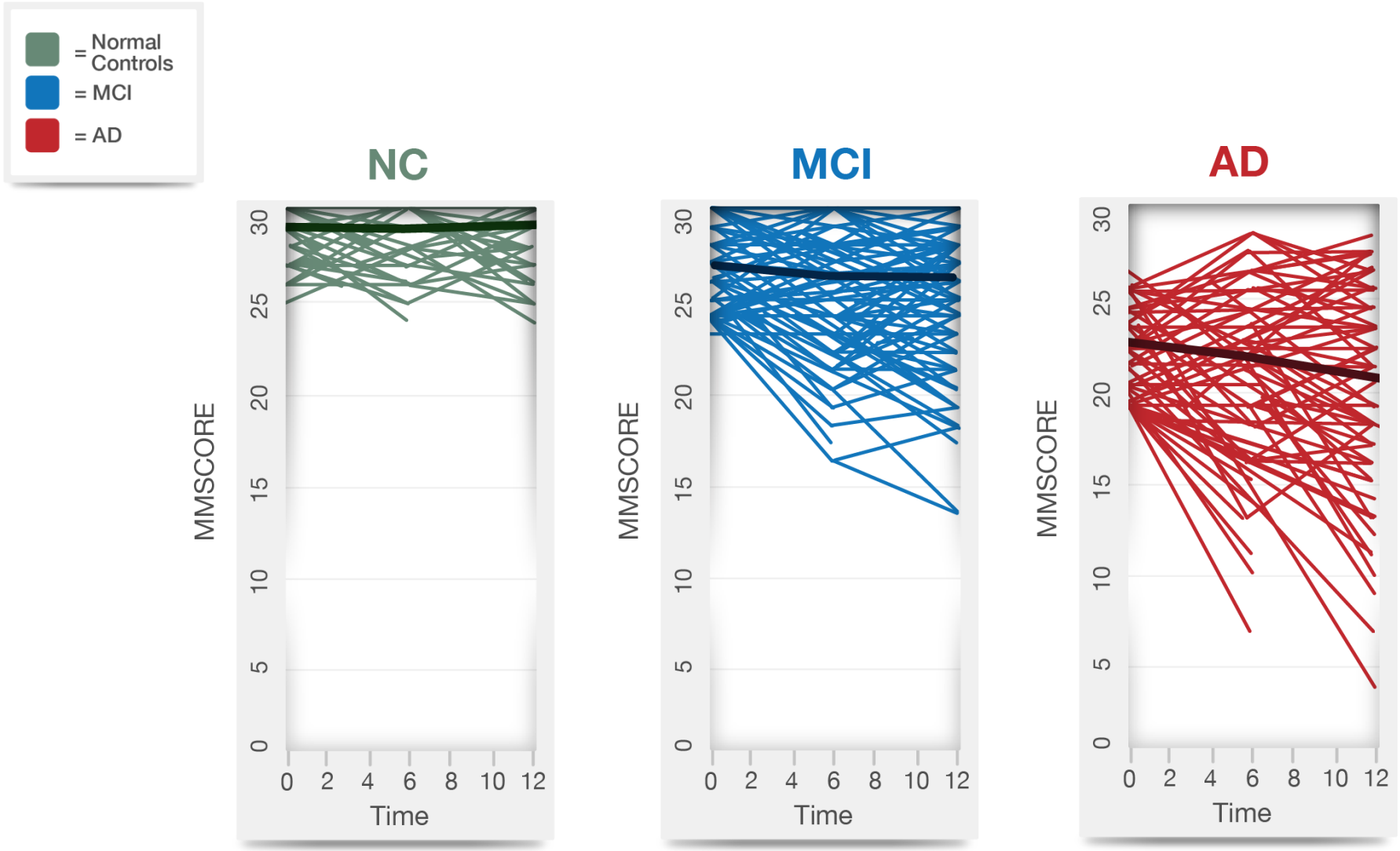
Overview

The proper methods for assessing cognition can vary considerably across diagnostic entities, age, education, and purpose.

The use of the MMSE for even significant cognitive disorders such as MCI and schizophrenia is inappropriate due to the lack of sensitivity at the high end of the scale

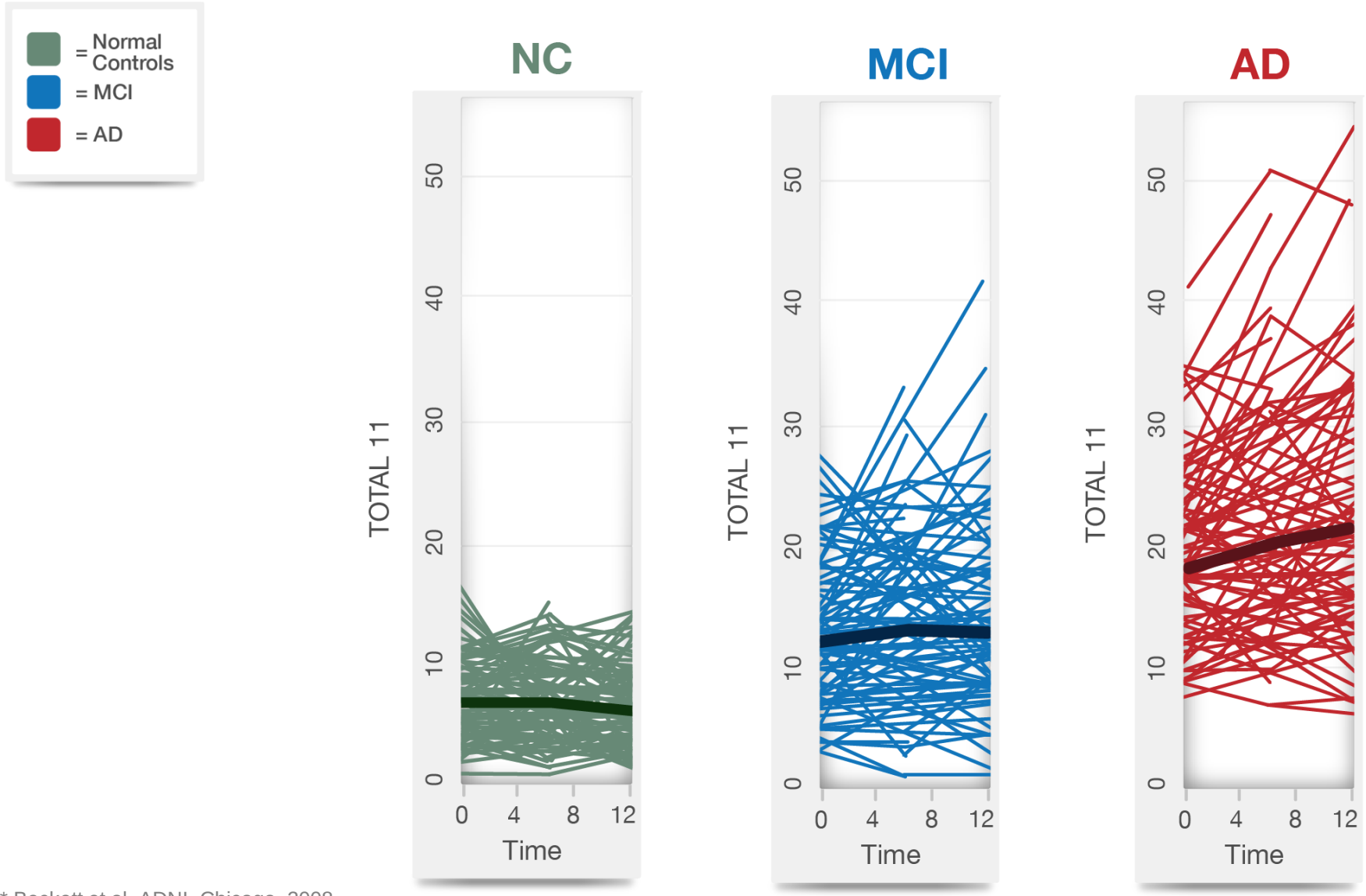


Ceiling Effects: 12-Month Changes in MMSE



* Beckett et al, ADNI, Chicago, 2008

Ceiling Effects: 12-Month Changes in ADAS-Cog



* Beckett et al, ADNI, Chicago, 2008

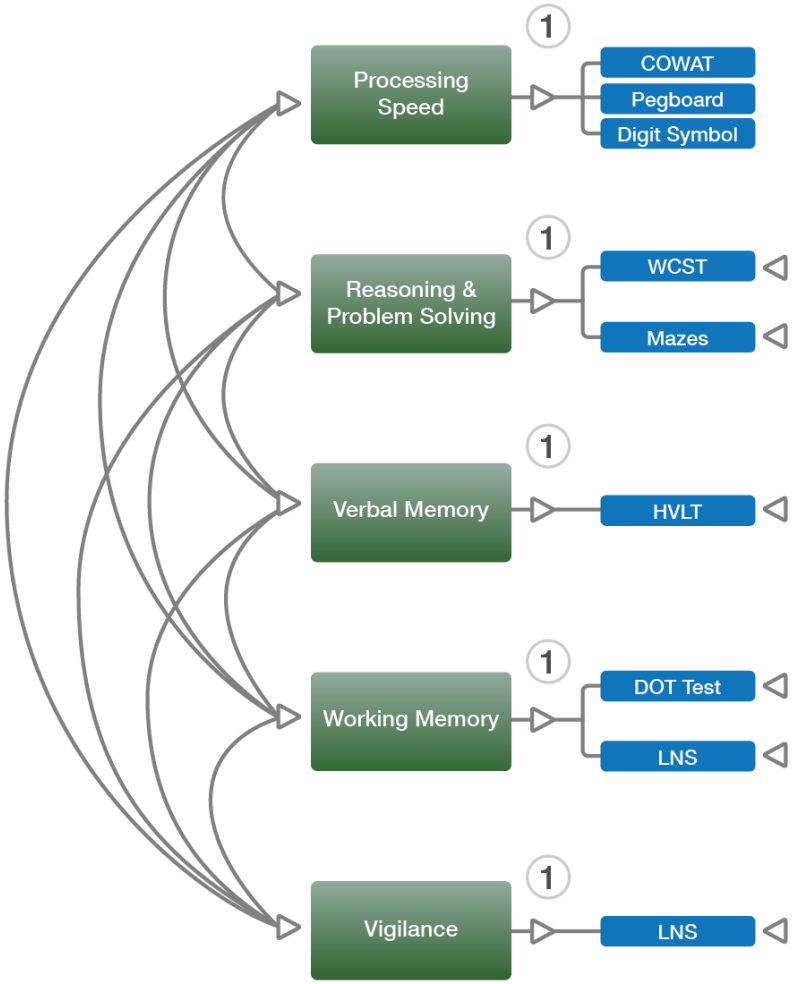
Applying CNS Tests to non-CNS disorders

The proper test battery for a clinical trial in cancer or cardiac disease must have tests that have sensitivity in the appropriate ranges of difficulty

General cognitive impairment, which is driven by a single factor, “g”, is assessed similarly across various conditions and circumstances.

Hippocampal Sclerosis

Structural Equation Modeling Analyses on CATIE Baseline Data (N=1331)



- Null model failed to fit the data
- A unifactorial model based on the nine tests was an improvement in fit; 2(27)=192.18, p<0.001; CFI=.94, GFI=.97, RMSEA=.077
- A unifactorial model including the five pre-defined domain scores was a considerable improvement in fit over the unifactorial model from the nine tests (2 (22)= 152.27, p<.001; CFI=.98, GFI=.97; RMSEA=.080 .
- A five-factor model that included the tests from each of the five cognitive domains as separate factors was a significantly poorer fit compared to the unifactorial model from the five pre-defined domain scores 2(14)=78.04, p<.001.

Keefe et al, Neuropsychopharmacology, 2006

Stepwise Multiple Regression Predicting Unweighted Mean of Variables

Variable Entry Based On Administration Time	Total R2	Change Est.	Time
WAIS-R Digit Symbol	.610	.610	3.1
HVLT Verbal Memory	.722	.112	4.1
Grooved Pegboard	.790	.068	5.0
U. Maryland LN Seq	.868	.078	5.98
Verbal Fluency	.889	.021	8.0
WISC-R Mazes	.935	.046	11.2
CPT-IP	.957	.022	13.4
Visuospatial WM Test	.978	.022	16.2
WCST-64	1.000	.022	more

F-statistic for all steps was greater than 193.0; all P-values <.0001; N=1035
WAIS-R=Wechsler Adult Intelligence Test, Revised; HVLT=Hopkins Verbal Learning Test; WISC-III=Wechsler Intelligence Test for Children, 3rd ed; WCST=Wisconsin Card Sorting Test

Test Batteries in Non-CNS Clinical Trials

- All batteries test cognition in general, with no specific cognitive domain or test standing out as pathognomonic:

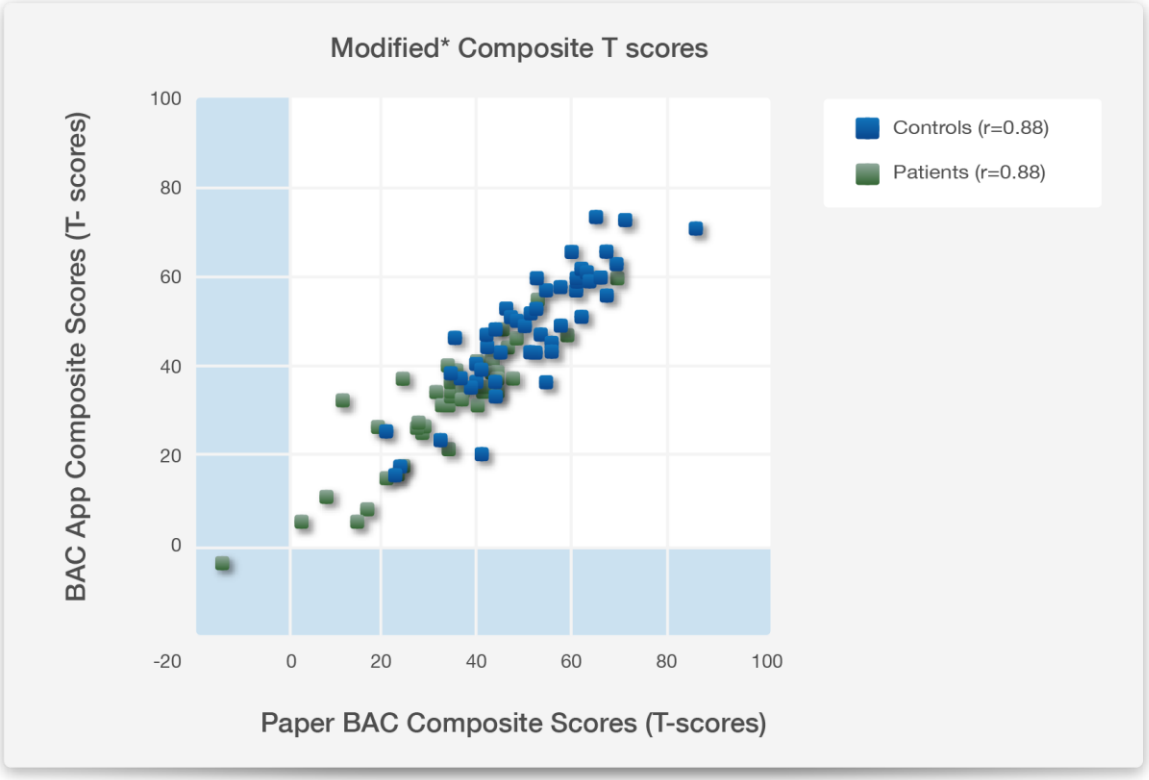
- Hachinski et al: National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006;37:2220–41.

- Blumenthal et al: Lifestyle and Neurocognition in Older Adults With Cardiovascular Risk Factors and Cognitive Impairment. Psychosomatic Medicine (in press).

- Meyers and Hess. Multifaceted end points in brain tumor clinical trials: Cognitive deterioration precedes MRI progression. Neuro-oncology, 2003;5: 89–95.

Test Batteries in Non-CNS Clinical Trials

- Published validation data suggest correlation between composite scores on BAC App are equivalent to those of the traditional pencil-and-paper tests.
- Demonstration of some of the tests from the Brief Assessment of Cognition



Keefe et al, Schiz Res, 2016

BAC App Robustly Predicts Early Difficulty

Table 11.4.1.3.8-2 Pearson Correlations of Baseline Composite BAC Score and SAUSS-HCP Score in Cohort 2 (ITT Sample

BAC Score	Baseline BAC Score				SAUSS-HCP Score					Pearson Correlation	P-Value
	N[a]	Mean	Median	SD	Visit	N[b]	Mean	Median	SD		
Composit BAC Score	30	30.3	29.50	10.17	Baseline	30	62.30	65.00	17.29	0.322	0.0825
					Week 1	29	70.24	75.00	18.13	0.564	0.0014
					Week 2	29	79.00	81.00	14.76	0.540	0.0025
					Week 3	27	84.70	89.00	13.73	0.426	0.0268
					Week 8	23	90.83	96.00	12.29	0.247	0.2550
					Last Visit	30	83.00	94.00	22.34	0.273	0.1437

[a]Number of subjects with non-missing BAC score at
[b]Number of subjects with non-missing SAUSS-HCP score at the specific visit.
Source: CT-5.3.8

Statistically significant positive Pearson correlations were observed between BAC composite scores at baseline and SAUSS-HCP scores at Week 1 (r=0.564; p=0.0014) and Week 2 (r=0.540; p=0.0025).

BAC App scores thus robustly predict difficulty applying and pairing the patch during those weeks