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Methodology Lessons Learned and Recommendations from Positive and Negative CIAS Studies

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Disclosures

Employee of AbbVie (Abbott) for 7 years

Hold AbbVie/Abbott stock and stock options

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Overview

Objective:

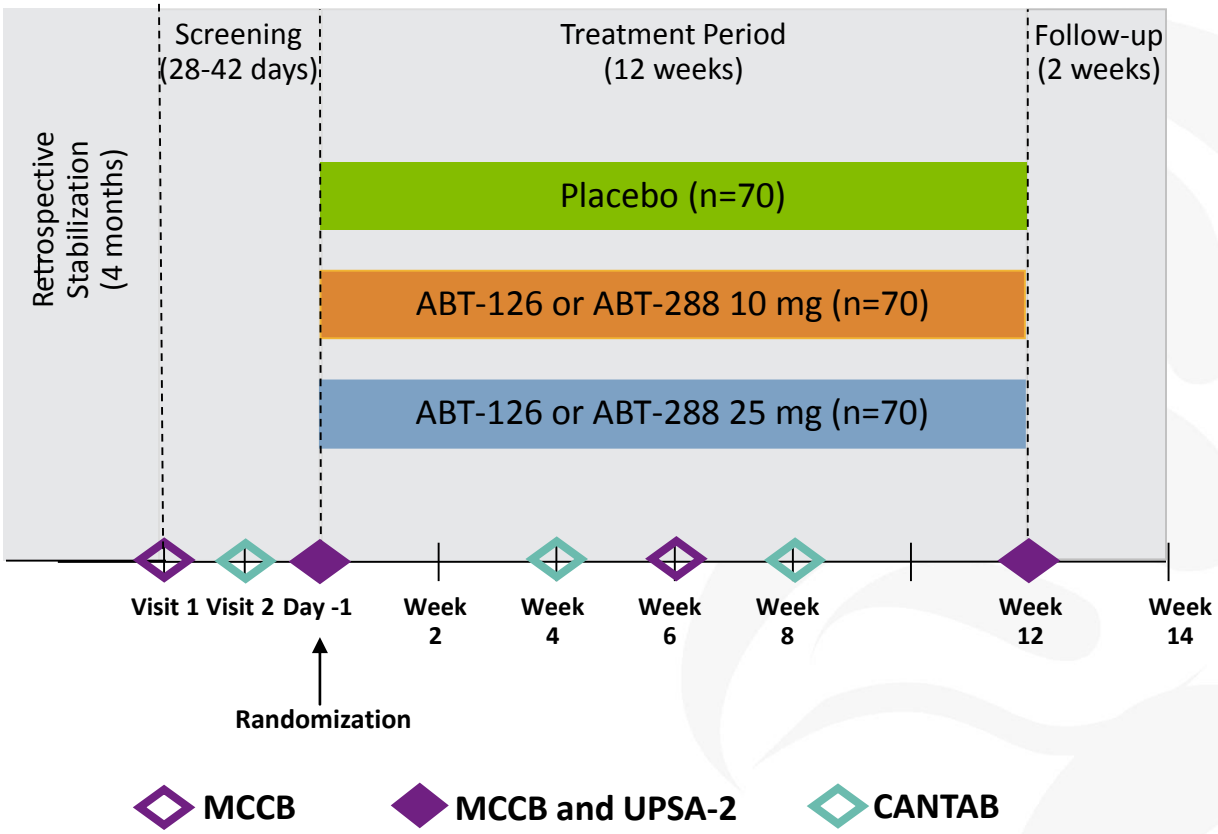
- Describe elements of CIAS clinical trials that did and did not work well
- Propose recommendations to optimize study design and operational execution of CIAS clinical trials

Outline:

- Overview of studies conducted
- Elements of studies reviewed
  - Patient selection criteria
  - MCCB and UPSA
    - Training
    - Practice effects
    - Ceiling effects
  - Operational execution
- Summary of recommendations

Study Design: Consistent with Elements Outlined by MATRICS and Published by Buchanan, et al.[1]

Design used for two POC studies conducted in the US:

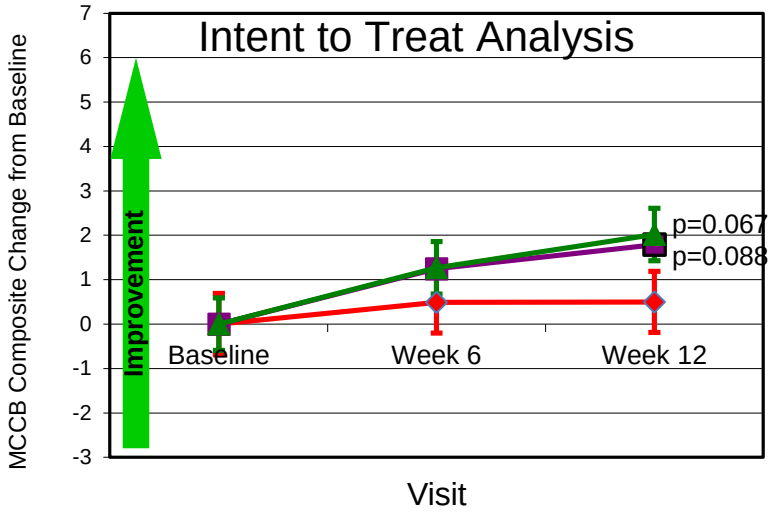


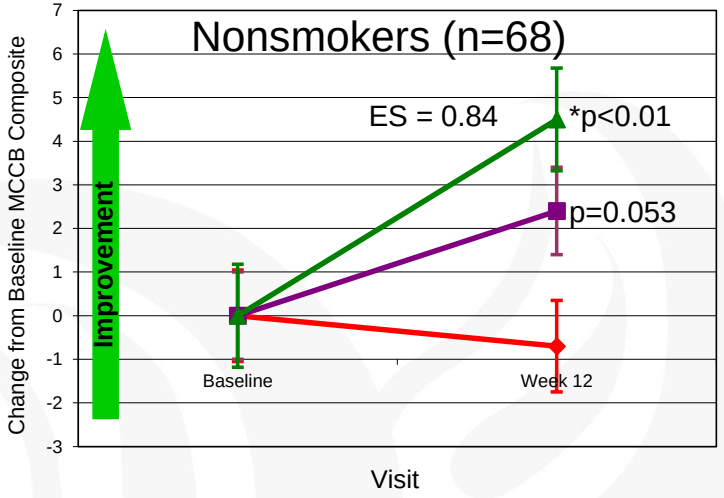
Key inclusion criteria:

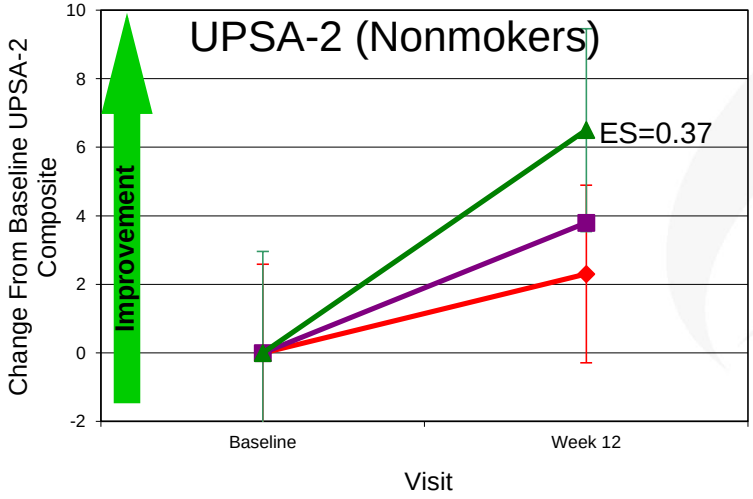
- Stable schizophrenia
- Receiving 1 or 2 atypical antipsychotics at stable doses
- No worse than moderate score on core (+) symptoms
- No significant EPS or depression
- No uncontrolled medical problems or other Axis I dx
- Screened for alcohol, substances of abuse

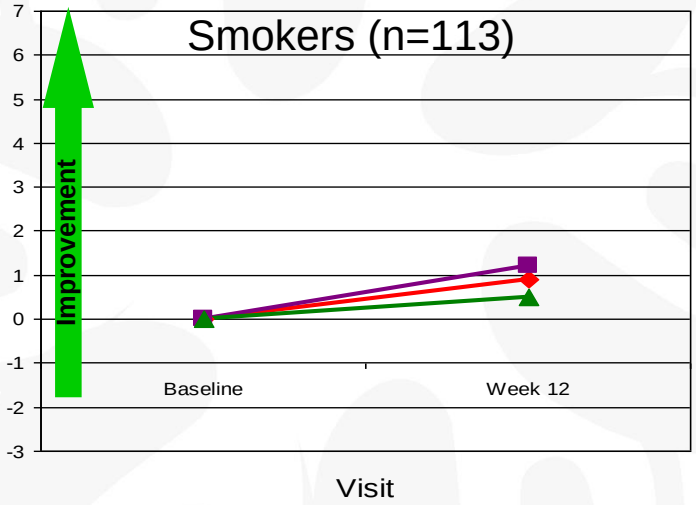
Buchanan R, Schizophrenia Bulletin(31) 1–15, 2005

High Level Results of ABT-126 (alpha-7 Agonist) Study*





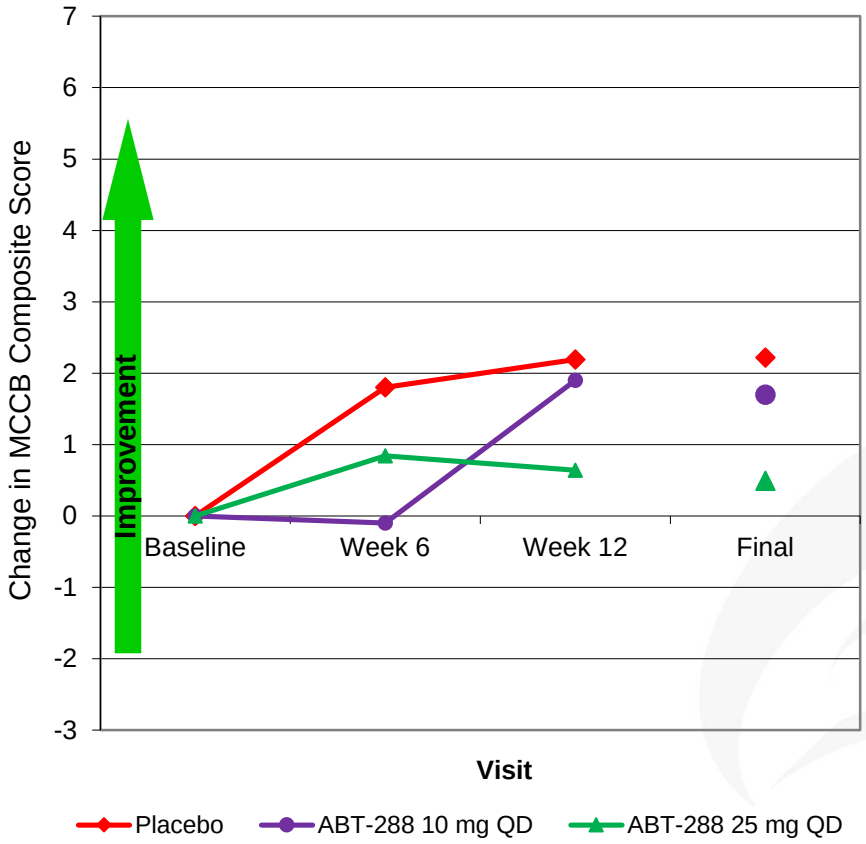




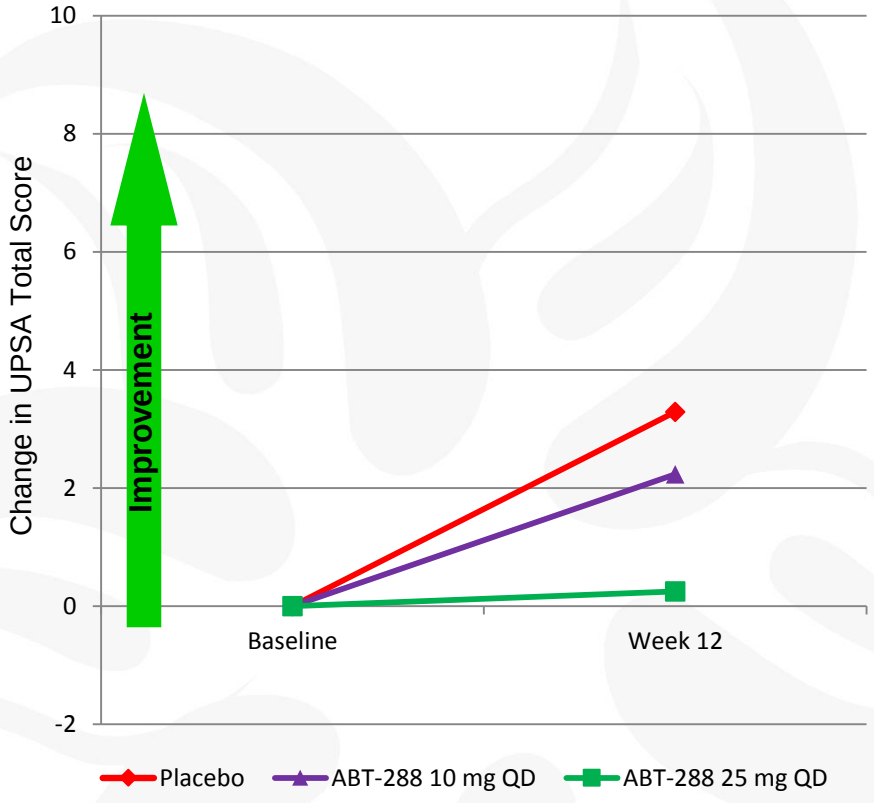
*Society of Biological Psychiatry 2014
*American Society of Clinical Psychopharmacology 2014

High Level Results of ABT-288 (H3 Antagonist) Study*

MCCB Results (ITT)



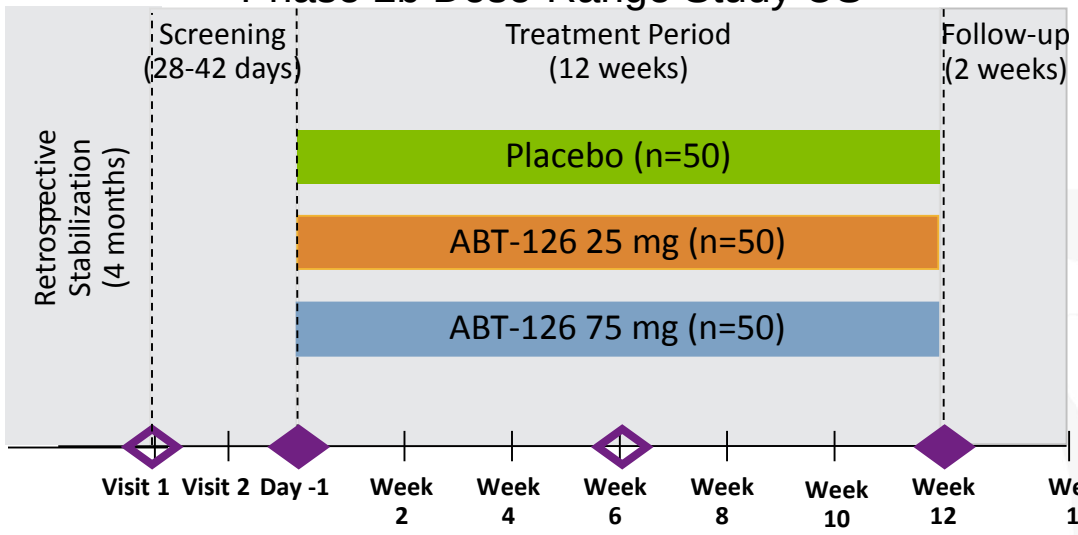
UPSA-2 Results (ITT)



*ICOSR 2013

Study Design of Current Phase 2b Studies with ABT-126

Phase 2b Dose-Range Study US

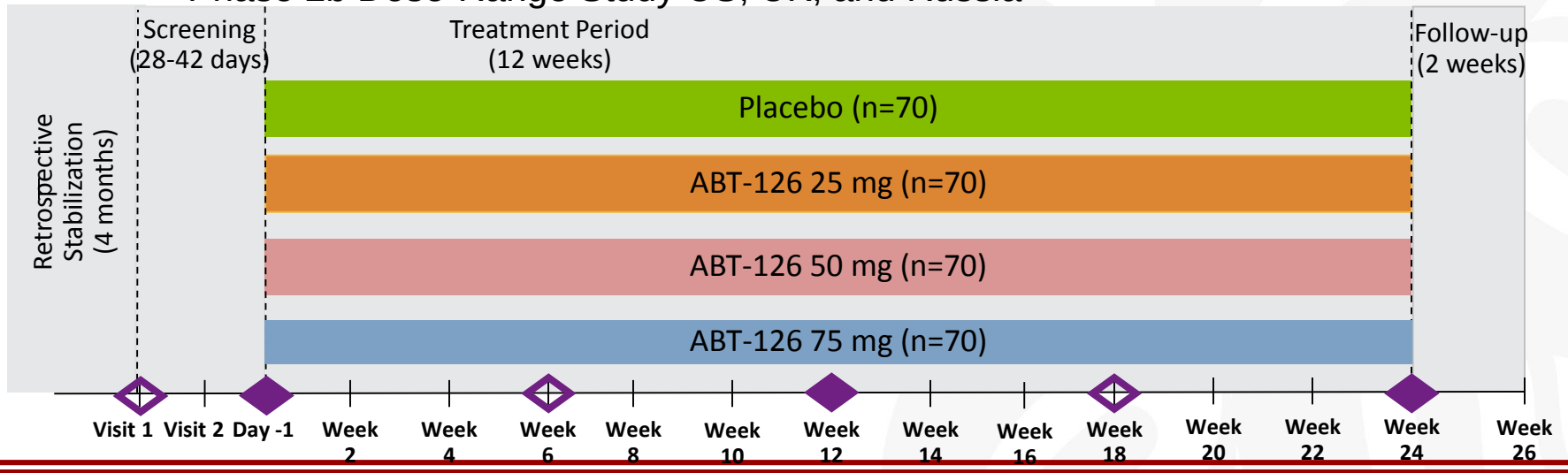


Expanded eligibility criteria:

- Age ≤65
- Allowed most conventional and atypical antipsychotics in any combination
- Allowed EPS meds at stable doses

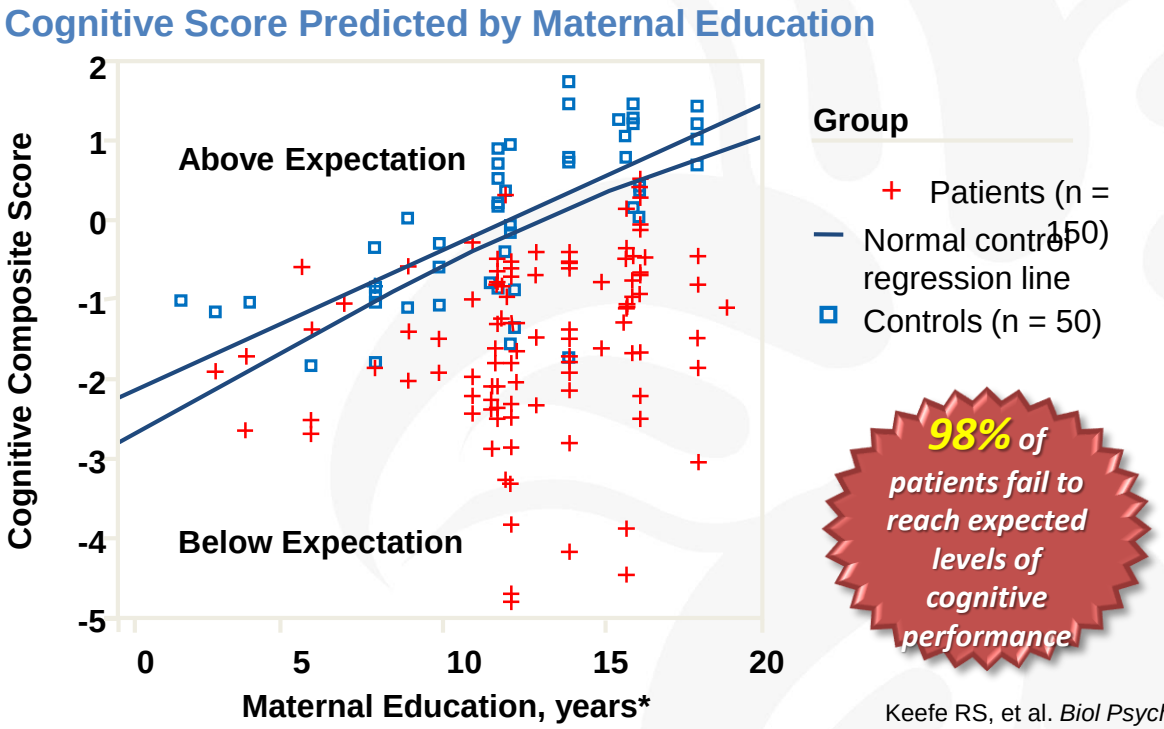
◇ MCCB ◆ MCCB and UPSA-2

Phase 2b Dose-Range Study US, UK, and Russia



Subject Selection Criteria

- Standard MATRICS eligibility criteria were used which assumes nearly everyone with schizophrenia is cognitively impaired
  - If pattern holds, will be one of the only psychiatric illnesses whose intended population is not defined by level of severity
- Rates of positive sx destabilization were as expected
- Data analyzed by various demographic segments



Keefe RS, et al. *Biol Psychiatry*. 2005;57(6):688-691.

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Analyses by Subject Type

Interaction	Subgroups	Treatment Interaction p-Value
Gender	Male; female	NS
Age	>40 years; ≤40 years	NS
Current tobacco use*	Current smoker; non current smoker	P=0.015
Baseline MCCB score	Tertiles: a. Mean 14.0 (-3 to 22) b. Mean 27.5 (23-33) c. Mean 40.5 (34-58)	NS
PANSS subscale score	PANSS positive > PANSS negative PANSS negative > PANSS positive	NS
Duration since schizophrenia diagnosis	< 10 years; ≥ 10 years	NS

*Due to pharmacology of study drug

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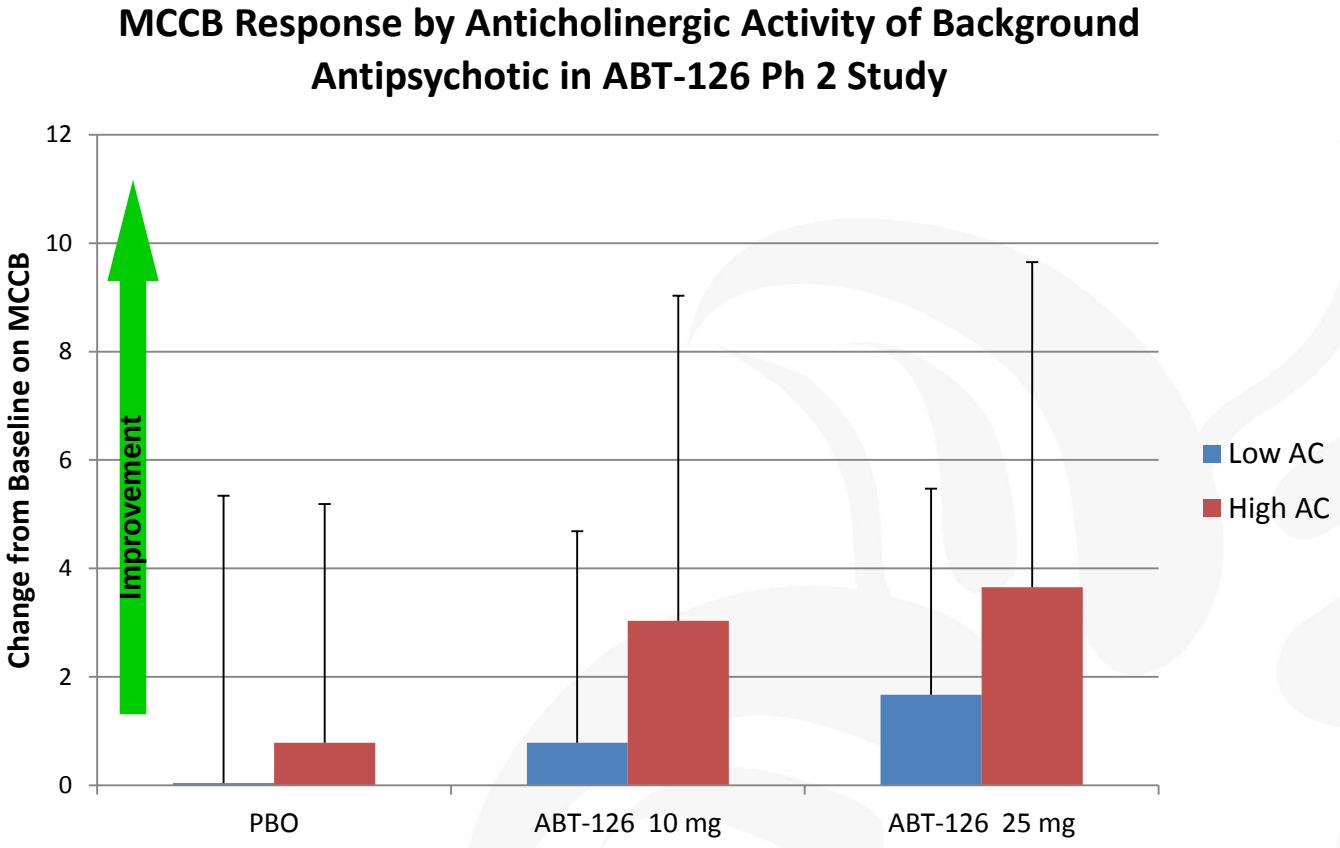
Censoring or Excluding Subjects with High Baseline Scores Results in Increased Treatment Effect

MCCB effect-size change after censoring subjects with high baseline UPSA-2 scores			
Population (non-smokers)	**Treatment Group**	**N**	**MCCB Effect Size**
All non-smokers	Placebo ABT-126 25 mg	23 19	0.84
Excluding subjects with UPSA baseline score >102	Placebo ABT-126 25 mg	22 10	1.18
Excluding subjects with UPSA baseline score >97	Placebo ABT-126 25 mg	21 9	1.25

MCCB effect-size change after censoring subjects with high baseline MCCB scores			
Population (non-smokers)	**Treatment Group**	**N**	**MCCB Effect Size**
All non-smokers	Placebo ABT-126 25 mg	23 19	0.84
Excluding subjects with MCCB baseline score >44	Placebo ABT-126 25 mg	22 16	0.91
Excluding subjects with MCCB baseline score >38	Placebo ABT-126 25 mg	21 12	1.00

Evaluation of the Impact of Concurrent Antipsychotic



Subject of subject selection recommendations:

- Use standard eligibility criteria; however consider exclusion of high baseline MCCB performance (e.g. >40)
- No documented evidence of improvement by excluding certain antipsychotics or anticholinergics

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Overview

- MCCB
  - Designed to measure all major cognitive symptoms associated with scz
  - Median completion time ~70 min; 75% in less than 80 min
  - Scoring is on a normative distribution
    - Average score of a person with schizophrenia is ~25 (2½ SD below average unaffected person)
  - Several tests have multiple versions
  - Low risk of ceiling effect
- UPSA-2 average completion time ~45 minutes
  - Raw scores; highly correlated with MCCB
  - Single version; prone to high practice effects and ceiling effects
- Both demonstrate good inter-rater and test-retest reliability
- Important to use experienced raters, and to train them for each study

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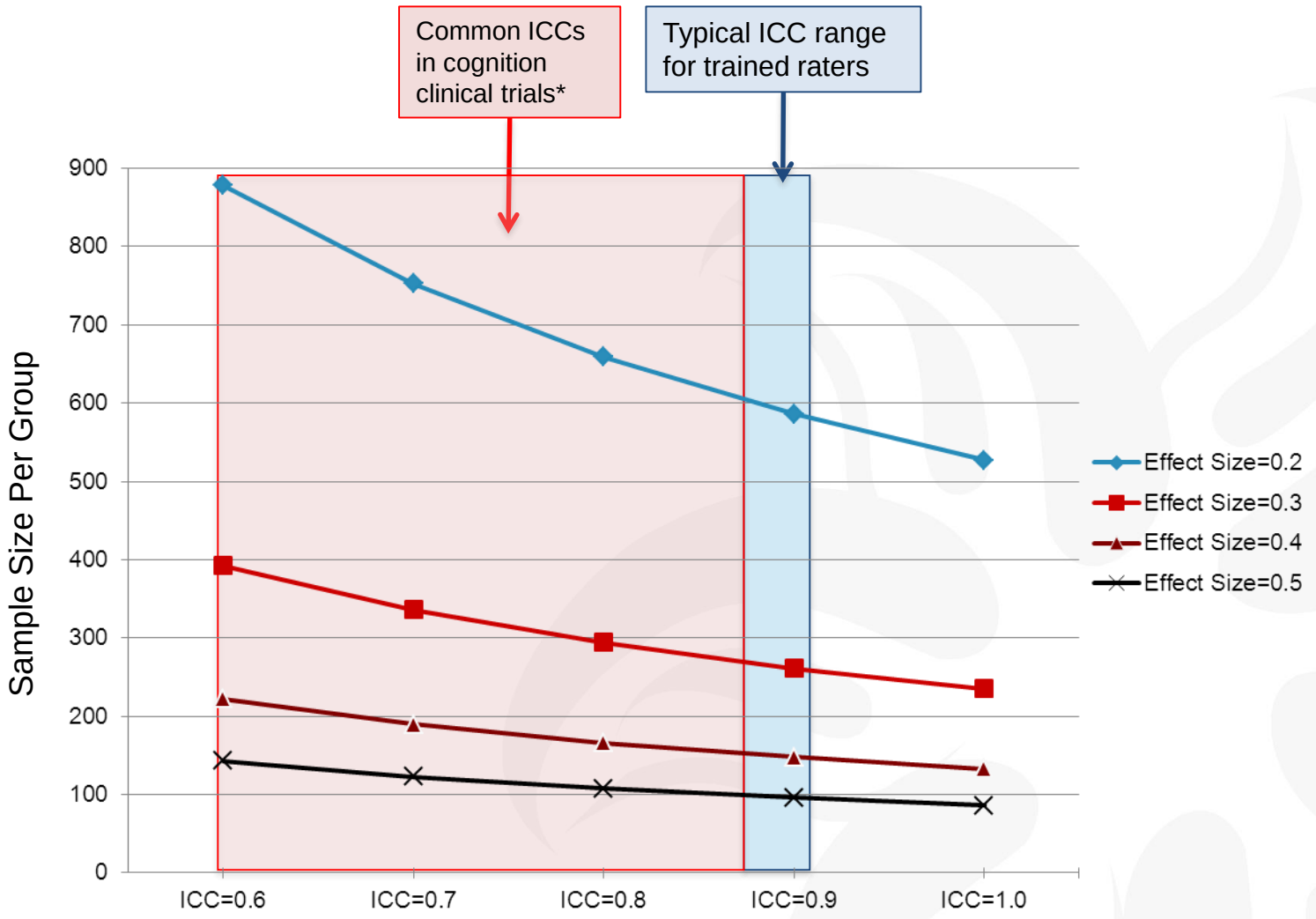
Training Raters and QCing Responses Reduces Noise, Resulting in Greater Precision and Lower Sample Size Requirements

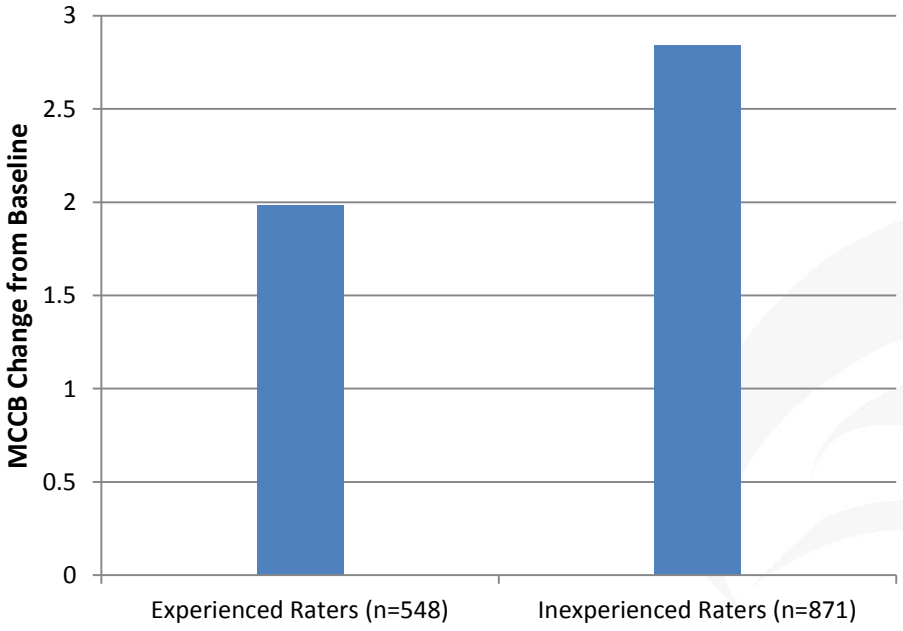


* Keefe, et.al. Schizophrenia Bulletin, 2013; 39(2): 417-435

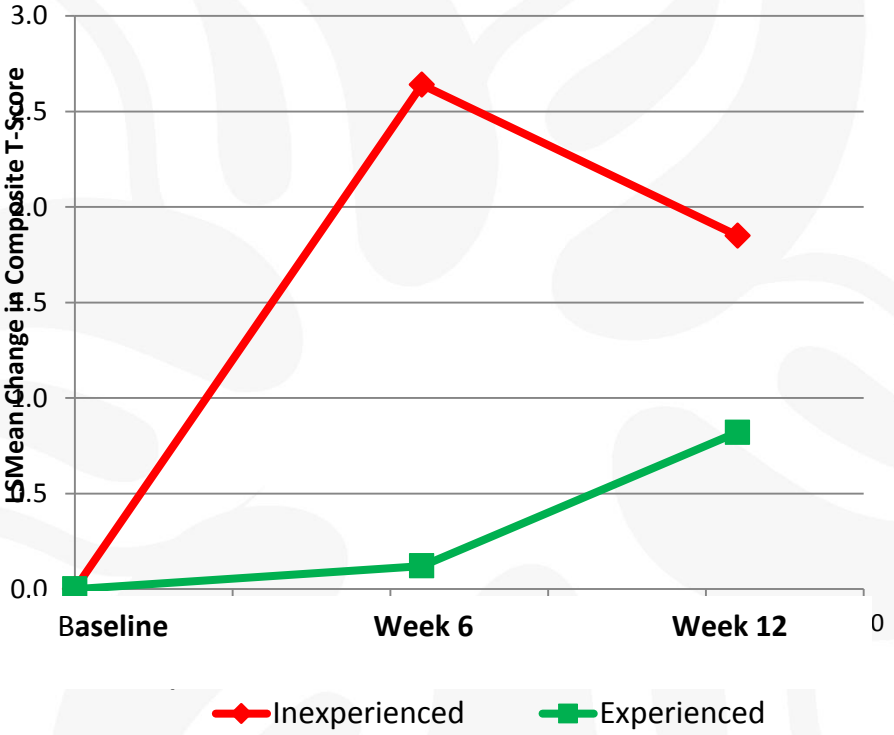
Practice Effects can Confound Interpretation of the Study: Impact of Rater Experience

- Expected MCCB practice effect in a 12-week study is ~1.5-2 points
- Larger practice effects expected for 6 month studies
- Recommend: Reduce frequency of administration for longer studies

MCCB Screening to Baseline Effects by Rater Experience



AbbVie MCCB Baseline to Week 12 Placebo Response by Rater Experience



NeuroCog Clinical Trials database analysis of 2,314 subjects with 7,713 assessments, 2014

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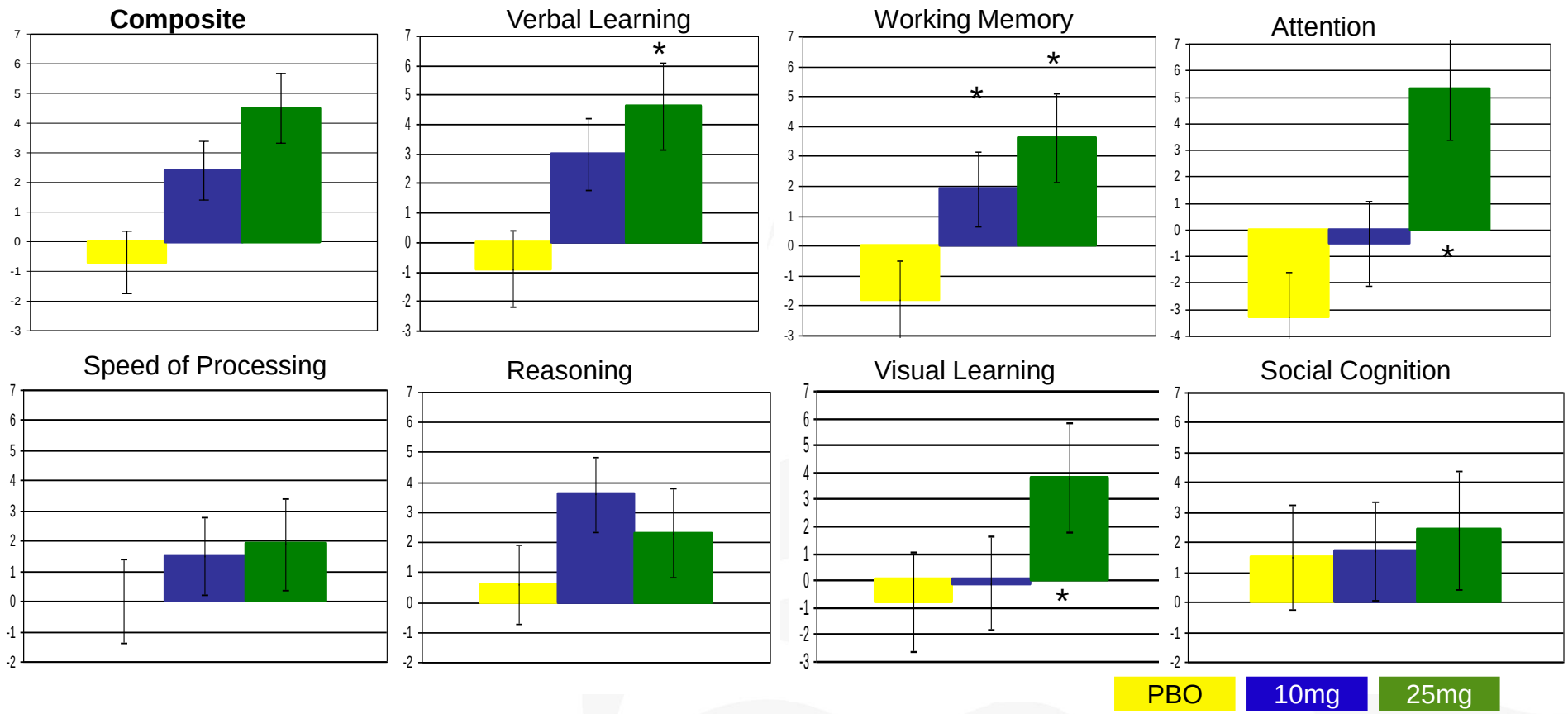
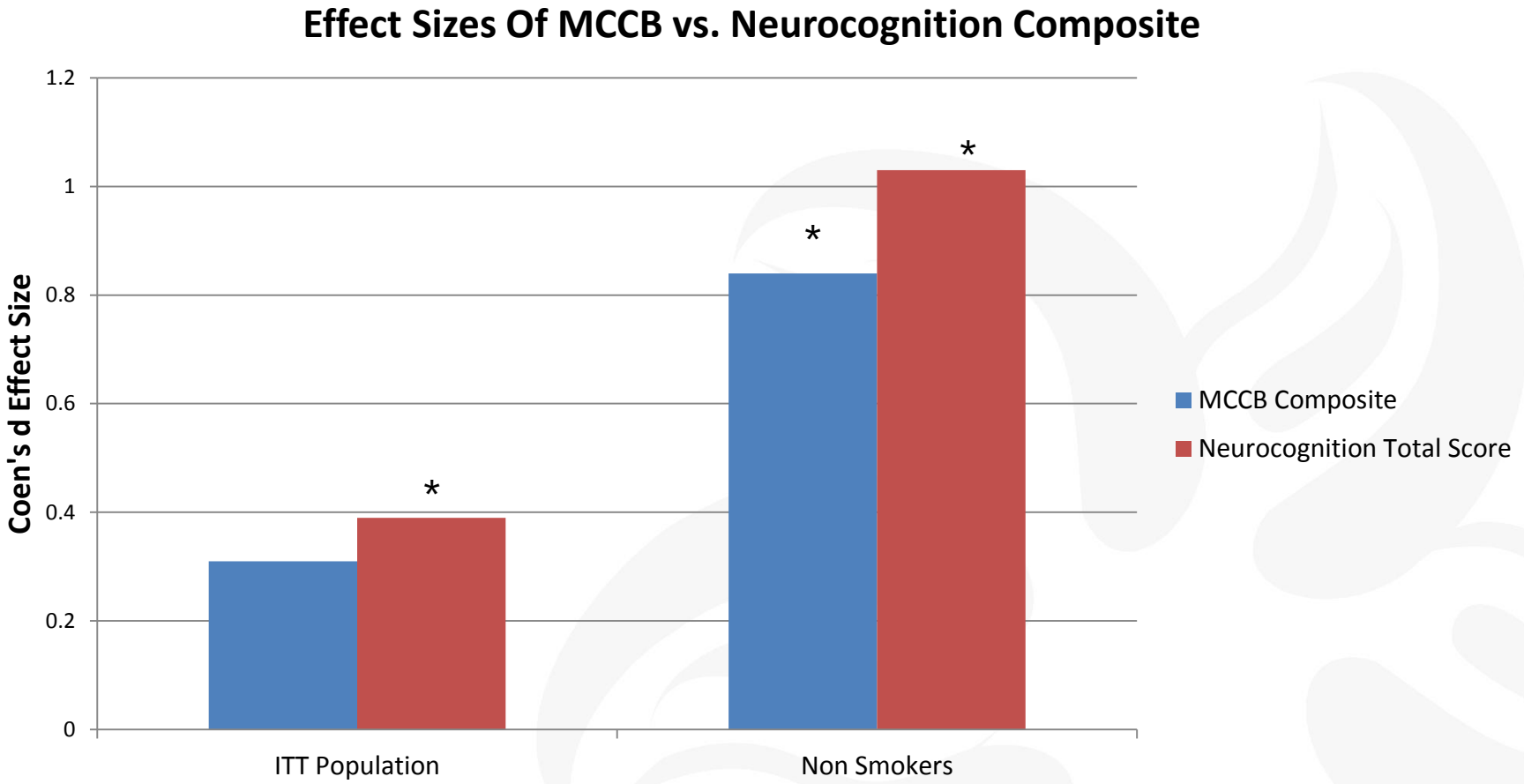
Dose-Response Observed Across all MCCB Domains with the Exception of Social Cognition



*P<0.05

Removing Social Cognition from MCCB Composite Results in Larger Effect Size in ABT-126 Ph 2 Study



*Statistical significance

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MCCB Recommendations

- The MCCB is a valid, reliable and pharmacologically sensitive battery suitable for clinical trials
- Train raters for each study
- QC each and every test
- The decision on the composite score is predicated on pharmacology of study drug and early study results
- To reduce magnitude of practice effect, consider:
  - Frequent administration prior to randomization
  - Reduced frequency of administration post randomization
  - Use experienced raters and sites

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UPSA-2 Ceiling and Practice Effects

- UPSA-2 demonstrates high correlation with MCCB
  - MCCB change score correlation is poor (r~0.15)
- Only 1 version – prone to large practice effects
  - Not practical to administer at Screening visit, or at <12 week intervals
  - Subject selection advisory: caution with frequent flyers
- In the ABT-126 Phase 2a study, the effect of removing subjects with high baseline values suggests damaging ceiling effects

UPSA-2 Ceiling Cutoff	Total Sample Size (non smokers)	Difference vs. Placebo (high dose group)
102	56	5.33
104	58	3.90
106	62	3.01
120 (no ceiling)	67	1.30

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UPSA-2 Extended Range: An Attempt to Address Ceiling Effect

- Added questions to all individual UPSA tests
- Number of tests remains at 6; total possible score remains at 120
- Effect on baseline scores shown in table below, however % of subjects with baseline scores >120 remains high

Study	Version	Baseline Score
ABT-288 Phase 2a	UPSA-2	88.3
ABT-126 Phase 2a	UPSA-2	86.1
ABT-126 Phase 2b smokers	UPSA-2 ER	79.7
ABT-126 Phase 2b nonsmokers	UPSA-2 ER	71.7

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UPSA Selected because of Superior Psychometric Properties in VIM Study

TABLE 2. Psychometric and Validity Data for Candidate Coprimary Measures for Clinical Trials of Cognition Enhancement in Schizophrenia Administered to a Sample of Patients With Schizophrenia (N=163)

	Key Scientific Criteria					Additional Scientific Criteria			
	Test-Retest Reliability			Correlation With MCCB[b]		Utility as a Repeated Measure			Correlation With QLS[c]
Measure	ICC[a]	r	95% CI	r	r^2	Floor/Ceiling at T1 (N)	Floor/Ceiling at T2 (N)	T1–T2 Effect Size	r
Full measures									
Independent Living Scales	0.76	0.77	0.69–0.83	0.51	0.26	4/0	2/0	0.15	0.30
Test of Adaptive Behavior in Schizophrenia	0.69	0.71	0.62–0.78	0.61	0.37	0/0	0/0	0.24	0.23
UCSD Performance-Based Skills Assessment	0.74	0.75	0.67–0.81	0.67	0.45	0/0	0/0	0.18	0.25
Clinical Global Impression Scale for Cognition	0.69	0.69	0.59–0.77	0.38	0.14	6/0	5/0	0.03	0.12
Cognitive Assessment Interview	0.76	0.77	0.69–0.83	0.23	0.05	1/0	1/0	0.10	0.27

TABLE 3. Ratings of Practicality and Tolerability of Candidate Coprimary Measures for Clinical Trials of Cognition Enhancement in Schizophrenia Administered to a Sample of Patients With Schizophrenia (N=163)[a]

Measure	Practicality	Tolerability[b]	Duration[c] (Minutes)
Independent Living Scales	4.6	5.4	46
Test of Adaptive Behavior in Schizophrenia	5.2	5.9	33
UCSD Performance-Based Skills Assessment	6.0	5.6	27
Cognitive Assessment Interview	4.1	6.0	25

[a] Practicality and tolerability were rated on 1–7 scale where 7=best.

Green, et. al. Am J Psychiatry 2011

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Alternative Cognitive Functional Measures may be Considered

- Other functional capacity measures:
  - Schizophrenia Cognition Rating Scale (SCoRS)
  - Maryland Assessment of Social Competency (MASC)
- Community functioning measures:
  - Specific Level of Functioning (SLOF)
  - Personal and Social Functioning Scale (PSP)
  - Schizophrenia Objective Functioning Instrument (SOFI)

UPSA recommendations:

- The UPSA-2 is a valid and reliable measure that has not demonstrated pharmacologic sensitivity, is prone to practice and ceiling effects. Alternative functional measures may be considered in early Phase trials and discussed with regulators.

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Other Topics

- Visit structure
- Order of administration of scales
- Subject and site burden
- Duplicate subjects
- Medication compliance

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Summary

- The general MATRICS study design recommendations are operational and executable
- The standard eligibility criteria work well, however evidence suggest subjects with high baseline values may reduce overall treatment effect
- No documented evidence of improvement by excluding certain antipsychotics or anticholinergics
- The MCCB is a valid, reliable and pharmacologically sensitive battery suitable for clinical trials
  - Use vigilance around training and QC
  - The decision on the composite score is predicated on pharmacology of study drug and early study results
  - Take steps to reduce practice effects
- The UPSA-2 is prone to practice and ceiling effects.
  - Alternative functional measures may be considered