SIGNANT HEALTH

SCHIZOPHRENIA

THE INDUSTRY'S MOST SPECIALIZED ECOA SOLUTION FOR SCHIZOPHRENIA CLINICAL RESEARCH

At Signant Health, we offer unparalleled scientific and clinical expertise and experience in schizophrenia clinical trials, including a proven track record for international delivery of our solutions that include Rater Training & Data Quality Monitoring, enhanced eCOAs (electronic clinical outcome assessments), Scientific & Clinical Consulting, and Data Quality Analytics.

A PLATFORM SPECIALIZED FOR SCHIZOPHRENIA RESEARCH

Signant's CNS-enhanced eClinRO (electronic clinician reported outcomes) solution, called Rater Station®, has been utilized in schizophrenia programs worldwide, including Japan, with extensive use of our validated, electronic versions of the:

PANSS | SCI-PANSS | IQ-PANSS | NSA-16 | CGI | PSP

Rater Station offers enhanced eClinRO functions and features for clinician administered scales including interviews, edit checks and alerts, and on-screen guidance. It works alongside our patient engagement solution, sponsor and site portals, and interactive response technology (IRT).

Our Data Quality Analytics are a proprietary risk-based monitoring solution that extract insights from your clinical data. It has been used for schizophrenia studies to identify quality issues at the study, site, rater, and patient level in near real-time, and our analytics experience is unmatched in the industry.

GLOBAL OPERATIONS

Our operational teams and scientific and clinical experts are international. We have "boots on the ground" in 10 international offices in the United States, United Kingdom, Europe, India, and Japan.

SCHIZOPHRENIA EXPERIENCE

Our schizophrenia-specific clinical trial experience includes global delivery of our solutions for:

- 10+ successful or pending NDAs or sNDAs
- 180+ protocols conducted in 60 countries with 75 different languages
- 5,600 sites and 17,000 unique raters trained across those 60 countries
- 90,000+ visits, for which data was analyzed with our proprietary analytics solution
- 8 late phase worldwide programs using our audio/video recordings and reviews

SCIENTIFIC & CLINICAL CONSULTING TEAM

Every schizophrenia study team is advised by our Scientific & Clinical Consulting team, comprised of leaders in evidence-based site selection, rater training and certification, electronic clinical outcome assessments, advanced predictive data analytics, and central review. By choosing us for your schizophrenia study, you will receive customized support from these individuals.

David Daniel, MD, Senior Vice President, Chief Medical Officer, Signant Health

Dr. David Daniel provides overall scientific, clinical, and strategic direction for our solutions and clients. He was the founder of the novel online rater training company, Bioniche Global Development, acquired by Signant Health.

Alan Kott, MUDr, Practice Leader, Data Analytics, Signant Health

Dr. Alan Kott and Dr. David Daniel have co-developed innovative, industry leading predictive analytic programs for early detection and remediation of flawed rating techniques.

Steve Targum, MD, Scientific Director, Signant Health

Dr. Steve Targum founded Pharmastart, pioneering rater training, and Clintara, delivering novel programs for subject eligibility and diagnostic review, both of which were acquired by Signant Health.

Amir Kalali, MD, Executive Advisor for Global Strategy, Signant Health

Dr. Amir Kalali is a globally recognized leader in clinical trial design and innovation, site selection, and maintenance of quality data.

Dan DeBonis, Principal, Signant Health

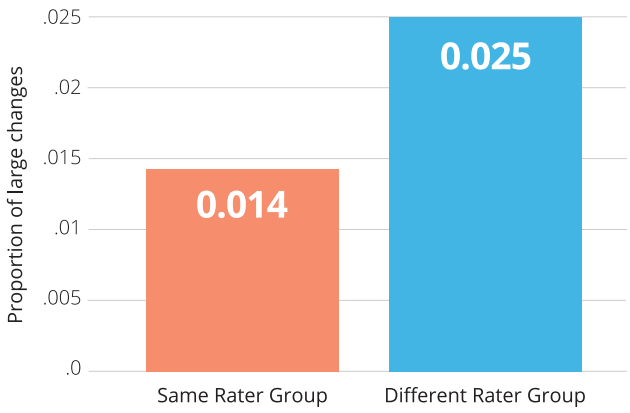
Dan Debonis was a founder of Concordant Rater Systems and along with Dr. Gary Sachs, invented the pioneering CNSenhanced eCOA platform, called Rater Station, which was acquired by Signant Health.

TYPICAL SCHIZOPHRENIA STUDY CHALLENGES

It is common for schizophrenia clinical trials to show inconsistent results or lack robust effect sizes when transitioning from phase II to phase III. Additionally, negative symptom schizophrenia trials frequently do not show significant separation between drug and placebo.

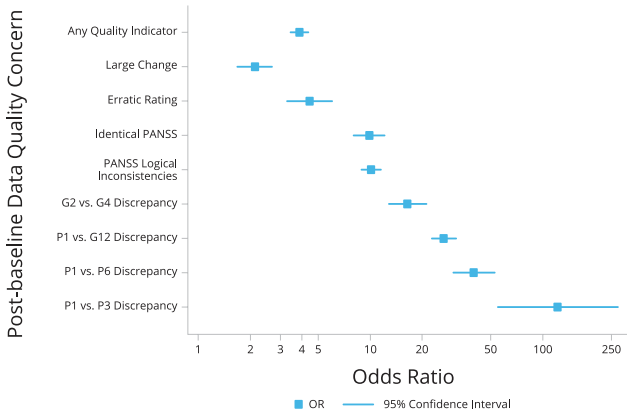
- Placebo response has increased in recent years without a concomitant increase in drug effect and placebo response is considered to have a serious confounding effect in schizophrenia clinical trials. It may be challenging or impossible to successfully modulate placebo response in a schizophrenia study due to expectation bias on the part of the rater, subject, and informant. Subjects may improve from the hospital environment, overly empathic interactions with the rater, or even the unintentional administration of psychotherapy especially when testing an exciting, plus novel and experimental approach to schizophrenia.
- Scales such as the PANSS, BPRS, NSA-16, BNSS, SANS, and PSP are long and complex, and raters are commonly unfamiliar with their subtleties. The job of rating in schizophrenia requires evaluation of multiple symptom domains, integration of patient and informant reports, and direct observation of behavior. Raters often do not perform thorough patient interviews and may neglect required informant information.
- Raters vary in their scoring basis for the CGI-S and in the case of changes in the rater, noise may be introduced into the ratings.
- Interview skills vary widely among raters and within the same rater over time, leading to information variance. Rater change across visits is associated with significantly increased data variability.
- Rater drift, known as changes in rater behavior across different test administrations, has the potential to undermine both intra-rater and inter-rater reliability, leading to measurement error, and undermining study success. An initial calibration of scale administration and scoring, to optimize inter-rater reliability, has been shown by multiple authors to enhance statistical power and thus increase the odds of study success. Periodic refresher training is associated with maintenance of high levels of agreement among raters. A typical scale certification plan assesses investigators by their proficiency in rating videotaped interviews alone. Rater training and certification plans should address standardization of interview technique.

Effect of Rater Change on Data Quality[5]



Changes of rater may be associated with erratic ratings which may increase placebo response and degrade signal. High levels of variability within a subject have been shown to be associated with reduced placebo-drug separation in schizophrenia trials.

Data Quality Errors are Often Recurrent[6]



In an analysis of 14 international double-blind placebo-controlled schizophrenia trials involving 7,752 subjects (and 64,947 visits), we found that post-baseline errors are, by large, related to the presence of the same or related errors in the screening phase.

OUR SOLUTIONS FOR SCHIZOPHRENIA CLINICAL RESEARCH

At Signant we take a comprehensive approach to address each of the above challenges.

RATER TRAINING & DATA QUALITY MONITORING

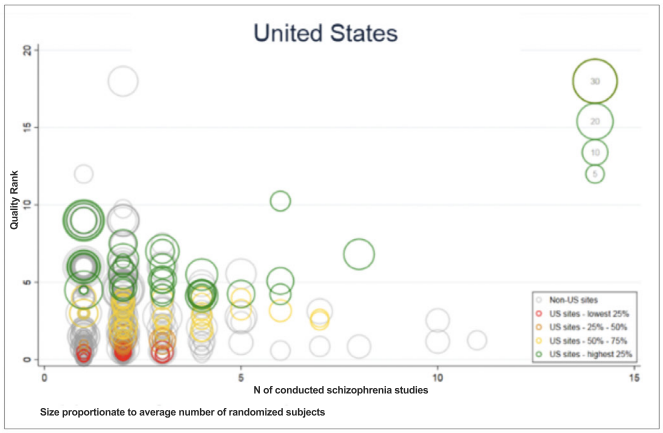
For the PANSS, CGI, and PSP scales, we train "new" raters (those raters for whom we do not have past certification and in-study performance data demonstrating interview and ratings proficiency) by utilizing a case-oriented approach that targets areas commonly scored erroneously. We incorporate placebo response and interview techniques into the training. Subject selection monitoring targets key inclusion and exclusion diagnoses and related diagnostic interview (e.g., SCID or MINI) procedures. We also conduct CGI standardization training and utilize annotated CGI anchor points (e.g. severity, frequency, impact) to increase accuracy and reliability of CGI ratings.

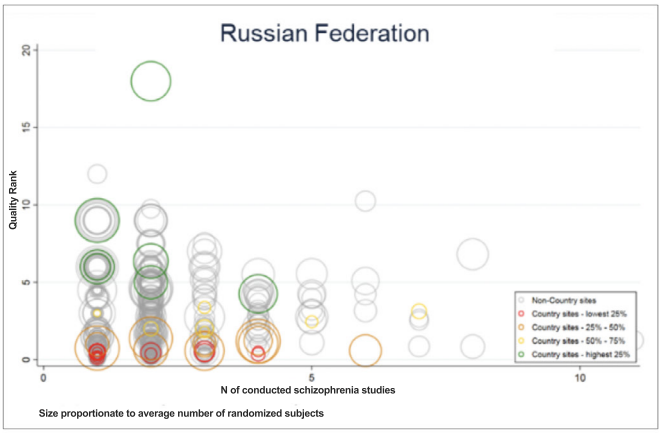
SCIENTIFIC & CLINICAL CONSULTING

EVIDENCE-BASED SITE AND RATER SELECTION

We will assist in rater and site selection. Where possible, we will utilize experienced, skilled, and calibrated raters who have previously been trained by Signant and have demonstrated proficiency in our scale certification testing and in-study data quality monitoring. To select sites and raters, we will consider previous performance by reviewing our blinded data analytics and historical external expert evaluations of recorded patient interviews (in which we conducted the training and monitoring). We can also provide color-coded graphical representations of site quality by country, as shown.

Site Quality in Schizophrenia Clinical Trials in the United States and Russian Federation





SUBJECT ELIGIBILITY REVIEW

A critical step in a successful study is to assure that only eligible, appropriate subjects are admitted. We use our proprietary methodology to conduct independent review of subject eligibility, diagnostic validation, and symptom severity confirmation to determine appropriateness of each subject for the study. We will ensure that only subjects meeting the diagnostic criteria, the PANSS total and positive symptom criteria, the acuity criteria, and other key requirements are admitted into the study.

ENHANCED ECLINRO WITH AUDIO AND VIDEO CAPTURE

ELECTRONIC SCALES ADMINISTRATION

We offer a complete eCOA solution that supports data collection via ePRO, eDiaries, eClinRO, eObsRO, ePerfO, and Connected Devices. Our enhanced eClinRO solution, Rater Station, uniquely incorporates edit checks that warn raters of potential errors in data quality prior to data submission. Data quality is improved by additional instructions and prompts built into the PANSS, CGI, and PSP. Alerts are sent when inclusion and exclusion criteria are violated after data submission, at screening and at baseline visits. Rater Station has been proven to significantly reduce errors in PANSS data (compared to paper administration).

AUDIO AND VIDEO CAPTURE

Audio or video recordings of PANSS interviews can be captured via Rater Station and assessed for interview and ratings quality by same language, same culture experts. Signant's expert reviewers undergo standardized in-depth scale training, qualification scoring, periodic calibration, and ongoing performance monitoring by Signant clinicians. Metrics, including intra- and inter-rater reliability, can be provided at critical points in the study.

DATA QUALITY ANALYTICS

Our proprietary, evidence-based data analytics can monitor and identify risks to your study data at the study, site, and rater level, while the study is ongoing. It identifies errors, erratic ratings associated with rater changes, illogical inconsistencies within eCOA data, and major inconsistencies between the CGI-S and PANSS. We help you interpret the findings and develop a remediation plan.

1. Fragas, Diaz-Caneja, Pina-Camacho, Umbricht and Arango, 2018.
2. Daniel, Bartko, Sartorius, Vieta, 2009.
3. Perkins, Wyatt and Bartko, 2000; Muller and Szegedi, 2002; Kane et al, 2005.
4. Daniel, Bartko, Allen, 2008, APA Annual Mtg.
5. Kott, Daniel. 2015
6. Kott, Daniel. 2016

WHO IS SIGNANT HEALTH?

The best technology succeeds in the background. Signant Health provides solutions that simplify every step of the patient journey to make it easier for people to participate in, and for sites and study teams to run, clinical trials. Signant unites eCOA, eConsent, Patient Engagement, IRT, Clinical Supplies and Endpoint Quality into the industry's most comprehensive patient-centric suite – an evolution built on more than 20 years of proven clinical research technology. Our intense focus on the patient experience, deep therapeutic area expertise and global operational scale enable hundreds of sponsors and CROs (including all Top 20 pharma) to extend the reach of drug development, expand patient opportunities and improve data quality – helping them bring life-changing therapies to our families and communities around the world. Take a significant step toward patient-centricity at signanthealth.com.

CRF Health and Bracket are now Signant Health.

SIGNANT HEALTH