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Negative Symptoms (NS) Working Group

Summary of Discussion of the NS Workshop:

Workshop goal: To re-evaluate recommentations regarding clinical trials methodology based on newly available data

- **Alternative Thresholds for Negative and Positive Symptoms in the CATIE Trial: Implications for Negative Symptom Clinical Trials -- Dunayevich**
  - Varying the PANSS-based criteria used to define entry criteria for negative symptom trials yields large differences in eligible population size
  - More restrictive criteria yield gradual increases in baseline negative symptom severity and generally lower baseline positive symptom severity
  - Change from baseline in both positive and negative symptoms increase with increased baseline severity. However, when adjusted for baseline score or change from baseline in positive symptoms, there is a comparable change from baseline across subsets
  - Overall, in a stable subset of CATIE participants with at least minimal baseline negative symptoms, varying negative and positive symptom severity thresholds had large impact on sample size and limited impact on observed treatment effects.
  - *There was general agreement in the workshop that these data did not support the use of overly restrictive positive symptom criteria for negative symptom studies.*

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- **Association of Prominent Positive and Prominent Negative Symptoms and Functional Health, Well-Being, Health Care–Related Quality of Life and Family Burden: a CATIE Analysis**
  - Both prominent positive and prominent negative symptoms of schizophrenia are independently associated with significant decline in functionality, HRQoL, and caregiver lost workdays.
  - Negative symptoms were more associated with impairment, as measured by the scale of functioning, than positive symptoms.
- **Which negative symptoms are hardest to rate? Observations from site monitoring**:
  - Discussion of in person or remote/video raters; differences in rating?
    - Negative symptoms were harder to get agreement on than positive symptoms
    - Negative symptoms rated based purely on behavioral observation were harder to get agreement on than those that included report by the patient or informant
    - Agreement between site and external raters was lower in the US than ROW
    - Implications:
      - Symptoms rated on the basis of behavioral observation alone may require more intensive training.
      - Measure of observational phenomena need to be divided into quantifiable components (eg, Blunted Affect into prosody, facial expression, gestures)
    - Discussion: Newer scales such as the BNSS or CAINS or NSA-16 may have advantages by focusing raters on negative symptoms items.

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- **Construction of an integrated negative symptom factor**
  - Which aspect of psychopathology should be part of the NS construct?
  - Review all published studies using PCA to assess PNASS domains in schizophrenia pts (24 selected), IRT (Item Response Analysis) conducted
  - The findings provide evidence for a reliable PANSS Negative dimension encompassing a broad spectrum of negative psychopathology.
  - The IRT resulted in negative symptom items with very good psychometric properties, subsumed as an integrated negative PANSS dimension.
  - Next step: Factor analysis of the Integrated Negative Dimension to examine underlying patterns.
- **Negative Symptoms Future topics**
  - Should NS be a working group topic in the future? When will there be sufficient new data to support another meeting?
  - Other analyses that may be helpful in re-evaluating guidelines:
    - Focus on studies that involved “head to head” comparisons of negative symptoms instruments.
    - Sensitivity of change of instruments in non-pharmacological interventions for negative symptoms
    - Evaluate the effects of depression on negative symptom response

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