Clinical Outcome Assessments for Trials in Cognitive Impairment Associated with Schizophrenia

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Objectives

The co-primary approach may set a high bar for statistical significance: a modest impact of correlation between endpoints is observed on required sample size; and a more important impact of effect size is observed, with sample size determined by the smaller. In recent draft guidance for early AD, FDA acknowledge cognition as meaningful and outline circumstances in which integrated cognition-function, or cognition only outcomes would be acceptable as single primary endpoints.

Furthermore, recent Patient Focused drug development initiatives at FDA have stressed the importance of patient-caregiver input in the development of outcomes and the generation of data for drug approval.

Thus, it may be timely to review current outcomes for clinical trials of Cognitive Impairment Associated with Schizophrenia.

Methods

A review was conducted of Phase 2 and 3 industry clinical trials for schizophrenia listed on clinicaltrials.gov, and which studied potential for cognitive improvement. Fifty-two trials were identified and the most commonly reported clinical outcome assessments (COAs) for cognition and function identified.

Cognitive Performance-based Outcome (PerfO) Assessments

Measurement and Treatment Research to Improve Cognition in Schizophrenia: NIMH MATRICS initiative

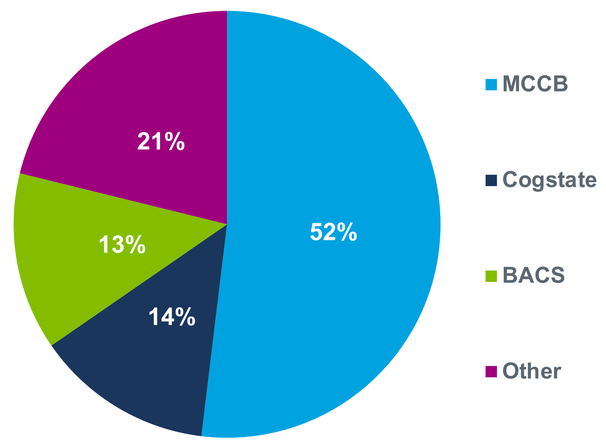
The MATRICS initiative identified seven "separable cognitive domains" based on an unpublished literature review of normative data and factor analytic studies, but also incorporating expert opinion and potential pharmacologic sensitivity (Green et al, 2004).

1. Working memory
2. Attention/vigilance
3. Verbal learning and memory
4. Visual learning and memory
5. Reasoning and problem solving
6. Speed of processing
7. Social cognition*

**Social cognition was added later due to concern regarding its omission and potential importance as a domain*

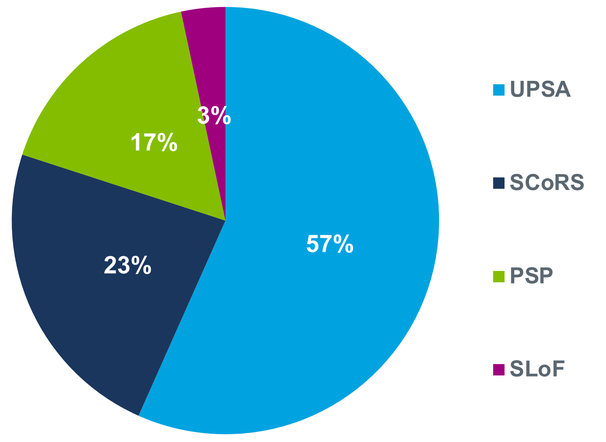
Phase 2 and 3 industry sponsored clinical trials for schizophrenia listed on clinicaltrials.gov

- Matrics Consensus Cognitive Battery (MCCB)
- Cogstate Schizophrenia Battery (CSB)
- Brief Assessment of Cognition in Schizophrenia (BACS)
- Other cognitive tests and test batteries



Functional Assessments

Instrument	Measurement domain/health aspect	Content Validity	COA Type
USCD Performance-based Skills Assessment (UPSA)	Functional capacity	Clinical experience and literature review (unpublished)	PerfO
Schizophrenia Cognition Rating Scale (SCoRS)	Interview-based assessment of cognition to cover the seven MATRICS domains	Clinical experience and adaptation of the Brief Cognitive Scale (unpublished)	PRO, ClinRO, ObsRO
Personal and Social Performance Scale (PSP)	Assessment of functioning in : 1) socially useful activities; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviours	Focus groups and adaptation of SOFAS (Morosini et al, Acta Psychiatr Scand 2000)	ClinRO
Specific Levels of Functioning (SLoF)	Behavioral functioning and daily living skills	Not reported	ObsRO



Potential for Single Primary Outcomes Development: Alzheimer's Disease Examples

Integrated Cognition-Function Primary

Clinical Dementia Rating – Sum of Boxes

- Developed to measure the 'functional impact of cognitive impairment'
  - Cognitive test items are integrated with informant report and clinical judgment applied to inform scoring

Potential Application

- Methods to integrate informant components of e.g., SCoRS with performance-based elements of e.g., MCCB or UPSA

ADCOMS

- Statistical modeling used to select and weight items from cognitive and functional assessments that are most sensitive to disease progression at the MCI/prodromal AD stage

Potential Application

- Statistical modelling approaches to identify items from existing instruments with e.g., the best signal to noise ratio to discriminate overall clinical or functional status

Single Cognitive Primary

ADCS-PACC

- Developed initial based on literature review for sensitivity at the preclinical AD stage
- Single cognitive primaries may only be acceptable at the earliest stages of AD where functional impairment is not evident and may also need to be demonstrated to be intermediate outcomes of later functional impact
- In CIAS, it is possible that cognitive changes would precede functional improvement

Potential Application

- Tests from existing cognitive tools such as MCCB, CSB, BACS could be evaluated via statistical modeling to develop and validate novel composites

Potential for Patient Focused COA Development

Adaptation of Existing COAs

Existing cognitive and functional assessments lack formal patient and caregiver input into content

- Building on prior work to develop more robust conceptual models of CIAS may highlight gaps in content validity
  - See draft conceptual model in Kitchen et al, Adv Ther (2012) 29(2):148-162

Inclusion of Novel COAs into Existing Endpoint Models

Patient-caregiver informed PRO instruments may provide addition patient focused data to support insights into potential treatment benefits

- Building on prior work to develop more robust conceptual models of CIAS may highlight gaps in content validity
  - See patient focused PRO instrument in Welch et al, Patient Related Outcome Measures 2017:8

Future Directions

Formal validation of cognition outcomes as intermediate or surrogate endpoints may have a number of benefits:

- Reduced patient and trial burden
  - Whilst multiple cognitive domains may be impaired in schizophrenia, assessment of fewer domains still support adequate assessment of cognition in the context of an intermediate outcome
- Increased sensitivity and responsivity versus functional outcomes
  - Facilitation of shorter, smaller PII clinical trials
  - Facilitation of PII to PIII bridging
  - Facilitation of shorter PIII clinical trials leading to accelerated or conditional approval

Development of a patient focused conceptual model of CIAS may help support FDA Patient Focused Drug Development data table requirements

- Evaluation of existing Clinical Outcome Assessments against a conceptual model development based on patient and caregiver insight may highlight gaps in the content validity of existing COAs/endpoint models
  - See "FDA to Collect Patient Experience Data"
    - Barlas, P&T, June 2018, Vol. 43 No. 6