Remote Independent Central Ratings
- The use of well-trained and blinded, calibrated expert central raters minimizes perception biases and reduces variability, which enhances separation between placebo and active treatment.
- Remote independent central raters screening subjects via evaluation of symptom severity and the SAFER Interview help ensure unbiased selection of appropriate subjects while avoiding baseline score inflation (Figure 1).

Central ratings ensure accurate post-baseline ratings and increase study power via high ICCs further enhancing the impact of the SPD identification of placebo non-responders for randomization in Stage 2.
- Central raters reduce variability by limiting the number of raters needed for any one trial. (Figure 2)
- Higher interrater reliability means higher study power. Experienced and calibrated raters ensure the highest level of reliability. (Figure 2)
- Ongoing calibration of central raters prevents rater drift throughout the course of the trial. (Figure 4)

The SAFER Interview
- The SAFER Interview is an operationalized version of the SAFER (Sensitivity, Acceptability, Face Validity, Ecological Validity, and Rule of the 3Ps) principles developed by clinicians at Massachusetts General Hospital (MGH).
- In a recent analysis of five trials in treatment resistant depression (TRD) all subjects had passed screening procedures at the site and were considered to be eligible for the trial.
- In addition to the 45-minute SAFER Interview performed remotely by MGH clinicians who called subjects, (N=935) directly, a structured severity interview was performed, 1,562 (81 percent) of the subjects were deemed eligible for continued screening. (Figure 5)
- Of the 373 (19 percent) subjects deemed ineligible: 97 (5 percent) did not meet severity criteria, 39 (2 percent) did not meet only SAFER criteria, 151 (8 percent) did not meet ATRC criteria for treatment resistance; and, 86 (4 percent) did not meet criteria on more than one component of the SAFER Interview.
- Across all of these five TRD studies, placebo response rates were within a range of 18 to 28 percent, below the 30 to 37 percent average in studies of treatments approved for TRD (allopurinol-flusoxetine combination, quetiapine and aripiprazole).

Sequential Parallel Comparison Design (SPCD)
- Goals of the Sequential Parallel Comparison Design (SPCD) are to reduce the impact of high placebo response and decrease study sample size.
- The SPCD model (Figure 6) incorporates two relatively short phases of treatment of equal duration: Phase 1: all subjects randomized to placebo or active treatment; more subjects than usual assigned to placebo arm to enrich phase 2.
- Phase 2: subjects on active treatment and placebo non-responders in Phase 1 are randomized to placebo or active treatment.

COMBINING THE THREE STRATEGIES

In combination, these three unique but complementary strategies offer a "triple safety net" that may dramatically reduce the risk of a failed trial and offer the best chance for a trial to succeed.

References

Are Different Methods to Reduce Placebo Response in CNS Trials Mutually Exclusive or Have Additive Effects?