The Challenge of Subject Selection in Clinical Trials: New Data

Methods

1. Site and Remote Centralized Ratings (Kobak, et al., 2010):
- 17 calibrated quality reviewers were rigorously trained and continuously monitored. 
- 1/4 to 1/2 of subjects may not meet protocol-specified diagnostic criteria. 
- Over 1/3 of subjects may not meet protocol-specified inclusion/exclusion criteria for Initial severity.
- Across several studies, an average of 39% of subjects who would have been included in studies based on site ratings of total severity would have been excluded by blinded Remote Centralized Ratings of total severity.

2. Remote Centralized Ratings in Schizophrenia:
- Baseline scores by centralized raters of 80 subjects with Schizophrenia from three different clinical trials were presented, including screen failures.
- The distributions of remote assessments by remote raters agreed well with site raters.
- The distributions are not skewed toward any inclusion criterion.

3. Controversial Quality Control in MDD of Site-Administered Baseline Interviews (Brown, et al., 2010):
- Continuous Quality Control (CQC) is a new approach to monitoring and evaluating the administration and scoring of clinical outcome measures. Data generated during training (CQC) are presented and evaluated for baseline distribution normally, as well as for potential score inflation.
- 17 validated quality reviewers were rigorously trained and continuously calibrated on scale scoring and interview skills.
- Site raters audio recorded all scale administrations and uploaded the recordings to a central server.
- Blinded reviewers scored the tapes for interview quality and scoring accuracy.
- Feedback was provided to the site raters.

4. Site and Remote Centralized Ratings in GAD (Korn, et al., 2006):
- 296 subjects with GAD were interviewed by both site and Remote Centralized raters with the Hamilton Anxiety Rating at 4 visits: Screening, Baseline, Weeks 4 & 8 (or earlier termination).
- Site raters were first and then determined eligible.
- Remote centralized ratings were conducted via videoconferencing and site raters were conducted face-to-face.
- We present the distributions of the baseline HAM-A scores separately for Site and Remote Centralized Ratings for all subjects, including screen failures.
- Internal consistency reliability was assessed using Cronbach's alpha.

5. Subject Ascertainment - Diagnosis:
- In two large ongoing studies, subjects referred by site raters were diagnosed by Remote Centralized raters, using the SCID.
- Site raters and Remote Centralized raters had 82% agreement.
- Results:

  - 1. Site and Remote Centralized Ratings (Kobak, et al., 2010):
    - 81 subjects with MDD participated in a study of placebo response. They were interviewed at three time points using both Site and Remote Centralized Ratings with the HDRS-GPQ.
    - All baseline site ratings were done first. Interview order was counterbalanced at other time points.
    - Remote centralized ratings were conducted via videoconferencing and site ratings were conducted face-to-face.
    - We present the distributions of the baseline HAM-D scores separately for Site and Remote Centralized Ratings for all subjects, including screen failures.
    - Internal consistency reliability was assessed using Cronbach’s alpha.

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RESULTS

Percentage of Study Subjects That Would Have Been Excluded by Remote Blindly Centralized Ratings Based on Symptoms Severity Scores (Rating only those subjects included by Site rater):%

<table>
<thead>
<tr>
<th>Condition</th>
<th>Site Rat</th>
<th>Remote Rat</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD</td>
<td>10%</td>
<td>20%</td>
<td>-10%</td>
</tr>
<tr>
<td>MDD</td>
<td>15%</td>
<td>30%</td>
<td>-15%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>20%</td>
<td>40%</td>
<td>-20%</td>
</tr>
</tbody>
</table>

References

- Kobak, et al., 2010: Site and Remote Centralized Ratings in GAD.
- Korn, et al., 2006: Site and Remote Centralized Ratings in MDD.

Figure 1: Comparison of Site and Remote Centralized Ratings in Schizophrenia

- Site raters had lower Cronbach's alpha (internal consistency reliability) than Remote Centralized raters.

Shapiro – Wilk Test of Non-Normality:

- Normal Fit

Figure 2: Comparison of Site and Remote Centralized Ratings in GAD

- Remote Centralized Ratings were conducted via videoconferencing and site ratings were conducted face-to-face.

Figure 3: Comparison of Site and Remote Centralized Ratings in MDD

- Remote Centralized Ratings were conducted via videoconferencing and site ratings were conducted face-to-face.

CONCLUSIONS

- Site selection issues are substantial – both in initial severity and diagnostic stability.
- Over 1/3 of subjects may not meet protocol-specified inclusion/exclusion criteria for Initial severity.
- Over 1/3 of subjects may not meet protocol-specified inclusion/exclusion criteria for Initial severity.
- The effect size for subjects qualified by the blinded Remote Centralized Ratings increased substantially over the effect size of subjects qualified by Site raters in site study of GAD.
- Site raters and Remote raters had 82% agreement.

Subject ascertainment with Remote Centralized Ratings may improve appropriate subject ascertainment as determined by Independent third party verification.

- Subject ascertainment with Remote Centralized Ratings roughly doubled the effect size between active comparator and placebo in site study of GAD.