SIGNANT HEALTH

DEMENTIA

THE INDUSTRY'S MOST SPECIALIZED eCOA SOLUTION FOR DEMENTIA CLINICAL RESEARCH

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

Dementia patients and their families have been yearning for new, and hopefully more effective treatment options. This is true both for cognition as well as for the neuropsychiatric symptoms that invariably accompany the illness and prove so challenging for all involved. Since the dementia clinical trial landscape has seen so many failures over the past 15 years, it is more important than ever that sponsors work with an experienced partner that can deliver the highest data quality. We have significant experience beyond Alzheimer's that includes Frontotemporal Lobar Degeneration (FTLD), Dementia with Lewy Bodies (DLB), and Parkinson's Disease Dementia (PDD), among others. Additionally, our scientific expertise extends beyond cognition to also include neuropsychiatric symptoms associated with dementia.

A PLATFORM SPECIALIZED FOR DEMENTIA RESEARCH

Signant's CNS-enhanced electronic clinician reported outcome (eClinRO) solution, called Rater Station®, has been utilized in dementia programs worldwide, including throughout Asia. Research has shown that it is able to significantly reduce rater error and improve data quality in these studies. Additionally, our validated, electronic versions of the:

- ADAS-Cog,
- MMSE,
- CDR,
- ADCS-ADL,
- RBANS,
- and more than 60 other scales have been extensively used in dementia related studies.

Rater Station offers enhanced eClinRO functions and features for clinician administered scales including interviews, edit checks and alerts, automated scoring as applicable, 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 extracts insights from clinical data. It has been used for dementia studies to identify quality issues at the study, site, rater, and subject level in near real-time, and our analytics experience is unmatched in the industry.

SIGNANT'S ALZHEIMER'S DISEASE AND OTHER DEMENTIA EXPERIENCE

160+
studies

75
languages

50+
countries

2,500
sites

18,000
raters trained

50,000
visits for which data was analyzed using our Data Quality Analytics solution

10
global late phase programs used our audio recordings and reviews

Dementia subtypes studied:

- Alzheimer's Disease
- Dementia with Lewy bodies (DLB)
- Frontotemporal dementia (FTD)
- Parkinson's disease (PD) dementia

Neuropsychiatric symptoms we address:

- Psychosis
- Agitation
- Apathy
- Depression
- Sleep disorders

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.

SCIENTIFIC & CLINICAL CONSULTING TEAM

Every dementia study team is advised by our Scientific & Clinical Consulting team comprised of leaders in evidence-based site selection, rater training and certification, eCOAs, advanced predictive data analytics, and data quality programs. You will receive customized support from these individuals.

David S. Miller, MD, MA
Clinical Vice President, Signant Health

Dr. Miller is a geriatric psychiatrist by training. He has over 25 years of experience in patient care, clinical research, and teaching, and has served as a principal investigator for dementia studies. He is the Chair of the Alzheimer's Association Research Roundtable, the Co-Chair of the ISCTM BPSD Work Group and was the founding Co-Chair of the ISTAART funded NPS-PIA.

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

Dr. Alan Kott, along with Dr. David Daniel, Senior Vice President and Chief Medical Officer, Signant Health, developed innovative, industry leading predictive analytic programs for early detection and remediation of flawed rating techniques.

Dan DeBonis
Principal, Signant Health

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

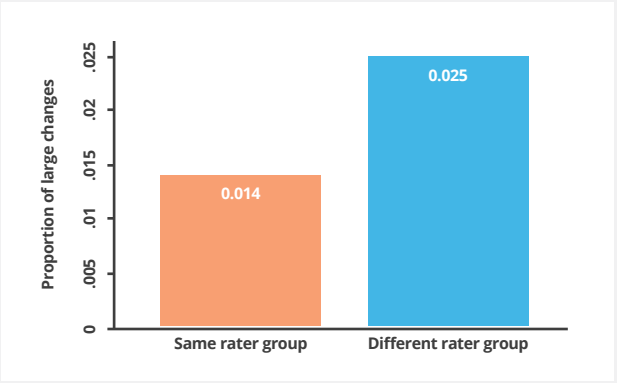
Additional support will be provided by in-house clinicians with deep dementia clinical trial experience to ensure we provide investigator and site selection, highly effective training, and data quality monitoring.

TYPICAL DEMENTIA STUDY CHALLENGES

For dementia clinical trials, whether seeking to confirm previously used therapeutic targets or to validate new ones, it is crucial to be able to be confident that the study results accurately reflect the study drug's ability to separate from placebo. We are experienced in addressing the special issues associated with dementia studies seen with all of the outcome measures commonly used in the United States and across the globe. Over the last 15 years, no new drugs have been approved for dementia. Many of the potential dementia therapies that initially showed promise in phase II, failed in phase III.

- 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 dementia clinical trials.[1]
- Identification of patients who meet the relevant diagnostic and severity criteria for study entry is the initial critical hurdle for study success. Assuring entry of appropriate patients may require close scrutiny in the United States, Eastern Europe, China, and Japan.
- Many of the scales used in dementia trials are long and complex. Raters are commonly unfamiliar with the subtleties of scales like the RBANS or NPI-C and frequently do not follow the complex rating rules of the CDR, RBANS, or DKEFS, scoring them erratically. Raters often do not document the rationale for their ratings. Scoring some of these scales requires evaluation of multiple symptom domains, integration of subject and informant reports, and direct observation of behavior. Raters often do not perform thorough subject interviews and may neglect required informant information.
- Raters vary in their scoring basis for the CGI-S, CGI-I, CIBIS/CIBIC+, and/or other global measures and in the case of changes in the rater, noise may be introduced into the ratings. Suggested probes and annotated anchors, which increase the reliability of the measurement, are often ignored or not uniformly applied.
- It may be challenging or impossible to successfully modulate placebo response in a dementia study due to expectation bias on the part of the rater, subject, and/or informant. Overly empathic interactions with the subject or even the unintentional use of therapeutic interventions particularly when testing an exciting novel experimental approach to dementia need to be monitored.
- Interview skills vary widely among raters and within the same rater over time[2], leading to information variance. Rater change across visits is associated with significantly increased data variability. For example, a relatively high prevalence of identical scoring of scale items across consecutive visits has been noted in some studies[3]. This is considered a marker for raters relying on previous interviews rather than completing an independent and thorough current interview.
- Rater drift has the potential to undermine both intra-rater and inter-rater reliability, leading to measurement error, and undermining study success. The objective of initial calibration of scale administration and scoring is to optimize inter-rater reliability which has been shown by multiple authors to enhance statistical power and thus increase the odds of study success[4]. Ongoing in-study data quality reviews help ensure that raters consistently adhere to the administration and scoring conventions they were initially taught. Typical scale certification plans assess investigators on 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.

OUR SOLUTIONS FOR DEMENTIA CLINICAL RESEARCH

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

RATER TRAINING & DATA QUALITY MONITORING

For the dementia scales, we provide enriched training to new or inexperienced raters (those raters who fall below the desired level of experience) by utilizing a case-oriented approach that targets areas commonly scored erroneously. We incorporate placebo response and interview techniques into the training.

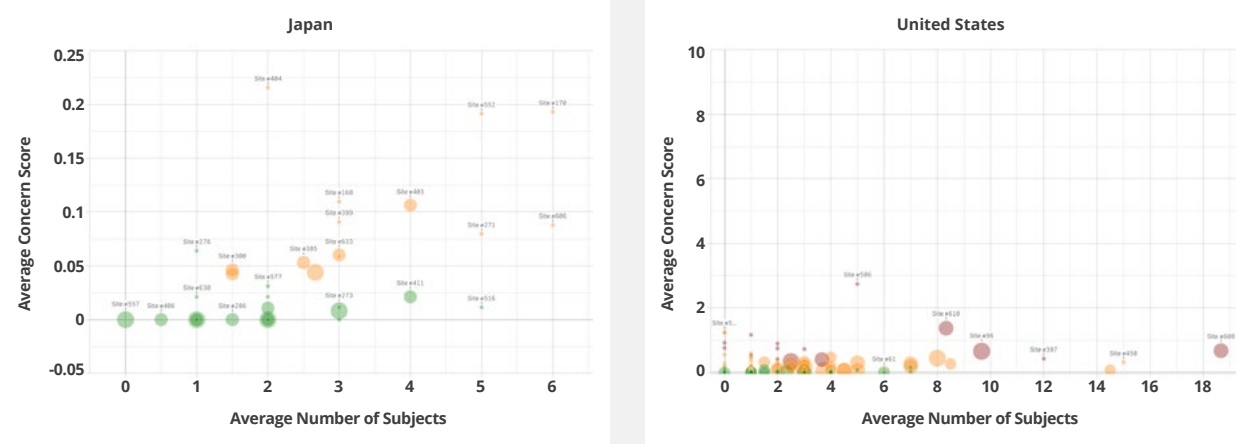
All data quality reviews will be conducted by Signant calibrated expert reviewers, which include an extensive team of in-house clinicians as well as a global team of expert reviewers. Training, qualification, calibration, and quality control of this group is critical to study success. For each scale reviewed/rated by our team of expert clinicians we provide standard in depth scale training review, qualification scoring, periodic calibration, and ongoing performance monitoring by Signant clinicians. Metrics, including intra- and inter-rater reliability, will be provided to you in-study and as part of the final report.

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 consider previous performance by reviewing our blinded data analytics and historical external expert evaluations of recorded subject 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 DEMENTIA CLINICAL TRIALS IN JAPAN AND THE UNITED STATES[6]



Subject Eligibility Review

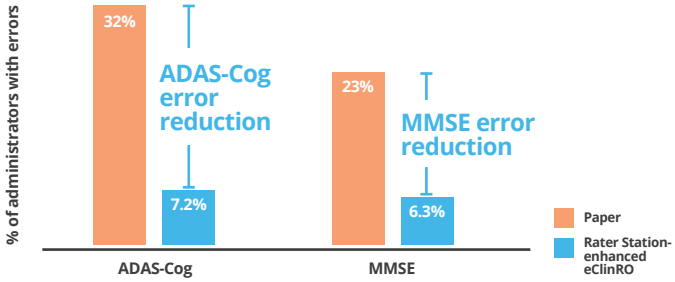
A critical step in a successful study is to assure that only eligible, appropriate subjects are enrolled. We use our proprietary methodology to conduct independent review of subject eligibility, diagnostic validation, and symptom severity confirmation to determine appropriateness of each subject for the study. We will ensure that only subjects who meet the designated diagnostic and severity criteria will be included in the study.

ENHANCED eCLINRO WITH AUDIO AND VIDEO CAPTURE

Electronic Scales Administration

We offer a complete eCOA solution that supports data collection via home or site-based ePROs, eClinROs, eObsROs, and collection of integrated wearable and sensor data. 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 scales. 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 data errors (compared to paper administration).

RATER STATION SIGNIFICANTLY REDUCED ADMINISTRATION ERRORS IN ALZHEIMER'S DISEASE SCALES[7]



Using Rater Station and Signant's Endpoint Quality solutions for in-study data quality monitoring (to identify errors in scoring and administration) has been proven to significantly improve data quality by reducing rater error, standardizing administration and scale scoring, and minimizing rater drift over the course of the trial.

Audio and Video Capture

Audio recordings of scales vital to determining inclusion and/or efficacy 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.

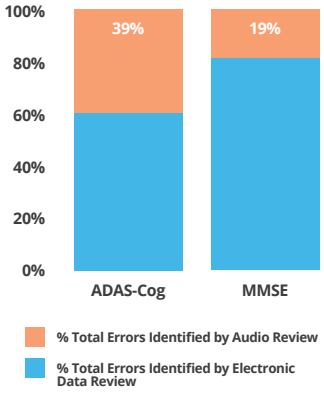
AUDIO REVIEWS IMPROVED ADMINISTRATION QUALITY OF ALZHEIMER'S DISEASE eCOA SCALES IN TWO STUDIES

STUDY 1:
AUDIO REVIEWS IMPROVED RATER PERFORMANCE

We evaluated the impact of audio review on rater performance across two time points to determine if remediation of administration issues resulted in subsequent improvement in administration. Administrative errors decreased from 16% (273/1735) of visits at screening to 9% (83/965) of visits at baseline, demonstrating a significant improvement (a 45% decrease in errors).[8]

STUDY 2:
AUDIO REVIEWS DETECTED ERRORS NOT FOUND VIA WORKSHEET REVIEW

Breakdown of All Identified Errors by Review Source



We found that adding audio reviews of scale administrations detects additional errors that are not apparent on worksheet review alone, thereby further improving data quality over the course of the trial. In our preliminary analysis of data from 96 ADAS-Cogs and 170 MMSEs from a clinical trial, we found that 39% of all errors in administration of the ADAS-Cog and 19% of all errors in administration of the MMSE were identified by audio review.[9]

DATA QUALITY ANALYTICS

Our proprietary, evidence-based Data Quality Analytics solution is an integral part of our Endpoint Quality offering that maximizes the accuracy and reliability of patient and clinician-rated endpoint data. It is an adaptive risk-based monitoring program for outcome measures. It identifies and monitors risks to your study data at all relevant levels while the study is ongoing. It detects errors, questionable patterns of data, data discordances both within and between instruments, as well as possible data tampering and fraud. Our team of dedicated clinicians interpret the findings and develop and execute a customized remediation plan for the identified issues and risks.

COMPUTERIZED COGNITIVE TESTING

Our computerized cognitive testing solution, called the Cognitive Drug Research (CDR) System, offers sponsors the potential to detect the earliest and most subtle evidence of cognitive impairment (e.g., attention, speed of processing, etc.). This system can be deployed as a complement to any dementia trial, but it is perhaps most useful in the earliest phases of dementia (i.e. preclinical) where the ability to detect change is beyond the scope of many traditional measures.

1. Fragas, Diaz-Caneja, Pina-Camacho, Umbricht and Arango. 2018.
2. Daniel, Bartko, Sartorius, Vieta. 2009.
3. Kott and Daniel. 2014.
4. Perkins, Wyatt and Bartko, 2000; Muller and Szegedi, 2002; Kane et al. 2005.
5. Kott, Daniel. 2015.
6. Signant Health Data Quality Analytics product.
7. H. Todd Feaster PsyD, Todd M. Solomon PhD, Danielle Abi-Saab PsyD, Annamarie Vogt, PhD, Jordan M. Barbone BA, John Harrison PhD and David S. Miller MD, MA. The Impact of Electronic Clinical Outcome Assessments (eCOA) on Alzheimer's Disease Clinical Trial Data Quality. Poster presented at AAIC 2017.
8. Todd M. Solomon, PhD, H. Todd Feaster PsyD, Jordan M. Barbone, BS and David S. Miller, MD, MA. Utilizing Audio Review to Improve ADCS-ADL Data Quality. Poster presented at CTAD 2017.
9. David S. Miller, MD, MA, Todd M. Solomon, PhD, and Jessica Meyer, BA. Intelligent Clinical Interviews for Alzheimer's Disease: How the Addition of Audio Reviews to eCOA Scale Administration Results in Improved Data Quality. Poster presented at AAIC 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.

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