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 In recent draft guidance for early AD, FDA acknowledge cognition as meaningful and outline circumstances in which integrated cognition-function, or cognition only outcomes would be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.

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The MATRICS initiative identified seven "separable cognitive domains" based on an unpublished literature review of normative data and factor analytic studies, but also incorporating expert opinion and potential pharmacologic sensitivity (Green et al,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

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
- ACO-MDOC
- 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

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

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 specificity versus functional outcomes
- Facilitation of shorter, smaller PI clinical trials
- 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

Development of a patient focused conceptual model of CIAS may help support FDA Patient Focused Drug Development data table requirements
Inclusion of Novel COAs into Existing Endpoint Models
Patient-caregiver informed PRO instruments may provide additional 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

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.