Risk-based Monitoring for Aberrant Rating Patterns and Patient Selection Anomalies in Global Schizophrenia Trials

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ABSTRACT

BACKGROUND: Risk-based outlier analysis of blinded data for aberrant rating patterns and patient selection anomalies can be paired with audio/video surveillance to cost effectively identify at-risk sites in global schizophrenia clinical trials.

METHOD: Utilizing centralized, blinded data quality monitoring of 41,555 PANSS assessments in eleven international schizophrenia clinical trials, norms were created for a library of data patterns selected by sponsors as potentially at risk for measurement error or idiosyncratic patient selection. Based on these risk factors, a composite score or “dashboard” was created ranking each site based on quality measures. Sites of concern were subsequently subjected to more intensive, remote, centralized review of recorded patient interviews by external experts. The quality of recorded interviews and ratings was remotely assessed by independent reviewers for 2,943 PANSS assessments.

RESULTS: Based on independent review of audio and/or video recorded PANSS assessments, interview quality was rated as excellent, adequate with some deficiencies, or inadequate in 75.44% (n=2221), 23.2% (n=683) and 1.36% (n=40) of visits, respectively. Proper application of the PANSS instructions and anchor points was independently rated as excellent, adequate with some deficiencies, or inadequate in 75.98% (n=2221), 22.8% (n=671) and 1.22% (n=36) of visits, respectively. The following illustrate examples of adaptive monitoring. Sites 397 and 762 were evaluated on three risk factors specified by the sponsor: 1) large between-visit changes in the total PANSS score; 2) erratic PANSS changes; and 3) 100% identical PANSS scores from visit to visit. If anomalies were determined by blinded data monitoring, additional scrutiny was employed by external review of recorded patient visits. Large between-visit changes were operationally defined as change >2 SD above the mean for all visits compared to other sites participating in the same protocol. Erratic between-visit changes were operationally defined as 2 consecutive visits with a large change as defined above and the changes to be in opposite directions.

BACKGROUND

- Risk-based outlier analysis of blinded data for aberrant rating patterns and patient selection anomalies can be paired with audio/video surveillance to cost effectively identify at-risk sites in global schizophrenia clinical trials.

METHODS

- Utilizing centralized, blinded data quality monitoring of 41,555 PANSS assessments in ten international schizophrenia clinical trials, norms were created for data patterns selected by sponsors as potentially at risk for measurement error or idiosyncratic patient selection. Based on these risk factors, a composite score or “dashboard” was created ranking each site based on quality measures. Sites of concern were subsequently subjected to more intensive, remote, centralized review of recorded patient interviews by external experts. The quality of recorded interviews and ratings was remotely assessed by independent reviewers for 2,943 PANSS assessments.

RESULTS

Case Study I:

- The Site of Concern was an outlier on factors 1 and 2 (> 3 SD above the mean) but refused to allow interviews to be recorded for external review to allow independent assessment of measurement error. The site was not allowed to enroll additional patients.

Case Study II:

- The Site of Concern was not an outlier on large score or erratic score changes but more than 15% of consecutive visits were 100% identical for all 30 PANSS items. Recordings of patient interviews were scrutinized. The proportion of discordant PANSS ratings (>2 difference between site and independent rater) exceeded 60%. Enrollment was placed on hold pending extensive remediation.

DISCUSSION

Risk based outlier analysis of blinded data for aberrant rating patterns and patient selection anomalies can be paired with audio/video surveillance to cost effectively identify at-risk sites in global schizophrenia clinical trials. Allowing sites to “opt out” of audio/video surveillance complicates interpretation of data anomalies. In addition, audio/visual surveillance has the potential to identify endpoint scoring irregularities that may not emerge in outlier analysis. Additional data is being collected. The analyses reported above are preliminary.