Conversations in CNS

Expert Notes from the Field on Trial Success

VOLUME ONE

SIGNANT HEALTH
THE EVIDENCE GENERATION COMPANY

Table of contents

SIGNANT HEALTH
THE EVIDENCE GENERATION COMPANY

Foreword

DAVID G DANIEL, MD
Executive Advisor

David G. Daniel, MD, leads scientific, clinical, and strategic direction for CNS solutions at Signant Health. With over 30 years of experience in psychiatric clinical trials, he has published extensively and holds patents for treatments in epilepsy, anxiety, and psychotic disorders.

A multitude of exciting and mechanistically novel CNS drugs have been approved in recent years, bringing our patients and their families more effective and better tolerated treatments. These successes have occurred in the face of the numerous challenges inherent to signal detection in CNS clinical trials. Early promising CNS trial successes often fail to replicate in larger trials. Overall, the likelihood of approval of investigational compounds in both psychiatry and neurology remains modest compared to many other therapeutic areas.[1] The reasons for these challenges are multifactorial:

01 CNS endpoints are typically subjective, and subject to variability in scoring.

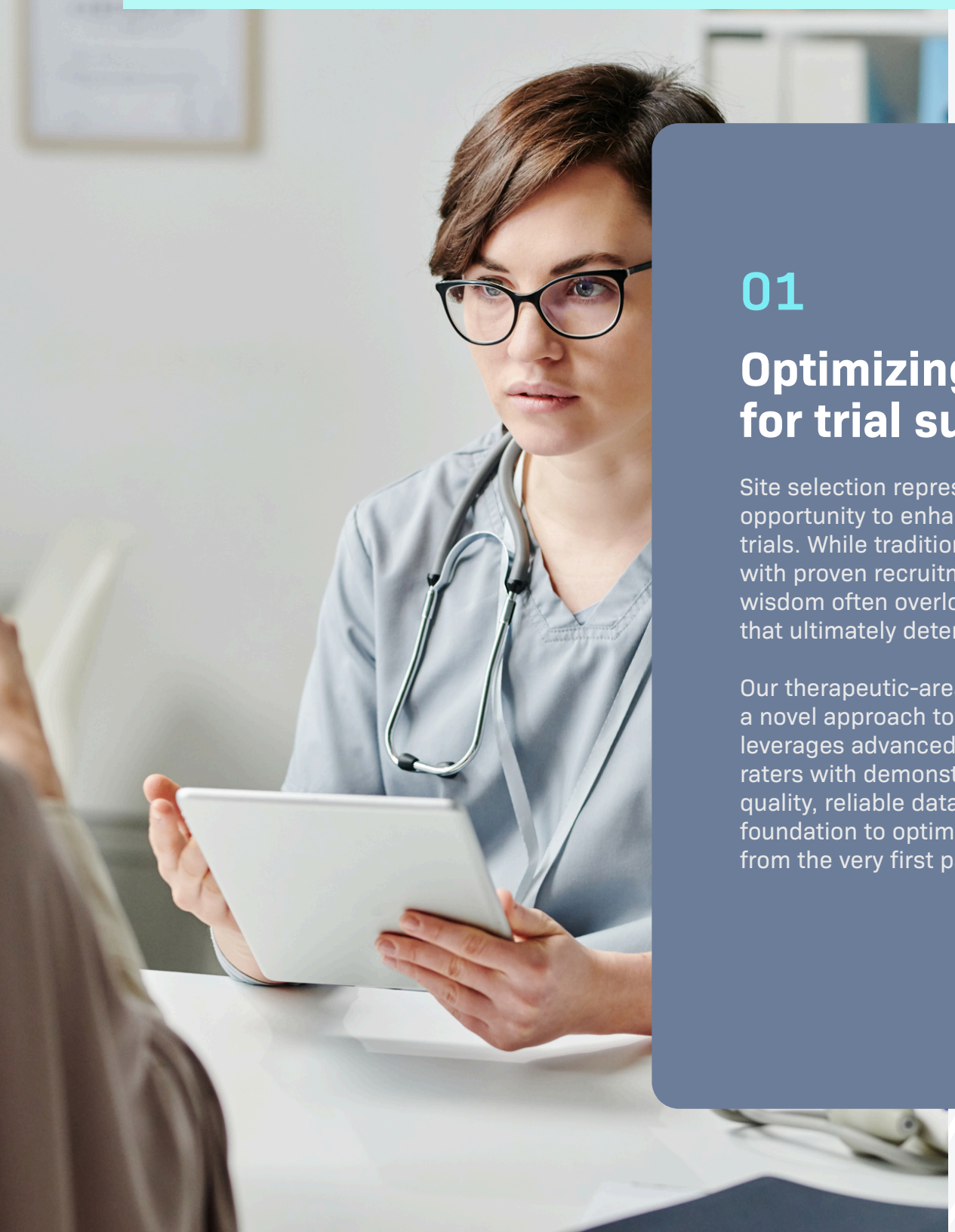
02 Placebo response can be high, obscuring treatment effects.

03 Patient selection may be complicated by diagnostic uncertainty, mixed motivations from trial participants, and baseline score inflation to meet eligibility criteria.

With CNS therapeutic development facing increasing scrutiny from regulators, investors, and patients, the need for methodological rigor and data quality excellence has never been more critical.

In our experience, optimization of data quality in CNS trials benefits from a comprehensive approach spanning trial design consultation, performance-based site selection, calibration of clinician ratings through tailored rater training, electronic capture to drive standardized administration and consistent scoring, sustained placebo response mitigation measures, and continuous in-study monitoring of rating quality coupled with remediation. At Signant Health, we have dedicated considerable resources to understanding and refining these approaches.

Each volume of Conversations in CNS – Expert Notes from the Field on Trial Success reflects our commitment to scientific rigor and methodological innovation, and represents the collective wisdom of veteran clinicians and scientists who have dedicated their careers to advancing CNS research. Each detailed topic area is explored through the lens of specific therapeutic areas—from Alzheimer's to Parkinson's disease to pediatric depression—providing practical insights and concrete examples of how these principles translate into practice.



01

Optimizing site selection for trial success

Site selection represents a critical yet underutilized opportunity to enhance data quality in CNS clinical trials. While traditional approaches rely on familiar sites with proven recruitment capabilities, this conventional wisdom often overlooks critical data quality indicators that ultimately determine trial success.

Our therapeutic-area and data analytics experts explore a novel approach to evidence-based site selection that leverages advanced data analytics to identify sites and raters with demonstrated excellence in generating high-quality, reliable data, thus establishing a robust foundation to optimize the probability of trial success from the very first patient enrolled.

A data-driven approach to clinical trial site selection

MARTINA MICALETTO, ALAN KOTT, & PETRA REKSOPRODJO

INTRODUCTION

Data quality and integrity are fundamental to clinical trial success. While sponsors invest heavily in post-site-selection quality measures like rater training and data quality monitoring, opportunities to enhance data quality exist much earlier in the process - particularly during site selection.

By leveraging historical performance data analytics at this crucial stage, sponsors can further optimize opportunities for trial success from the very beginning.

SITE SELECTION AND SITE VERIFICATION IN CLINICAL TRIALS

Selecting the right research sites is one of the most critical decisions sponsors make when planning a clinical trial. Site selection involves evaluating and choosing research centers that will conduct the trial, while site verification provides detailed quality assessment of pre-selected sites. These processes directly impact patient recruitment, data quality, and ultimately, trial success.

COMMON CHALLENGES WITH CLINICAL TRIAL SITE SELECTION

The industry has historically relied on familiar sites with proven recruitment capabilities and extensive trial experience. However, research shows that even experienced sites can present unexpected data quality issues.

Poor site selection can lead to enrollment delays, protocol deviations, and compromised data integrity - issues that become extremely costly to address once a trial is underway.

This traditional approach can limit participant diversity and potentially impact treatment efficacy assessment across broader populations.

OUR SOLUTION:
EVIDENCE-BASED SITE SELECTION/VERIFICATION WITH PURESIGNAL ANALYTICS

PureSignal Analytics, Signant's blinded data analytics solution, enables sponsors and CROs to harness advanced data science capabilities to transform the site selection process. It can analyze historical performance data across multiple dimensions while maintaining data privacy and trial integrity. By analyzing patterns in anonymized historical data, the system provides sponsors and CROs with evidence-based insights to optimize site selection.

HOW IT WORKS

01 Our Digital Health Science team employs PureSignal Analytics to identify sites and raters with demonstrated excellence in data quality.

02 The platform evaluates performance across multiple parameters:

- Historical data quality metrics
- Cross-indication experience
- Geographic performance patterns
- Patient recruitment efficiency
- Protocol compliance rates
- Assessment consistency
- Data completion rates

03 The system generates intuitive, ranked site lists based on customizable quality metrics designed by clinical and scientific experts.

04 This enables sponsors to:

- Identify sites requiring specific training interventions
- Detect potential eligibility or placebo response concerns
- Target areas for enhanced monitoring
- Make evidence-based site selection decisions
- Optimize resource allocation

For sponsors with predetermined sites of interest, our verification reviews provide detailed quality assessments to inform training and monitoring strategies. This targeted approach helps sponsors maximize the return on their site management investments.

CONCLUSION

Evidence-based site selection and verification represent powerful opportunities to enhance clinical trial quality before the first patient is enrolled. Powered by PureSignal Analytics, our comprehensive site performance analysis helps sponsors identify and select sites with proven track records of generating high-quality data. This data-driven approach enables sponsors to optimize their site networks, enhance protocol compliance, and improve data integrity from study start.

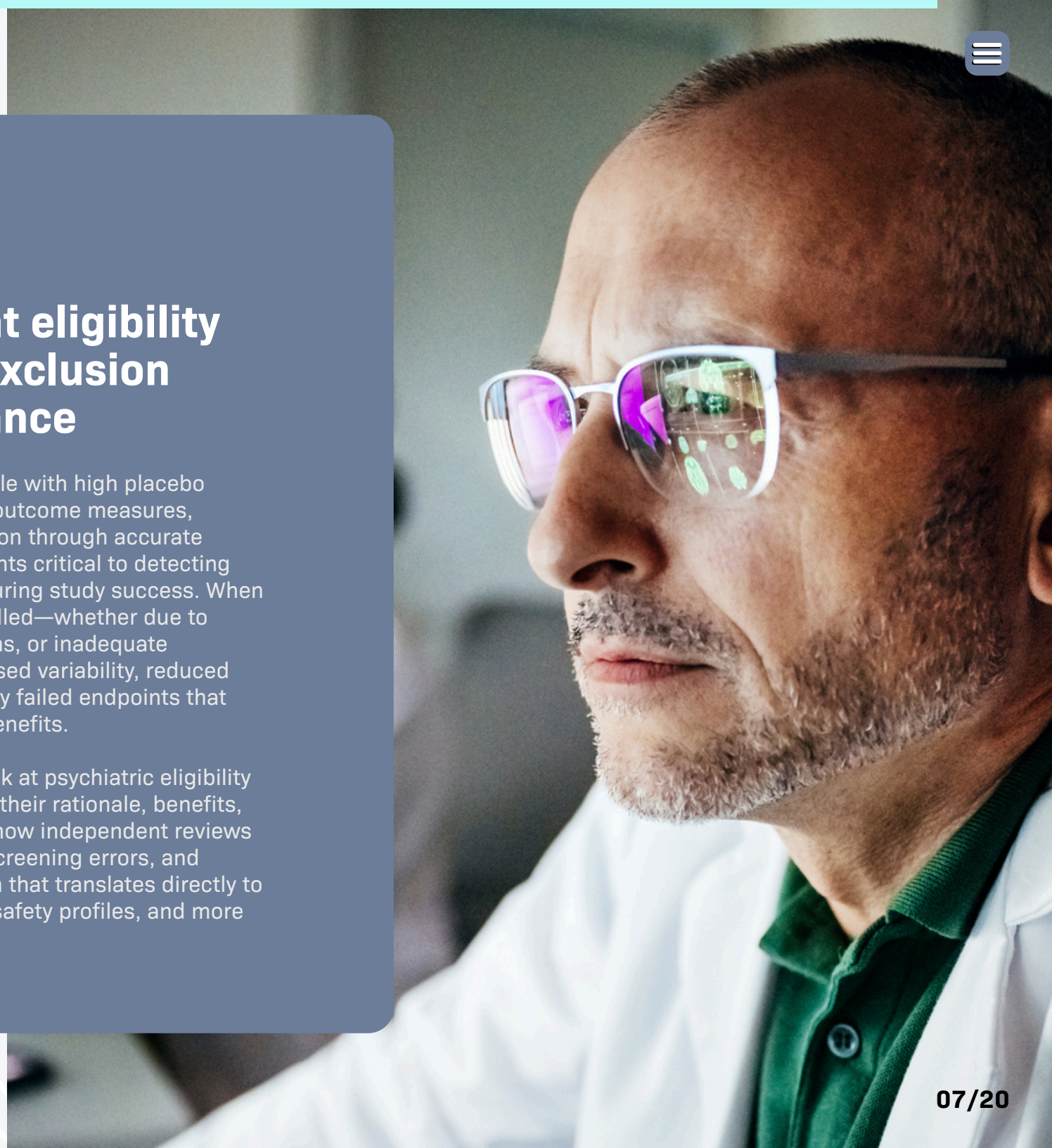
When sponsors make evidence-based decisions in selecting the best-performing sites for their trials, they build stronger foundations for study success and accelerate the development of new treatments.

02

Ensuring patient eligibility and inclusion/exclusion criteria compliance

CNS disease areas often struggle with high placebo response rates and subjective outcome measures, making rigorous patient selection through accurate psychiatric eligibility assessments critical to detecting true treatment effects and ensuring study success. When inappropriate patients are enrolled—whether due to misdiagnosis, protocol violations, or inadequate screening—studies face increased variability, reduced statistical power, and potentially failed endpoints that obscure genuine therapeutic benefits.

This article offers a detailed look at psychiatric eligibility reviews in CNS trials, including their rationale, benefits, and best practices. It explains how independent reviews enhance consistency, reduce screening errors, and support better patient selection that translates directly to improved effect sizes, cleaner safety profiles, and more successful study outcomes.



Understanding and Optimizing Independent Psychiatric Eligibility Reviews in CNS Trials

JULIET BROWN, RACHEL BERMAN

INTRODUCTION

Ensuring accurate psychiatric eligibility assessments is critical to the success of CNS clinical trials. Variability in diagnostic practices, investigator subjectivity, and the complexity of psychiatric conditions can introduce inconsistencies that impact data quality and study outcomes. Independent Psychiatric Eligibility Reviews help mitigate these challenges by providing a standardized, objective approach to screening decisions.

Let's explore the key aspects of Independent Psychiatric Eligibility Reviews—what they are, why they matter, when they are needed, and how they can be optimized to enhance trial integrity and patient safety. By leveraging expert clinical adjudication, sponsors can improve diagnostic accuracy, reduce bias, and strengthen the overall reliability of CNS trial data.

WHAT ARE INDEPENDENT PSYCHIATRIC ELIGIBILITY REVIEWS?

Standardized, independent adjudication of screening data and supporting information is common in CNS clinical trials. In some trials, adjudication takes the form of Psychiatric Eligibility Reviews, in which an independent cohort of highly trained clinicians considers relevant psychiatric screening information, including documented diagnostic evaluation results, inclusionary scale data, data from other key scales, safety data, site investigator clinical notes, and audio/visual recordings of site rater assessments if collected at the site.

WHY ARE INDEPENDENT ELIGIBILITY REVIEWS NEEDED?

Independent Psychiatric Eligibility Reviews ensure standardization of the information that is considered for psychiatric eligibility, as well as uniformity of the processes used in patient disposition decision-making across cases, sites, and geographical regions. Such reviews also provide assurance that key pieces of information are considered in the final eligibility decision.

Third-party Psychiatric Eligibility Reviews also ensure sound clinical decision-making and appropriate patient disposition.

Not all site investigators have clinical expertise in disease course, varying disease symptom manifestations and severity levels, and common comorbidities, especially in studies for which the indication is a rare or complex disease.

Additionally, rates of diagnostic scale administration errors and misapplication of psychiatric diagnostic conventions are surprisingly high.[3,6] Combining Eligibility Review-related site investigator queries with scale administration and scoring feedback produces two positive outcomes: increased confidence in patient selection and prospective improvements in data validity and reliability.

When patients who do not actually have the target indication or those who fail to satisfy all eligibility criteria are randomized, data noise and placebo response may increase, and the drug's efficacy signal may be clouded. Having an external expert review the eligibility data can help ensure that only appropriate patients are admitted into the study, thus increasing the likelihood of study success.

Independent Psychiatric Eligibility Reviews also control for the influence of cognitive bias. Debiasing one's own beliefs is complex. It requires both awareness of one's personal biases and the deleterious effects they can have on patient safety and study success, and successful application of debiasing strategies, which vary from person to person.[7]

A neutral "second opinion" can be invaluable, particularly in pivotal trials or studies involving more complicated primary indications and exclusionary diagnostic rule-outs. Third-party, centralized eligibility reviewers are divorced from site-related pressures and objectivity-hampering relationships with screening patients and have more time to dedicate exclusively to each case.

A robust, independent Psychiatric Eligibility Review system can mitigate the risk of excessive heterogeneity in a study population that could lead to atypical endpoint data variability and impede signal detection.

The diagnostic confidence and consistency afforded by secondary reviews will lesson potential noise introduced by patient psychosocial, gender, sex, and cultural variability. Controlling for excessive heterogeneity is critical in large, global trials and those purposively attempting to gather a diverse sample to achieve research and treatment equity goals.

In clinical trials, there is wide agreement that patient safety is paramount. Third-party Psychiatric Eligibility Reviews add an extra layer of patient safety protection. Such safety cross-checks can be invaluable in busy trials and studies of high-risk populations.

WHEN ARE INDEPENDENT PSYCHIATRIC ELIGIBILITY REVIEWS NEEDED IN CNS TRIALS?

There is a clear case for the use of third-party Eligibility Reviews in studies of more complex or at-risk psychiatric diagnoses (e.g., Borderline Personality Disorder), those investigating treatment of indications with more heterogenous symptom presentations (e.g., Dementia[3]), or studies involving diagnoses that commonly present with features that can increase the differential diagnostic challenge and lower diagnostic confidence (e.g., Major Depressive Episode with Mixed Features).[7]

Approximately one third of adults with a confirmed diagnosis of psychiatric disorder within the past year had a comorbid psychiatric disorder.[2] Differential diagnosis can be daunting, particularly with patients who are suboptimal reporters, have an unclear history, or have overlapping or conflicting comorbidity courses, or in studies where the chosen diagnostic scale does not allow for formal evaluation of all potential differentials.

The effects of clinical trial misdiagnoses extend well beyond the patient's trial completion, with potential stigma and adverse impact to treatment (e.g., unnecessary hospitalizations, inappropriate pharmacotherapies) and quality of life (e.g., occupational impairment) - risks that cannot be overstated.[3]

SOME COMMONLY ENCOUNTERED DIFFERENTIAL DIAGNOSTIC MISTAKES INCLUDE:

- **Misdiagnosis of Major Depressive Disorder in a younger adult patient with Bipolar I or II Disorder**
- **Misdiagnosis of Bipolar I Disorder in a patient with Major Depressive Disorder within which some Major Depressive Episodes have included Mixed Features**
- **Misdiagnosis of Schizophrenia in a patient with Bipolar I Disorder with a history of positive psychotic symptoms in the context of one or more lifetime Manic Episodes**
- **Misdiagnosis of Generalized Anxiety Disorder in a patient with Adjustment Disorder with Anxiety caused by a current, major life stressor**
- **Misdiagnosis of Bipolar Disorder in a patient with Polysubstance Abuse**

Agreement between a site-based study diagnostician and a centralized, independent clinician helps ensure ascertainment of appropriate patients who can safely participate in a trial safely.

Independent Eligibility Reviews can be especially helpful when a protocol's inclusion and exclusion criteria allow room for investigator subjectivity. For example, in studies whose protocols disallow psychiatric disorders that are commonly comorbid with the illness under study only if the comorbidity is the primary driver of treatment relative to the study indication-related diagnosis, determination of the primary vs. secondary nature of psychiatric disorders is complicated and prone to decision-making bias.

The degree of complexity increases for patients who are not currently receiving standard of care treatment. A third-party psychiatric adjudicator can provide a fresh, objective perspective and increase diagnostic and decision-making certainty.

STEPS TO BETTER ELIGIBILITY DECISIONS

We propose that independent Eligibility Review clinicians employ the DSM-5-TR Differential Diagnosis Model to ensure accurate Diagnostic Validation decision eligibility decisions in CNS trials. Following the model's step-wise logical flow described below will bring uniformity and thoroughness to the independent review process.

Rule out malingering and Factitious Disorder

- Consider the face validity of the presenting syndrome
- Consider signals that an individual is a career patient

Rule out substance-related etiology

- Evaluate whether symptoms are directly caused by substance, withdrawal or intoxication

Rule out medical etiology

- (Direct/biological or indirect/psychological)

Determine the primary diagnosis in cases with psychiatric comorbidities

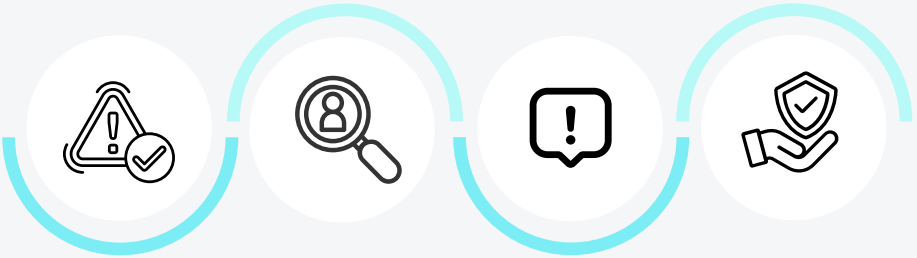
- Determine which diagnosis is the main driver of treatment decisions

Rule out the possibility that the primary syndrome is representative of Adjustment Disorder or an Other Specified or Unspecified Disorder

Rule out syndromes that are on the boundary of normalcy

- Choose patients for whom there is confirmed pathological impairment or distress
- Consider signals that a patient may be an overzealous reporter whose symptoms are less severe than reported

This step-wise approach ensures that reviews go well beyond a protocol-associated 'checkbox' approach. Extended from the above system for diagnostic validation, Signant Health reviewers are trained to also consider the following additional case factors:



Potential psychosocial, medical, and psychiatric data confounds

Temporal instability of illness severity, particularly recent improvement

Ability of patients to clearly and frankly report symptoms

Prospective safety risks

HOW CAN WE OPTIMIZE INDEPENDENT PSYCHIATRIC ELIGIBILITY REVIEWS?

At Signant Health, we strive to enhance the value of our Eligibility Review service by incorporating the following:

01 **Robust and extensive reviewer training at the universal and site-specific level**

02 **Ongoing reviewer access to clinical consultation and case discussion meetings**

03 **Ease of access to all relevant information, including electronic data, paper source, audio or video recordings of site rater scale interviews**

04 **Timely, collegial contact with site investigators via email or phone for information clarification and provision of scale administration and scoring reminders**

05 **Use of the Signant Health Clinical Validation Inventory for Study Admission (C-VISATM) as a low burden electronic platform for site investigators to synthesize all case information for independent reviewer reference[5]**

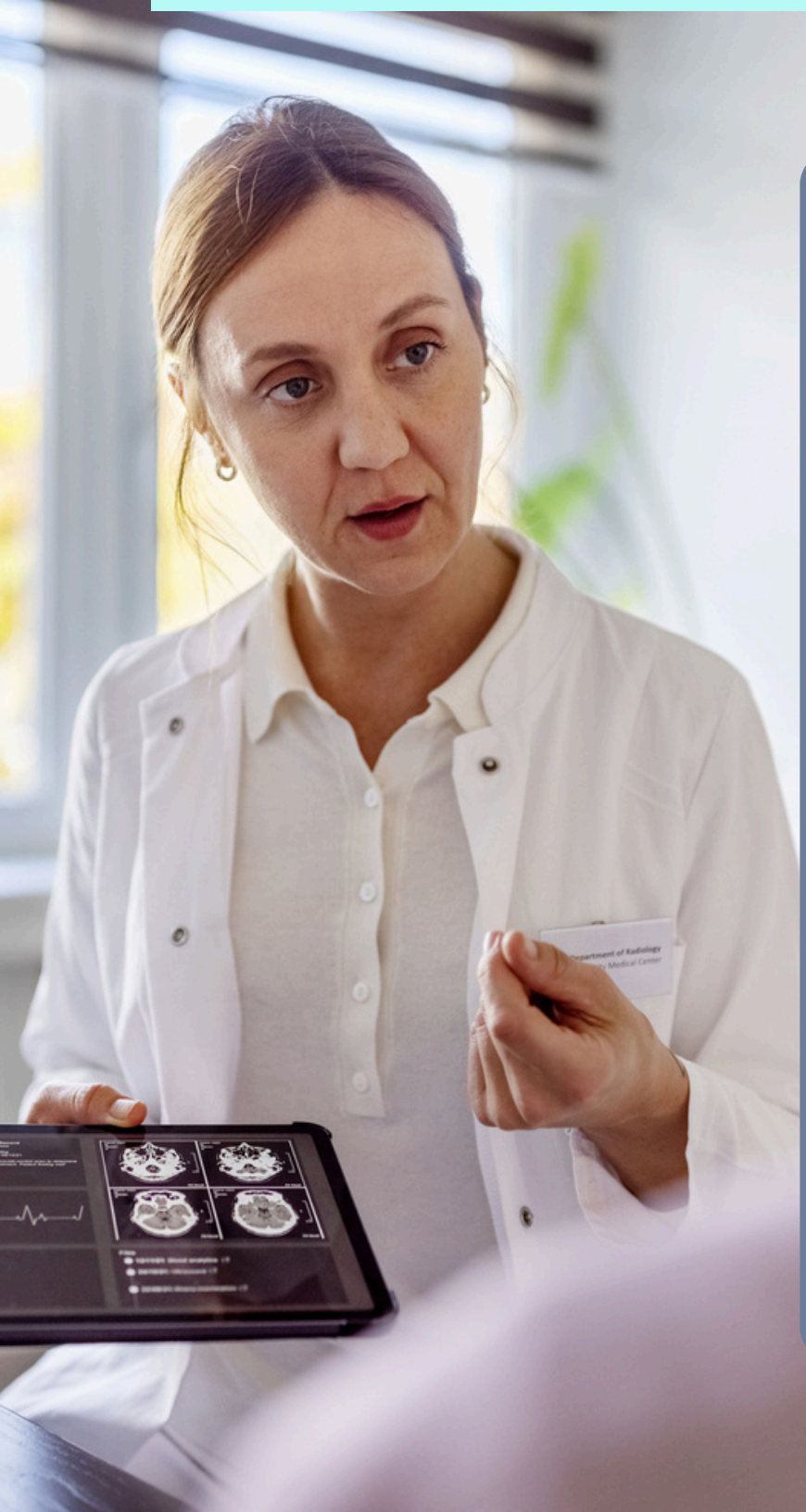
06 **Review by a second independent clinician for particularly complex cases**

07 **Understanding that site investigators are the experts regarding each screening patient and are partners in ensuring patient safety and appropriate patient ascertainment**

08 **Close collaboration with study sponsors**

PULLING IT ALL TOGETHER

Incorporation of Signant's psychiatric eligibility review services combined with its Data Quality Monitoring (DQM) offerings (e.g., eCOA exclusion and safety alerts, edit checks and data quality flags, Central Scoring, Tandem Rating, Central Quality Reviews of administration and ratings associated with endpoint scales, PureSignal Analytics) result in high-quality data and mitigation of risks to study success.



03

Standardizing clinician ratings technique for accuracy and consistency

Alzheimer's trials face unique challenges with cognitive assessment reliability and the detection of subtle disease progression. The subjective nature of the gold-standard measures including the MMSE and ADAS-Cog can lead to inter- and intra-rater variability that can obscure true treatment effects.

This article explores how subtle rater errors such as scoring drift or misinterpretation can impact Alzheimer's trial outcomes, with parallels to trials in other CNS disease indications. It highlights how data-driven detection methods and targeted training reduce variability and improve signal detection.

Uncovering Common Rater Errors in Cognitive Assessments for Alzheimer's Clinical Trials

MARCELA ROY, SAYAKA MACHIZAWA, MARTA PEREIRA, DAVID MILLER

INTRODUCTION

Cognitive assessments are the backbone of Alzheimer's disease (AD) clinical trials, providing crucial data on disease progression and treatment efficacy. Among the most widely used tools, the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) serve as gold-standard measures for assessing cognitive decline.

The MMSE, a quick 30-point screening tool, evaluates key cognitive domains such as orientation, memory, attention, language, and visuospatial skills. Its efficiency and ease of use make it a preferred tool for both initial screening and clinical trial endpoints.

The ADAS-Cog, designed specifically for tracking cognitive changes in AD patients, has long been a cornerstone in research. The original 11-item version, with scores ranging from 0 to 70, is widely used, but a newer ADAS-Cog 13 has been introduced to improve sensitivity in detecting mild cognitive impairment (MCI) and early-stage AD.

Both assessments play an essential role in trials, but ensuring their accurate administration is just as critical as choosing the right scale.

WHY DATA SURVEILLANCE MATTERS

High-quality data in AD trials depends on rigorous data surveillance programs. At Signant Health, we use centralized reviews of collected responses, video-recorded written or drawn responses, and audio evaluations of clinical assessment interviews to identify rater errors in time. By identifying deviations, data surveillance ensures assessments remain accurate, standardized, and reliable across sites. This timely approach prevents inconsistencies from skewing trial results.

Some instruments or tasks are prone to mistakes due to complexity, lack of unfamiliarity, or other factors.

The MMSE and ADAS-Cog are no exceptions; unique factors make it challenging to standardize the administration and scoring of these instruments.

HOW CAN WE OPTIMIZE INDEPENDENT PSYCHIATRIC ELIGIBILITY REVIEWS?

One major issue with ADAS-Cog is confusion between different versions of the manual. The 1994/1998 version and the 2013 version have distinct instructions and scoring conventions, yet raters who have worked with both often mix them up. Many earlier large-scale AD trials used the 1994/1998 version, while newer studies tend to favor the 2013 version. However, some modern trials still revert to the older version, increasing the risk of administration errors.

The MMSE, in use for over 50 years, presents its own set of challenges. As one of the most widely administered cognitive screening tools, it is routinely used in both clinical practice and research. While this widespread use makes it accessible, it also results in inconsistent administration. Multiple MMSE versions exist, including the official version sold by Psychological Assessment Resources (PAR) and various free adaptations found online. Unlike ADAS-Cog, the MMSE manual lacks detailed scoring guidelines, making it difficult to maintain consistency across different raters and trial sites.

In clinical practice, minor deviations in MMSE administration may not significantly impact a patient's diagnosis. However, in clinical trials, even small inconsistencies can introduce noise into the data, making it harder to detect meaningful treatment effects. Standardization is crucial—without it, trial results become less reliable.

UNCOVERING COMMON MMSE RATER ERRORS

To better understand and reduce inconsistencies in MMSE administration, we analyzed central review data from two large multinational Phase 3 AD trials. A total of 10,203 MMSE assessments were reviewed, revealing 26.8% flagged for administration errors and 27.0% flagged for scoring errors.

The most frequently observed issues included:

- **Administration errors in Orientation to Place (11.8%)**
- **Scoring errors in Orientation to Place (9.5%)**
- **Administration errors in Attention and Calculation (9.7%)**
- **Administration errors in Orientation to Time (7.0%)**

COMMON MMSE RATER ERRORS AND THEIR IMPACT

One of the most common MMSE administration errors occurs in Orientation to Place, where raters within the same site apply inconsistent scoring criteria. Each trial site establishes pre-approved correct responses—such as the official name of the building where the assessment takes place—but some raters fail to follow these guidelines, leading to discrepancies. Another frequent issue is providing leading cues, which can unintentionally influence participant responses, compromising data integrity.

In the Attention and Calculation task, particularly the Serial 7s subtest, errors often arise when raters provide feedback or prompts that aren't allowed. For example, reminding participants of their last response or the number they are meant to subtract fundamentally alters the nature of the task. Since this test is designed to measure independent cognitive processing, any outside assistance distorts its validity.

Similarly, Orientation to Time errors often involve raters giving multiple-choice options rather than allowing participants to recall the correct answer independently. Another issue is failing to prompt participants to complete responses. For instance, if a patient responds with "hospital" when asked to name the building, they should be encouraged to give the name of the hospital. Ignoring these nuances leads to inconsistent data, ultimately weakening trial reliability.

UNCOVERING COMMON ADAS-COG RATER ERRORS

Signant Health conducted an internal study in an effort to better identify and understand what the most common errors in the ADAS-Cog. We pooled from 14 global dementia clinical trials where the ADAS-Cog was used as an efficacy outcome. A total of 47,238 ADAS-Cog assessments were reviewed. Findings included the following:

01 **ADAS-Cog administration and/or scoring errors occurred in 9,288 (19.6%) visits.**

02 **Administration errors were found in 4467 instances (9.46%) and scoring errors were found in 6494 instances (13.75%).**

03 **The items with the largest number of errors were the following:**

- **Number Cancellation (23.38%)**
- **Constructional Praxis (20.48%)**
- **Orientation (12.25%)**
- **Word Recognition (11.9%)**
- **Naming Objects and Fingers (10.84%)**

Our study identified a substantial prevalence of scoring and administration errors on the ADAS-Cog, which tend to occur independently of one another. This number of flags decreased across flag reviews over the course of the clinical trials, which can be partially explained by ongoing remediation and rater re-training.

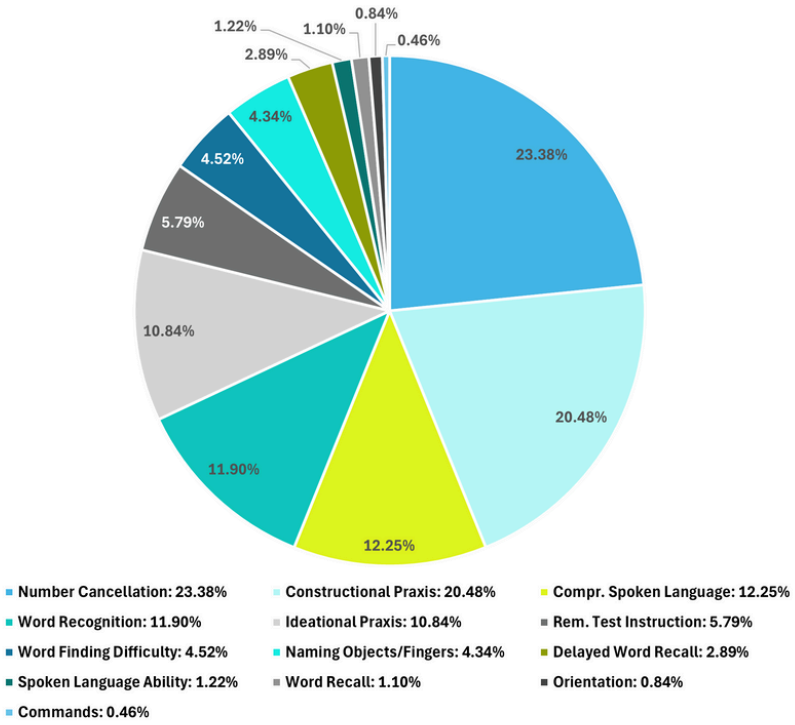
The lack of association between administration and scoring errors may be explained by unique scale specificities such as differences in manual versions and unfamiliarity with administration and scoring conventions.

TURNING INSIGHTS INTO ACTION

Our analysis of the central review data provides critical insights that can improve rater training and data monitoring for MMSE and ADAS-Cog. Effective rater training should go beyond theoretical instruction and integrate real-world data on administration and scoring errors to prepare raters for the challenges they may encounter. Training programs should combine effective tools such as didactic sessions, quizzes, scoring exercises, targeted tip sheets, and/or supplemental materials that highlight common pitfalls and reinforce standardized administration.

Beyond rater training, these insights also play a critical role in central data monitoring. Incorporating knowledge of common rater errors into training materials for central reviewers helps ensure focused attention on specific areas of concern, fosters a calibrated and consistent review process, and enables standardized feedback to raters.

FIGURE 1. PERCENTAGE OF ERRORS IN ADAS-COG PER ITEM



FINAL THOUGHTS

Accuracy and standardization in cognitive assessments are critical to the success of Alzheimer's disease clinical trials. By leveraging data-driven insights to refine rater training and enhance central data monitoring, we can improve the reliability and validity of these assessments, ultimately strengthening the quality of trial outcomes.

CLOSING REMARKS

The expert insights shared in this collection of Conversations in CNS demonstrate that successful CNS trials require a comprehensive, integrated approach to data quality optimization. From evidence-based site selection and independent eligibility reviews to electronic outcome assessments and comprehensive qualification, training, and calibration of clinical raters, each pillar works synergistically to address the unique challenges inherent in CNS research. The common thread across all interventions is the principle of proactive, prevention-focused strategies that establish robust foundations for signal detection rather than attempting to remediate issues after they arise.

In future issues of Conversations in CNS, we will dive deeper into advanced data analytics, innovative trial designs, central ratings and reviews, and other indication-specific strategies that complete a comprehensive approach to optimizing CNS clinical research.

By continuing to combine scientific rigor with practical application, we can accelerate the development of transformative treatments for patients and families affected by CNS disorders.

MARTINA MICALETTO, MSC, BSC

Manager Clinical Program & Performance, Digital Health Sciences

Martina Micaletto, MSc, BSc, is a Clinical Scientist at Signant Health, with extensive experience in the pharmaceuticals industry. She specializes in computerized cognitive batteries, scale administration and scoring, rater training and certification, and endpoint assessments. Martina is skilled in statistics, research, negotiation, psychology, and customer care. She holds an MSc in Social and Cultural Psychology from The London School of Economics and Political Science (LSE) and an MSc in Development and Psychopathology from The University of Reading.

ALAN KOTT, MUDr

Practice Leader, Data Analytics

Alan Kott, MUDr, is the Practice Leader for Data Analytics at Signant Health, with both academic and industry experience in clinical trials. He has led the development of Signant's Data Analytics Program, overseeing data analytics in over 200 clinical trials across multiple indications. Prior to joining Signant, Dr. Kott was an Assistant Professor at Charles University and a house officer in psychiatry at General Teaching Hospital in Prague. He holds a Medicinae Universae Doctor (MUDr.) from Charles University.

PETRA REKSOPRODJO, MUDr

Director, Clinical Program & Performance

Dr. Petra Reksoprodjo is Director of Clinical Program and Performance at Signant, where she leverages over 20 years of expertise in the clinical trials industry, with a particular focus on CNS clinical trials. Holding a medical degree from Charles University in Prague, she oversees clinical project delivery and maintains quality assurance across a large portfolio. Petra collaborates closely with Signant's data analytics team to prepare and deliver clinical data analyses for clients and is a frequent presenter at international investigator meetings. Based in Signant's Prague office, she also contributes to internal training programs and fosters clinical excellence through mentoring and leadership.

JULIET BROWN, PHD

Director, Endpoint Reliability

Juliet Brown, PhD, is a Director of Endpoint Reliability and a Clinical Thought Leader at Signant Health with over 25 years of clinical and research experience, specializing in MDD, Bipolar Disorder, Anxiety Disorders, Psychotic Spectrum Disorders, Substance Use Disorders, and Cognitive Behavioral Psychotherapy. She holds a PhD and Master's Degrees in Clinical Psychology from Drexel University. Before joining Signant Health 8 years ago, Dr. Brown provided psychotherapy to individuals with Severe Mental Illness and treated Substance Use Disorders.

RACHEL BERMAN, PHD

Associate Director, Digital Health Sciences

Dr. Berman brings two decades of neuropsychology experience to Signant Health, including clinical science work in behavioral sciences and geriatrics. Specializing in psychiatric and neurological disorders, Rachel supports sponsors and CROs running trials in these and other CNS indications. She also lends her expertise to Signant's original research projects and business development team, ensuring that the highest caliber scientific solutions are offered to meet each sponsor's unique clinical needs.

MARCELA ROY, MA

Executive Director, Clinical Science & Medicine

Marcela Roy, MA, is an Executive Clinical Director in Signant's Digital Health Science department. She has been with Signant for over 15 years and has over 20 years of clinical and research experience. Her focus is Mood Disorders and Endpoint Reliability quality monitoring. She provides strategic direction in the organization, as well as team leadership and business development support.

MEET THE AUTHORS

SAYAKA MACHIZAWA, PSYD

Associate Director, Clinical Science

Sayaka Machizawa, PsyD, is an Associate Director of Clinical Science at Signant Health, bringing over 18 years of expertise in neurodegenerative and psychiatric diseases. She has played a key role in supporting large-scale global clinical trials across a wide range of indications. Fluent in both Japanese and English, Sayaka has led rater training sessions at numerous Investigator Meetings worldwide.

MARTA PEREIRA, PHD

Clinical Scientist

Marta Pereira, PhD, is a Clinical Scientist at Signant Health specializing in neurodegenerative and neuromuscular disorders. With an academic background spanning three continents, she earned her Psychology degree and MSc in Neuropsychology from the University of Porto, Portugal, followed by a PhD in Neurosciences from the University of São Paulo, Brazil. A published author on cognitive impairment in Alzheimer's, Parkinson's, and Progressive Supranuclear Palsy, she provides vital clinical expertise for neurodegenerative and rare disease trials. Dr. Pereira currently leads a portfolio of five Myasthenia Gravis studies across both adult and pediatric populations, furthering the development of treatments for these challenging conditions.

DAVID MILLER, MD, MA

Clinical Vice President

David Miller, MD, MA, is a geriatric psychiatrist with over 20 years of clinical, research, and teaching experience. Prior to joining Signant, he served as Chief of Geriatric Psychiatry and Medical Director of ECT at Friends Hospital in Philadelphia, PA. He has been a Principal Investigator in multiple dementia trials and has lectured internationally on dementia research. Dr. Miller co-chairs the ISTAART and ISCTM working groups on neuropsychiatric syndromes in dementia and is a co-author of the updated ADCS ADAS-Cog manual. As Clinical Vice President at Signant, he consults on dementia protocols and has presented at investigator meetings worldwide.

ABOUT SIGNANT HEALTH

For over 25 years, Signant Health has been at the forefront of CNS clinical research, pioneering evidence-based solutions to the industry's most persistent challenges. Our expertise extends across the CNS spectrum—from Alzheimer's disease and schizophrenia to depression, Parkinson's disease, and rare neurological disorders.

What sets Signant apart is our comprehensive understanding of both the scientific and operational dimensions of CNS trials. Our team includes world-class clinical scientists, data quality experts, and operational specialists who work together to deliver integrated solutions tailored to your specific trial needs. We don't just provide technology – we partner with you to implement proven, science-driven approaches that enhance signal detection and improve outcomes.

Conversations in CNS

SIGNANT HEALTH
THE EVIDENCE GENERATION COMPANY

REFERENCES

1. Thomas D, Chancellor D, Micklus A, et al. Clinical Development Success Rates and Contributing Factors 2011–2020. © BIO, QLS Advisors, Informa UK Ltd; February 2021.
2. Valerie L, et al. Comorbid mental disorders among adults in the mental health surveillance survey. Ann Epidemiol. 2018;28(7):468-474.
3. Bradford A, et al. Diagnostic error in mental health: a review. BMJ Qual Saf. 2024;33:663-672.
4. Schneider LS, et al. Adjudicating mild cognitive impairment due to Alzheimer's disease as a novel endpoint event in the TOMMORROW Prevention Clinical Trial. J Prev Alzheimers Dis. 2022;9:625-634.
5. Targum SD, Pendergrass JC. Site-independent confirmation of subject selection for CNS trials: 'dual' review using audio-digital recordings. Ann Gen Psychiatry. 2014;13:21.
6. Al-Huthail YR. Accuracy of referring psychiatric diagnosis. Int J Health Sci (Qassim). 2008;2(1):35-38.
7. Targum SD, et al. Major depressive disorder with subthreshold hypomania (mixed features): Clinical characteristics of patients entered in a multiregional, placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry. 2016;68:9-14.
8. Corrao S, Argano C. Rethinking clinical decision-making to improve clinical reasoning. Front Med. 2022;9:900543.