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2024 ABSTRACTS OF POSTER PRESENTATIONS

VOL. 21, NO. 10–12 • OCTOBER–DECEMBER 2024 • SUPPLEMENT 1

NOVEMBER 10–13, 2024, IN EVERETT, MASSACHUSETTS

Dear Colleagues:

Welcome to the annual CNS Summit Abstracts of Poster Presentations supplement to *Innovations in Clinical Neuroscience*. We are pleased to provide you with this reference guide to some of the innovative research presented during the CNS Summit 2024 event. The supplement is also available online by visiting www.innovationscns.com.

This supplement is just a small representation of the cutting-edge research, innovative ideas, and collaborative efforts shared via the CNS Summit platform. The annual CNS Summit and its year-round programming are designed to encourage and facilitate open channels of communication and data sharing across all disciplines of medical research—with the ultimate goal of achieving optimal patient outcomes.

In this abstract supplement, we've organized CNS Summit 2024 poster abstracts into the following groups for your convenience and easy reference:

- Artificial Intelligence (AI)/Machine-based Learning
- Assessment Devices and Tools
- Biomarkers
- Decentralized and Virtual Clinical Trials
- Investigative Drug Compounds and Therapies
- Treatment Devices and Tools
- Trial Methodology

You will also find an alphabetical index by poster title on pages S32 to S33 of this publication.

We hope you find the CNS Summit 2024 Abstracts of Poster Presentations supplement to *Innovations in Clinical Neuroscience* informative and that it provides you with a useful snapshot of the research being presented at the annual CNS Summit event. Visit www.cnssummit.org for more information.

As always, we welcome your feedback and participation.

Sincerely,

Amir Kalali, MD
Editor, *Innovations in Clinical Neuroscience* ICNS

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ARTIFICIAL INTELLIGENCE (AI)/MACHINE-BASED LEARNING

BEYOND THE EYE: AI-ENHANCED VISUAL BIOMARKER DISCOVERY AND TRACKING FOR AMYOTROPHIC LATERAL SCLEROSIS

Authors: Terry Heiman-Patterson, MD;[1]* John Furey;[2] Sarah Feldman;[2] Zachary Bides;[2] Jaroslaw "Jerry" Winniczek;[3] Meghan Conroy[3]
*Principal investigator
Affiliations: [1]Director, ALS Center of Hope, Temple University; [2]Temple University Hospital, Department of Neurology, Philadelphia, PA, US; [3]CaptureProof, South San Francisco, CA, US

Background/Objective: Amyotrophic lateral sclerosis (ALS) is a progressive degenerative neuromuscular disorder causing muscle weakness and impaired mobility. Clinical scales used to monitor disease progression can be time-consuming, labor-intensive, and tiring for patients. Digital biomarkers can alleviate these burdens. This study aims to leverage CaptureProof's video capture application enhanced by artificial intelligence (AI) to identify visual biomarkers that can remotely monitor ALS progression.

Design: Participants were recruited from the ALS Center of Hope at Temple University Hospital in Philadelphia, PA. Participants were recorded completing sit-to-stand, timed up and go, and various motor tasks of the face, fingers, arms, and legs. CaptureProof's AI software generated objective biometric markers through analysis of symmetry, fluidity, speed, range, and rate of motor tasks. ALS Functional Rating Scale and Rasch Overall Disability Scale were recorded for and compared against biometric markers. Enrollment and data analysis is still ongoing.

Results: Compared to healthy controls, patients with ALS demonstrated differences in finger tapping rate and distance. Enrollment, data collection, and analysis is still ongoing. Similar objective biomarkers will be generated for each motor task and analyzed.

Conclusion: Our preliminary data suggests CaptureProof's AI-enhanced video capture application's ability to identify biomarker metrics associated with ALS disease progression. These biomarkers are potentially more granular, precise, and accessible compared to standardized clinical assessments. This deepens the potential for ALS monitoring through continuous, remote, real-time data collection, leading to timely interventions and improved patient outcomes. Future research will explore scalability and broader clinical applications.

Funding/financial disclosures: TH-P has received personal compensation in the range of $500 to $4,999 for serving as a Consultant for ITF; personal compensation in the range of $500 to $4,999 for serving as a Consultant for MTPA; personal compensation in the range of $500 to $4,999 for serving as a Consultant for Samus; personal compensation in the range of $500 to $4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for MTPA; personal compensation in the range of $500 to $4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Biogen; personal compensation in the range of $500 to $4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Amylym; personal compensation in the range of $500 to $4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Biohaven; and personal compensation in the range of $500 to $4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Cytokinetics.

MULTICOUNTRY EVALUATION OF THE ALTOIDA DIGITAL NEUROMARKER PLATFORM: ADVANCING THE DETECTION OF MCI AND ALZHEIMER'S DISEASE WITH AR AND ML-BASED DIGITAL BIOMARKERS

Authors: Victoria Brugada Ramentol,[1] M. Florencia Iulita,[1] Emmanuel Streel,[1] Silvia Fallone,[1] Alberto Ferrari,[1] Nicholas Griffin,[1] Sean Lorenz,[1] Gonzalo Sánchez Benavides,[2,3,4] Alba Cañas,[2,4] Carolina Minguillon,[2,4] Ioannis Tarnanas,[1] Marc Jones[1]
Affiliations: [1]Altoida, Inc., Washington, DC, US; [2]Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain; [3]IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain; [4]Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Instituto de Salud Carlos III, Madrid, Spain

Background/Objective: Traditional cognitive assessments are not fit to detect the earliest signs of Alzheimer's disease due to their subjectivity, bias, and lengthy administration. Digital biomarkers, derived from assessments that engage the brain in daily living-like exercises, have the potential to enable early, accurate, and accessible diagnoses.

Design: The Altoida NeuroMarker Platform enables the objective evaluation of cognitive functional abilities. Patient data is collected through a series of tasks that take 10 to 15 minutes to complete using a tablet (iOS). These include motor activities, such as tapping and tracing shapes, and interactive augmented reality (AR) tasks that use the tablet's camera, accelerometer, and gyroscope to map the room. The patient is instructed to place and retrieve virtual objects that appear on the screen, utilizing AR. Machine learning (ML) is then used to produce a binary classification predicting the presence or absence of mild cognitive impairment (MCI).

Results: When evaluated across six clinically characterized cohorts (n=390; 469 assessments) recruited across 13 countries (Greece, The Netherlands, Spain, United Kingdom, Romania, Germany, Portugal, Switzerland, Italy, Sweden, Norway, Slovenia, and Brazil), Altoida's Platform differentiated individuals with MCI from

those without MCI with an area under the curve (AUC) of 0.87±0.03. In a subset of 116 participants, predominantly with subjective cognitive complaints, Altoida's classification showed excellent concordance with the clinical classification of cognitively unimpaired (101/106; 95.3%) and with the cutoff of greater than 25 in the Mini-Mental State Examination (MMSE) (105/111; 94.6%). The assessment also differentiated cognitively unimpaired individuals with amyloid pathology (Aβ+) versus those without (Aβ–) (AUC: 0.67±0.13).

Conclusion: The Altoida Platform provides an accurate, time-efficient, and accessible solution for large-scale assessment of cognitive impairment.

Funding/financial disclosures: VBR, MFI, ES, SF, AF, NG, SL, IT, and MJ are employees of Altoida, Inc. and may hold stock options in the company. The other authors have no conflicts of interest to disclose. Part of this work was financed by the Alzheimer's Drug Discovery Foundation (#GDADB-201906-2018897).

ROBUST DETECTION OF SLOW OSCILLATIONS IN ELECTROENCEPHALOGRAPHIC DATA USING DEEP LEARNING

Authors: Michael Lagler,[1] Marco Ross,[1,2] Cristiana Dimulescu,[3] Georg Dorffner,[1,4] Peter Anderer[1]

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Background/Objective: Electroencephalographic (EEG) microstructures contribute to the analysis of sleep macrostructure, but they also possess value in assessing sleep-dependent memory consolidation as well as various neurological disease states. An algorithm for detecting slow oscillations in EEG recordings using a long short-term memory (LSTM) architecture indicating excellent accuracy based on 10 subjects was recently published. Our goal was to validate and possibly improve it using a larger, more diverse dataset to prove its applicability in central nervous system (CNS) trials.

Design: The Siesta pattern database comprises 113 hours of annotated EEG data from 226 participants. Subjects were between 20 and 95 years of age, and 43 percent were female. Various microstructures were annotated, including slow oscillations. Scorers were randomly selected from a pool of 12 experienced experts. Interscorer agreement was assessed using six segments scored by all experts. We retrained the previously published LSTM network and developed a new detection algorithm based on a convolutional residual neural network (ResNet) architecture. Using five-fold cross validation, agreement to expert scorings was evaluated using the Mathews Correlation Coefficient (MCC).

Results: Interscorer agreement was quantified with a median pairwise MCC between human experts of 0.52 and an interquartile range (IQR) of [0.43, 0.61]. The retrained LSTM network achieved a median MCC of 0.47 (IQR: [0.36, 0.55]). The newly developed convolutional network performed best with a median MCC of 0.58 (IQR: [0.49, 0.67]).

Conclusion: We showed on a large, diverse dataset that deep learning algorithms can detect slow oscillations in EEG equivalent to human experts. Validation using external data is part of ongoing research.

Funding/financial disclosures: ML and MR are employees of The Siesta Group GmbH, Vienna, Austria, a service provider for measuring electrophysiological signals, including sleep, in clinical trials. PA works as a freelancer for and is a shareholder of The Siesta Group GmbH, Vienna, Austria. GD is an employee and shareholder of The Siesta Group GmbH, Vienna, Austria. CD declares no conflicts of interest.

ASSESSMENT DEVICES AND TOOLS

AUTOMATED DETECTION OF ALZHEIMER'S DISEASE FROM RESTING-STATE EEG

Authors: Leif E.R. Simmatis,[1] Irene E. Harmsen,[1] Nardin Samuel[1]

Affiliations: [1]Cove Neurosciences, Inc., Toronto, Ontario, Canada

Background/Objective: To explore the clinical validity of a novel, automated electroencephalography (EEG) data processing pipeline for use in individuals with Alzheimer's disease (AD).

Design: Resting-state EEG data were retrospectively analyzed from a previously collected, open-source dataset composed of 29 healthy individuals and 36 individuals with varying stages of AD (i.e., case-control design). Patients were clinically assessed using the Mini-Mental State Exam (MMSE) to summarize cognitive functioning. Data were preprocessed using a novel, automated pipeline, and features (e.g., representing connectivity, signal complexity, power) were then extracted. Supervised machine learning was employed to distinguish between patients and controls, including analysis of different feature subsets. Spearman correlations between individual features and MMSE were quantified, and false discovery rate (FDR) correction was performed using the Benjamini-Hochberg method.

Results: Patients and controls were accurately distinguished using various combinations of features from the overall feature set. The area under the receiver operating characteristic curve (AUROC) was as high as 0.84. Measure of skewness, complexity, and entropy stood out as the strongest predictor feature groups. Furthermore, 70 individual features had statistically significant correlations with the MMSE after correction for FDR, primarily in the domains of complexity and entropy.

Conclusion: These results highlight the ability of our novel, automated pipeline to capture disease presence and status in a small cohort of individuals with AD. Further work on larger datasets and additional external validation is needed to determine the validity of this technology in clinical settings.

Funding/financial disclosures: LERS, IEH, and NS are all affiliated with Cove Neurosciences, Inc., a company that commercializes the technology described in this work. LERS is a full-time employee of Cove and has a financial interest in the company. IH and NS are co-founders of Cove and have financial interests in the company.

BRAIN ASYMMETRY SUITE: A FRAMEWORK FOR THE COMPREHENSIVE EXAMINATION OF THE BRAIN'S ASYMMETRY

Authors: Tommy Boshkovski,[1] Óscar Peña-Nogales,[1] Evie Neylon,[1] Marc Ramos,[1] Paulo Rodrigues,[1] Vesna Prčkovska,[1] Kire Trivodaliev[1]

Affiliations: [1]QMENTA Inc., Boston, MA, US

Background/Objective: Hemispheric asymmetries are a fundamental aspect of human brain organization and have intrigued neuroscientists for decades. While it is known

that patterns such as hemispheric language dominance begin *in utero*, brain laterality remains a complex and highly variable trait. Changes in hemispheric asymmetry are linked to various neurological conditions, including traumatic brain injury, sparking interest in asymmetry indices as potential biomarkers. To date, these indices have been derived from volumetric, cortical thickness, white matter integrity, and functional imaging measures, though results often vary due to limited sample sizes and methodological differences. Thus, in this work we introduce the Brain ASymmetry Suite (BASS), a fully automated framework designed to preprocess brain images and compute asymmetry biomarkers.

Design: BASS supports volumetric, cortical thickness, functional, and structural network asymmetry indices using T1-weighted, functional magnetic resonance imaging (fMRI), and diffusion tensor imaging (DTI) images. BASS employs advanced preprocessing techniques, including denoising and motion and susceptibility artifacts correction, computes cortical volume and thickness, and reconstructs functional and structural connectomes. It calculates asymmetry indices for both hemispheres: Asymmetry Index (AI) and Asymmetry Percentage (AP).

Results: Validation with 600 subjects from the Human Connectome Project showed that BASS's volumetric asymmetries aligned with established patterns, exhibiting leftward lateralization in frontal regions and rightward in temporal-occipital regions. Functional network asymmetries were observed in the left orbitofrontal gyrus and structural asymmetries in the left amygdala, cingulate, and middle occipital gyrus.

Conclusion: BASS enables detailed analysis of brain asymmetry, potentially enhancing research in neuroscience and improving the diagnosis and treatment of neurological disorders.

Funding/financial disclosures: The presenters are employed and own stocks or hold options of QMENTA.

CONTENT CONFIRMATION OF THE SCHIZOPHRENIA COGNITION RATING SCALE (SCoRS): A QUALITATIVE STUDY WITH PRIMARY AND SECONDARY CAREGIVERS

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Background/Objective: Cognitive impairments associated with schizophrenia are burdensome and detrimental to everyday life. The Schizophrenia Cognition Rating Scale (SCoRS) is a 20-item interview-based assessment requiring input from patients, caregivers, or clinicians. Confirmation with the informant population is needed, particularly primary caregivers (PCs), which this study aims to address.

Design: A qualitative, cross-sectional, noninterventional study was conducted in the United States. Interviews were conducted with PCs (unpaid) and secondary caregivers (SCs; professionally trained).

Results: Forty caregivers were interviewed, 20 per group. Half of PCs were parents of patients, 40 percent were relatives, and 10 percent were partners. The SC group included 25 percent therapists. Most caregivers accurately interpreted questions, items, and response options (70–100%). Ease of response appeared slightly lower for PCs, typically due to the profile of some patients or uncertainty concerning patient thoughts/understanding, rather than scale properties. Most items were endorsed by the majority in both groups. However, two items were observed less frequently: language difficulties leading to conversational confusion and attention in conversation; nevertheless, these items were understood by most caregivers, responses were easy to select, and examples were considered useful. Additionally, all domains were endorsed by at least 50 percent of caregivers. Attention and Problem-solving were endorsed by 95 percent of caregivers living with patients. Memory and Working Memory were endorsed by all SCs.

Conclusion: The content and usability of the SCoRS were confirmed with both informal and professional caregivers. These data suggest that impact of relevant cognitive issues can be assessed with caregivers of patients with schizophrenia using interview-based methodology.

Funding/financial disclosures: This study was funded by Boehringer Ingelheim Pharmaceuticals, Inc. CR-F and AW are employees of Boehringer Ingelheim Pharmaceuticals, Inc. ST is an employee of Boehringer Ingelheim International GmbH. MH and A Giardi are employees of Parexel. Parexel was commissioned by BI to conduct the study. KR has worked for PAREXEL International on the design of the study, analysis, and write up. The project was funded by Boehringer Ingelheim, and there are no other conflicts of interest with regard to the publication. CC has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Saladax, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Tolmar, Vertex, Viatris and Xenon. RK has been on advisory boards for WCG, Merck, Karuna, Pangea, Sirtsei, Gedeon Richter, Boehringer Ingelheim, Biogen, Recognify, Vandria, Kynexis and receives royalties from sales of BACS, BAC, and VRFCAT. A Goldring has nothing to disclose.

EVALUATION OF THE CORRELATION BETWEEN THE CLINICAL GLOBAL IMPRESSION OF IMPROVEMENT SCALE AND THE PATIENT GLOBAL IMPRESSION OF IMPROVEMENT SCALE IN ACUTE SCHIZOPHRENIA

Authors: Maria Companioni,[1] Judith Montero,[2] Patricia Ruiz,[1] Lisa Nguyen[3]

Affiliations: [1]CenExel Research Centers of America; [2]CenExel Clinical Research; [3]LMN PsyD, LLC

Background/Objective: The Clinical Global Impression of Improvement (CGI-I) and the Patient Global Impression of Improvement (PGI-I) scales are often used as outcome measures of efficacy in acute schizophrenia clinical trials. This study evaluates the correlation between these two scales as it assesses symptom improvement in subjects with acute schizophrenia.

Design: Data from 458 visits across 108 adult individuals participating in two double-blind,

placebo-controlled studies in acute schizophrenia were evaluated for convergent validity of these two scales. The agreements between clinician and patient ratings were assessed using the intraclass correlation coefficient (ICC) while the Pearson correlation coefficient (*r*) was used to analyze the strength and direction of the linear relationship between the scales.

Results: The statistical analysis indicated that there is a poor-to-fair agreement between the CGI-I and PGI-I. Evaluation of the data showed that in 24 percent of visits (n=112), there was at least a two-point difference between the CGI-I and PGI-I scores at the same timepoint. The study findings provide insight into the potential impact of self-reported measures of schizophrenia symptoms in clinical trial outcomes.

Conclusion: This study shows that discord between clinician and patient viewpoints poses an obstacle, possibly leading to inconsistencies in the reported scores. The study results highlight the importance of bearing in mind both clinician and patient perspectives in clinical trial assessments, as well as the need for further researching and understanding of treatment outcomes in acute schizophrenia clinical trials.

Funding/financial disclosures: All authors have no conflicts of interest or bias in the conclusions of the current investigation or promotion of the current study results.

BIOMARKERS

AUTOMATED ANALYSIS OF SPEECH LATENCY AS A BIOMARKER IN SCHIZOPHRENIA AND DEPRESSION

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Affiliations: [1]Cronos Clinical Consulting Services, Inc., an IQVIA business

Background/Objective: Development of quantitative biomarkers based on naturalistic behavior (e.g., speech) could complement clinical assessments in psychopharmacology trials. We aim to evaluate the sensitivity of speech latency as a biomarker of schizophrenia and depression severity.

Design: Speech analysis was conducted using audio recordings of assessment interviews from 40 patients with schizophrenia and 15 patients with depression across three clinical trials. The distribution of latencies between raters' questions and patients' responses during the clinical interviews were generated using automated algorithms, and median speech latency was used as an index of central tendency for these distributions. Schizophrenia severity was evaluated using Positive and Negative Syndrome Scale (PANSS) total and positive, negative, and general psychopathology subscale scores. Depression severity was evaluated using Montgomery–Åsberg Depression Rating Scale (MADRS) total score. The relations between the median speech latency for each patient and schizophrenia or depression severities were evaluated using Pearson and Spearman correlation coefficients.

Results: In patients with schizophrenia, speech latency correlated significantly only with PANSS negative subscale score [$r_{\text{PANSS Negative}}(38)=0.391$, $p=0.012$; $r_{\text{PANSS Total}}(38)=0.204$, $p=0.206$; $r_{\text{PANSS Positive}}(38)=-0.055$, $p=0.737$; $r_{\text{PANSS General}}(38)=0.128$, $p=0.433$;]. In patients with depression, there was a significant correlation of speech latency with MADRS total score [rho(13)=0.540. $p=0.038$].

Conclusion: The study provides preliminary evidence for the feasibility of using speech latency as a quantitative biomarker of negative symptoms in schizophrenia and clinical severity in depression. Speech latency is robust to expectation biases inherent to clinical interviews that increase the placebo response and hence represents a promising outcome that can increase signal detection in medication clinical trials.

Funding/financial disclosures: All authors report no conflicts of interest for this work. All are current employees of Cronos Clinical Consulting Services, Inc., an IQVIA business. Cronos provides rater training and oversight.

AUTOMATIC MEASURE OF SPEECH INTELLIGIBILITY AS A MEANINGFUL DIGITAL BIOMARKER FOR PATIENTS WITH MOTOR SPEECH DISORDERS

Authors: Nicklas Linz,[1] Simona Schäfer,[1] Louisa Schwed,[1] Felix Doerr,[1] Johannes Tröger[1]

Affiliations: [1]ki elements GmbH, Saarbrücken, Germany

Background/Objective: Speech problems often accompany motor disorders, such as Parkinson's disease (PD) and Huntington's disease (HD), significantly affecting patients' daily functioning. Objective measurements of speech intelligibility could serve as new outcome measures in clinical trials. This study uses the ki speech biomarker for motor speech symptoms (SB-M) to quantify intelligibility in PD and HD patients.

Design: Speech data was collected from 93 patients with PD, 40 patients with HD, and 100 controls, speaking three different languages. The SB-M intelligibility measure was assessed by comparing the word accuracy rate of automatically recognized text to the presented text.

Results: SB-M intelligibility was significantly lower in patients than controls (1. Czech HD data: $H=37.432$, $p<0.01$, Cohen's $d=1.872$; 2. Czech PD data: $H=6.221$, $p<0.05$, Cohen's $d=0.675$; 3. Colombian PD data: $H=16.266$, $p<0.01$, Cohen's $d=0.859$). Intelligibility scores correlated significantly with dysarthria items of the Unified PD Rating Scale (UPDRS) in patients with PD and Unified HD Rating Scale (UHDRS) in patients with HD (1. Czech HD data: $r=-0.37$, $p<0.05$; 2. Czech PD data: $r=-0.328$, $p<0.05$; 3. Colombian PD data: $r=-0.403$, $p<0.01$).

Conclusion: SB-M-measured intelligibility differed significantly between controls and patients with HD or PD in all datasets. Scores also correlated with dysarthria items in the UPDRS and UHDRS. These findings suggest that automatic intelligibility measures can be effective across diseases and languages. Future research could investigate combining additional objective measures, such as Vowel Space Area, to enhance detection of impaired intelligibility.

Funding/financial disclosures: NL, SS, LS, FD, and JT are employees of ki elements GmbH. NL and JT are shareholders of ki elements GmbH.

DEVELOPING A NOVEL BRAIN-BASED BIOMARKER OF MILD COGNITIVE IMPROVEMENT USING TIME-DOMAIN FUNCTIONAL NEAR-INFRARED SPECTROSCOPY

Authors: Julien Dubois,[1] Ryan M. Field,[1] Erin M. Koch,[1] Zahra M. Aghajan,[1] Naomi Miller,[1] Katherine L. Perdue,[1] Moriah Taylor[1]

Affiliations: [1]Kernel, Culver City, CA

Background/Objective: There is an urgent need to develop novel, objective, brain-based biomarkers in support of therapeutic development and timely diagnostics for mild cognitive impairment (MCI). Time-domain functional near-infrared spectroscopy (TD-fNIRS) may fill this need.

Design: Patients with MCI (n=50, age [mean±standard deviation (SD)]: 73.7±6.5 years) and age-matched healthy controls (HC; n=51, age [mean±SD]: 71.4±6.9 years) completed the self-reported Alzheimer's Disease Cooperative Study Activities of Daily Living (ADL) scale for MCI and brain recordings using TD-fNIRS during cognitive tasks implicated in MCI (verbal fluency task [VFT] and n-back working memory task). Brain recordings took less than 15 minutes. Brain function and behavioral features were extracted. Logistic regression classifiers, which incorporated feature selection, regularization, and nested 10-fold cross-validation, were built and trained to distinguish MCI from HC using ADL only or the combination of VFT and n-back features and the ADL.

Results: The ADL-only model was able to classify MCI versus HC with good performance (area under the curve [AUC]: 0.81). Combining task and survey data yielded a model with improved performance (AUC: 0.88), especially considering the MCI cohort, where sensitivity was nearer to chance (sensitivity: 0.65) using only ADL.

Conclusion: Combining a self-report survey with brain and behavior measurements increases classifier performance, indicating that the brain, behavior, and self-report are complementary. A short, objective brain and behavior measurement of cognition can have utility for MCI diagnosis and clinical development in therapeutic areas related to cognition.

Funding/financial disclosures: All authors of the study are employed by Kernel, the company that developed the TD-fNIRS system.

ENRICHMENT BASED ON SPEECH LATENCY ENHANCES TREATMENT EFFECTS IN A PHASE III STUDY OF BRILAROXAZINE

Authors: Alex S. Cohen,[1,2,3] Brian Kirkpatrick,[3,4] Mark Opler,[5] Jan A. Sedway,[5] Kazunori Tatsumi,[5] Seema Bhat,[6] Laxminarayan Bhat[6]

Affiliations: [1]Louisiana State University, Department of Psychology; [2]Louisiana State University, Center for Computation and Technology; [3]Quantic Innovations, Inc.; [4]Psychiatric Research Institute, University of Arkansas for Medical Sciences; [5]WCG Clinical, Inc. [6]Reviva Pharmaceuticals, Inc.

Background/Objective: Speech latency, a measure of verbal response times, is an objective marker of cognitive, social, and motivational factors that can be assayed directly from psychiatric interviews. We recently used speech latency to enrich participants for an antidepressant clinical trial, resulting in nearly double the drug-placebo effects at half the sample size. Here, we evaluate speech latencies in a clinical trial of schizophrenia.

Design: Audio recordings from psychiatric interviews in a Phase III trial of brilaroxazine were evaluated (k=2,590 recordings for 408 participants from 3 countries representing 8 languages).

Results: Speech latency showed excellent internal consistency, good temporal stability, and minimal convergence with potential confounds. Patients high in negative symptoms showed longer speech latencies, with large effects sizes observed in every country (*d*'s from 1.00–1.47).

A single speech latency value (area under the curve [AUC]: 0.74) identified 179 and 229 participants as being vocal biomarker-negative (i.e., VBM-neg; unremarkable speech) and -positive (i.e., VBM-pos; relatively long pauses), respectively. Brilaroxazine, versus placebo, showed improved outcomes from baseline to end of treatment for the VBM-pos group as compared to the VBM-neg group. Treatment effects were larger for VBM-pos versus VBM-neg patients in Positive and Negative Syndrome Scale (PANSS) total scores (246% improvement), positive symptoms (193%), negative symptoms (1,017%), Clinical Global Impressions (90%), and certain Personal and Social Performance scales (144% and 329%).

Conclusion: Speech latency is a face-valid, objective biomarker that can be derived from natural speech during standard clinical assessments. As an enrichment tool, it can reduce sample size needs and enhances outcomes with minimal study burden.

Funding/financial disclosures: Not provided.

DECENTRALIZED AND VIRTUAL CLINICAL TRIALS

APPLICATION OF THE METASITE™ MODEL TO A PHASE IIB/III TREATMENT STUDY FOR BIPOLAR DEPRESSION WITH SUICIDAL IDEATION

Authors: Christopher Reist,[1] Jason Bain,[1] Jonathan Javitt,[2] Michael Sapko,[2] Heather Lothamer[2]

Affiliations: [1]Science 37, Culver City, CA; [2]NRx Pharmaceuticals, Inc., Wilmington, DE

Background/Objective: Decentralized clinical trials (DCTs) utilize digital innovations including telemedicine and smartphone applications to allow trial conduct at patients' homes. Here, the metasite model, a variation of the DCT strategy, was used to augment conduct of a complex interventional trial.

Design: The NRX101-003 study was a double-blind comparison of NRX-101 with lurasidone for subjects with bipolar depression and subacute suicidal ideation. NRx and Science 37 collaborated to expand enrollment beyond traditional study sites. Study procedures were conducted remotely with the exception of those requiring face-to-face interaction (e.g., physical exam, electrocardiogram vital signs, phlebotomy). All key clinical diagnostic and endpoint assessments were conducted by Science 37 centralized raters. This included assessment of akathisia. Trial data were captured directly through the Science 37 platform.

Results: Enrollment began May 2022 and was completed in March 2024 with 72 total subjects randomized. Science 37 began recruitment in 47 states November 2022. The telemedicine platform provided a mechanism for subjects to communicate with study staff, complete patient-reported outcome measures, and schedule study visits. Safety protocols were established to surveil for and manage any escalation of suicidal ideation among subjects. Recruitment conducted jointly by Science 37 and a third-party vendor resulted in successful screening of 159 subjects. Of those, 104 subjects consented to the study and 14 were ultimately randomized. Nine subjects completed all visits, and five were discontinued for various reasons. There was one occurrence of suicidal behavior.

Conclusion: Operational feasibility of the metasite model was demonstrated using the Science 37 telemedicine platform.

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DIRECTION OF JAPAN'S DCT AND THE DEVELOPMENT OF A DCT/DX

ENVIRONMENT LED BY INVESTIGATOR SITES

Authors: Kiyoshi Aoyagi,* Takateru Inokawa, Teppei Maejima
*Presenting author

Background/Objective: Japan has many hospitals, dispersing the patient population. To improve clinical trials, it's essential to build trust between sites, streamline processes, and create an environment that encourages easier patient participation.

Design: By positioning StudyWorks as a collaboration hub between investigator and partner sites, we will build a network for continuous trials, reduce workload, promote DX, centralize information, and visualize site status to maintain partner motivation.

Results: Of 150+ partner sites, about 75 percent have referred patients, showing that in decentralized clinical trials (DCTs), both digital tools and "wet" communication, such as building relationships, are essential. A strong partner network can significantly reduce clinical trial durations.

Conclusion: In Japan's clinical trials, DCT helps address dispersed patients but needs enough cases to be effective. Building trust between investigator and partner sites and using DX to centralize and visualize information is key to shortening trial durations.

Funding/financial disclosures: Over the past year, I have held shares in Buzzreach Co., Ltd. and received compensation as an executive.

DRIVING THE ADOPTION OF DECENTRALIZED TRIALS: 1572 AND REGULATORY DOCUMENT RECOMMENDATIONS FOR DCTS

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Affiliations: [1]Decentralized Trials & Research Alliance (DTRA)

Background/Objective: The objective was to create awareness to the deliverables created as best practices for regulatory document completion for trials using decentralized clinical trial (DCT) methods. Primary investigator (PI) oversight requirements are not different when DCT methods are used, and there is ambiguity about the expected documentation and oversight of decentralized staff conducting assessments in trials. Our aim was to clarify and provide best practice recommendations and tools to teams.

Design: A CoLab was chartered, including representatives from research sites, technology and service providers, sponsors, and contract research organization (CROs) to create resources/recommendations to help clarify ambiguity of the completion of United States Food and Drug Administration (FDA) Form 1572 and other documents when DCT methods are used. The team referenced the FDA Draft DCT guidance and aligned the deliverables, aiming to provide more clarity for scenarios that are not specifically called out in the guidance document. These resources include:

- Delegation of activities decision tree
- Standard of care decision tree
- Resource table
- Scenarios for PI oversight and delegation

Results: These resources are now available to the greater research community to educate best practices for 1572 and regulatory document completion in trials using DCT methods.

Conclusion: The cross-industry representation of the team helped identify ambiguous aspects for regulatory documentation for sites when using DCT methods in trials. These points of ambiguity also apply to traditional trials, but our focus was on providing best practice guidance and tools, with case studies, to help study teams at sites, sponsors, and CROs navigate the ambiguity of who needs to be documented where when DCT methods are used, including new locations and new roles that are executing clinical trial assessments.

Funding/financial disclosures: DTRA is a 501c3 non-profit organization.

INVESTIGATIVE DRUG COMPOUNDS AND THERAPIES

ADJUNCTIVE LUMATEPERONE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: RESULTS FROM AN ADDITIONAL RANDOMIZED, DOUBLE-BLIND, PHASE III TRIAL

Authors: Willie R. Earley, MD;[1]* Suresh Durgam, MD;[1] Susan G. Kozauer, MD;[1] Yifan Mo, PhD;[1] Hassan Lakkis, PhD;[1] Margaret Martin, PharmD;[1] Susan G. Kornstein, MD;[2] Maurizio Fava, MD[3]
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Affiliations: [1]Intra-Cellular Therapies, Inc., New York, NY; [2]Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, VA; [3]Massachusetts General Hospital and Harvard Medical School, Boston, MA

Background/Objective: Lumateperone is a United States Food and Drug Administration (FDA)-approved antipsychotic for schizophrenia and bipolar depression. This Phase III, randomized, double-blind, placebo-controlled, multicenter trial (NCT05061706) investigated adjunctive lumateperone 42mg in patients with major depressive disorder (MDD) with inadequate antidepressant therapy (ADT) response.

Design: Eligible adult outpatients met *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for MDD with inadequate response to 1 to 2 prior ADT courses (<50% improvement on the Antidepressant Treatment Response Questionnaire) and had Montgomery–Åsberg Depression Rating Scale (MADRS) total score of 24 or greater, Clinical Global Impression-Severity (CGI-S) score of 4 or greater, and Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) score of 14 or greater. Patients were randomized to six-week placebo or lumateperone 42mg adjunctive treatment to ADT. Primary and key secondary endpoints were change from baseline to Day 43 in MADRS total score and CGI-S score. QIDS-SR-16 score and safety were also evaluated.

Results: Of 480 patients (placebo, n=238; lumateperone, n=242; mean age: 46 years, 70% women, 95% White), 89 percent completed treatment. Primary and key secondary endpoints were met, with significant improvement for adjunctive lumateperone versus placebo from baseline to Day 43 in MADRS total score (least squares mean difference vs. placebo [LSMD]: −4.5; effect size [ES]: −0. 56; $p<0.0001$) and CGI-S (LSMD: −0.5; ES: −0.51; $p<0.0001$). Adjunctive lumateperone significantly improved QIDS-SR-16 total score at Day 43 versus placebo (LSMD: −2.2; $p<0.0001$). Adjunctive lumateperone was relatively well tolerated, consistent with prior studies. Adverse events were mostly mild-to-moderate.

Conclusion: Lumateperone 42mg adjunctive to ADT demonstrated robust, clinically

meaningful efficacy over adjunctive placebo to ADT and was generally safe and well tolerated, indicating that lumateperone is a promising treatment as adjunctive therapy to ADT for MDD in adults.

Funding/financial disclosures: WRE, SD, SG Kozauer, YM, HL, and MM are full-time employees of Intra-Cellular Therapies, Inc. and may hold equity in the company.

SG Kornstein receives research support from the National Institutes of Health and the National Science Foundation. She has served as a consultant for Lilly, Sage Therapeutics, Reunion Neuroscience, Relmada, AbbVie, Gerbera, and Arrivo Bioventures.

MF reports the following disclosures related to the last three years: Research Support: Abbvie; Acadia Pharmaceuticals; Aditum Bio Management Company, LLC; Allergan, Alkermes, Inc.; Altimate Health Corporation; Alto Neuroscience, Inc.; Ancora Bio, Inc.; Angelini S.p.A; Aptinyx; Arbor Pharmaceuticals LLC; Avanir Pharmaceuticals, Inc.; Axsome; Benckiser Pharmaceuticals, Inc.; BioClinica, Inc.; Biogen; BioHaven; BioShin Limited; Cambridge Science Corporation; Centrexion Therapeutics Corporation; Cerecor; Cybin IRL Limited; Damona Pharmaceuticals; EmbarkNeuro; Eliem Therapeutics, LTD; Gate Neurosciences, Inc.; GenOmind, LLC; Gentelon, LLC; Gerbera Therapeutics, Inc.; Happify; Johnson & Johnson; Lundbeck, Inc.; Marinus Pharmaceuticals; Medpace, Inc.; Methylation Sciences, Inc.; Millennium Pharmaceutics, Inc.; Minerva Neurosciences; Neuralstem; Neurocrine Biosciences, Inc.; NeuroRX, Inc.; Novaremed; Novartis; Otsuka; Pfizer; Premiere Research International; Praxis Precision Medicines; Protagenic Therapeutics, Inc.; Relmada Therapeutics, Inc.; Reckitt; Shenox Pharmaceuticals; Stanley Medical Research Institute (SMRI); Taisho; Takeda; University of Michigan; Vistagen; WinSanTor, Inc.; Xenon Pharmaceuticals, Inc.; National Institute of Drug Abuse (NIDA); National Institutes of Health (NIH); National Institute of Mental Health (NIMH); and PCORI. MF has not done any personal consulting. Any consulting he has done has been on behalf of Massachusetts General Hospital, except for Revival Therapeutics and Sensorium Therapeutics. Speaking/publishing: Lecture given at Global Medical Education, Inc. Mood Disorders Summit, November 2020. Stock/other financial options, equity holdings: Compellis; Neuromity; Psy Therapeutics; Revival Therapeutics; Sensorium Therapeutics. Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD), licensed by MGH to Pharmaceutical Product Development, LLC (PPD) (US_7840419, US_7647235, US_7983936, US_8145504, US_8145505); and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven. Patents for pharmacogenomics of Depression Treatment with Folate (US_9546401, US_9540691). Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; Belvior; Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. Pte. Ltd.

BHV-7000, A NOVEL KV7 POTASSIUM CHANNEL ACTIVATOR, IN DEVELOPMENT FOR MAJOR DEPRESSIVE DISORDER AND BIPOLAR DISORDER

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Background/Objective: Kv7.2/7.3 potassium channels play a key role in moderating pathological neural hyperexcitability that underpins mood disorders. Kv7 activation attenuates depressive and manic behaviors in rodent models, human genetics studies link Kv7 to the risk of bipolar disorder (BD), and Kv7 activators have demonstrated clinical efficacy in treating major depressive disorder (MDD). BHV-7000 is a selective activator of Kv7.2/7.3 and has improved motivation and impulsivity in preclinical studies. Our objective is to evaluate the clinical efficacy and safety of BHV-7000 in MDD and BD.

Design: A Phase II, randomized, double-blind, placebo-controlled trial of BHV-7000 monotherapy in MDD is being conducted in adults with one or more prior depressive episodes who are currently experiencing a depressive episode with anhedonia. Participants are randomized 1:1 to BHV-7000 75mg or placebo once daily for six weeks. The primary endpoint is the change in Montgomery–Åsberg Depression Rating Scale (MADRS) total score from baseline to Week 6.

A Phase II/III randomized, double-blind, placebo-controlled, inpatient trial of BHV-7000 for acute treatment of manic episodes, with or without mixed features, associated with bipolar I disorder is being conducted in adults with one or more prior mood episodes who are currently experiencing a manic episode. Participants are randomized 1:1 to BHV-7000 75mg or placebo once daily for three weeks. The primary endpoint is the change in Young Mania Rating Scale (YMRS) total score from baseline to Day 21.

Results: These studies are currently ongoing.

Conclusion: BHV-7000 offers a novel and differentiated mechanism of action with the potential for robust efficacy and improved tolerability in treating MDD and BD.

Funding/financial disclosures: These studies are funded by Biohaven, and all authors are employed by and hold stock/options in Biohaven.

EFFICACY AND SAFETY OF ICLEPERTIN (BI 425809) IN PATIENTS WITH SCHIZOPHRENIA: CONNEX, A PHASE III RANDOMIZED CONTROLLED TRIAL PROGRAM

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Background/Objective: No effective pharmacological treatments are available for cognitive impairments in schizophrenia. Iclepertin (BI 425809), a glycine transporter-1 inhibitor, enhances N-methyl-D-aspartate receptor signaling by increasing synaptic levels of its co-agonist, glycine. In a Phase II

proof-of-clinical-concept trial (NCT02832037), iclepertin was well tolerated and improved cognition in schizophrenia. The Phase III CONNEX program aims to confirm the efficacy and safety of iclepertin in improving cognition/functioning across a large cohort of patients with schizophrenia.

Design: The CONNEX program consists of three replicate randomized, double-blind, placebo-controlled parallel trials in patients with schizophrenia. A total of 586 patients per trial will be recruited across 41 countries, and randomized 1:1 to receive daily iclepertin 10mg or placebo over 26 weeks. Primary efficacy endpoint is change from baseline (CfB) in overall composite T-score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery. Key secondary efficacy endpoints include CfB in total Schizophrenia Cognition Rating Scale score and CfB in the adjusted total time in the Virtual Reality Functional Capacity Assessment Tool. Long-term safety/tolerability data will be collected in an open-label safety extension study (CONNEX-X).

Results: The studies are currently recruiting (first enrollment August–September 2021), with completion expected in Q1 2025. Current study status, including screening failures and data collection experiences, are presented.

Conclusion: Most industry-sponsored studies testing compounds for cognitive deficits have failed to show proof-of-clinical-concept. If successful, the CONNEX program would provide evidence for iclepertin as the first efficacious medication addressing cognitive impairments in schizophrenia.

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Conflict of Interest: CR-F, ZB, and BAE are employees of Boehringer Ingelheim. SI has received consultancy fees from Boehringer Ingelheim Pharma GmbH, Lundbeck, Takeda Pharma, Sumitomo Dainippon Pharma. SI is now an employee of the International University of Health and Welfare, Mita Hospital, Tokyo, Japan. SRM has financial agreements with Boehringer Ingelheim Pharma GmbH, Merck, Biogen, and Sunovion. PF has received consultancy fees from Boehringer Ingelheim Pharma GmbH and is a member of the Boehringer Ingelheim Pharma advisory board. JHK is a co-founder of Freedom Biosciences, Inc.; has received consultancy fees from Aptinyx, Atai Life Sciences, AstraZeneca Pharmaceuticals, Biogen, Biomedisyn Corporation, Bionomics, Boehringer Ingelheim International, Cadent Therapeutics, Clexio Bioscience, COMPASS Pathways, Concert Pharmaceuticals, Epiodyne, EpiVario, Greenwich Biosciences, Heptares Therapeutics, Janssen, Jazz Pharmaceuticals, Otsuka America Pharmaceutical, Perception Neuroscience Holdings, Spring Care, Sunovion Pharmaceuticals, Takeda Industries, Taisho Pharmaceutical Co.; is a member of the Advisory Board of Biohaven Pharmaceuticals, BioXcel Therapeutics, Cadent Therapeutics, Cerevel Therapeutics, Delix Therapeutics, EpiVario, Eisai, Jazz Pharmaceuticals, Novartis, PsychoGenics, RBNC Therapeutics, Tempero Bio, and Terran Biosciences; and has investments in Biohaven Pharmaceuticals, Sage Pharmaceuticals, Spring Care, Biohaven Pharmaceuticals Medical Sciences, EpiVario, RBNC Therapeutics, Terran Biosciences, and Tempero Bio.

EFFICACY AND SAFETY OF NR2B NAM BI 1569912 AFTER SINGLE ORAL ADMINISTRATION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Background/Objective: Nonselective N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine/esketamine) have demonstrated efficacy in the treatment of major depressive disorder (MDD); however, these agents are associated with frequent and distressing/unacceptable adverse events (e.g., dissociation). NMDA receptor subunit 2b selective negative allosteric modulators (NR2B NAMs) may offer efficacy without the side-effect burden of nonselective NMDA receptor antagonists. BI 1569912, an oral NR2B NAM in development for MDD, did not produce dissociation or any serious adverse events in Phase I studies.

Design: Here, we report data from a randomized, double-blind, placebo-controlled Phase Ib trial (NCT04937829) of a single dose of BI 1569912 (5mg and 20mg) versus placebo as an adjunct to antidepressants in adults with moderate-to-severe MDD and insufficient response to ongoing antidepressant monotherapy. Efficacy was assessed by evaluating the change from baseline in Montgomery–Åsberg Depression Rating Scale (MADRS) total score at individual time points (exploratory). Drug-related adverse events were recorded.

Results: Median age (range) of treated patients (N=59) was 54.0 (18–65) years; 54.2 percent (n=32) were female. The mean (standard deviation) baseline MADRS total score was 34.6 (5.8) points. A single BI 1569912 20mg administration provided 3.4- to 4.9-point improvements in MADRS total score versus placebo at Days 2, 4, and 6.

Conclusion: A single dose of adjunctive BI 1569912 produced a rapid antidepressant effect with early separation from placebo on MADRS total score and was well tolerated with no dissociation, supporting progression into Phase II (NCT06280235). NR2B NAMs represent potential antidepressant treatments that may offer rapid, well-tolerated efficacy.

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GS has served as consultant to Abbvie, Atai, Biogen, Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Clexio, Cowen, Denovo Biopharma, ECR1, EMA Wellness, Embark, Daiichi Sankyo, Freedom Biosciences, Gilgamesh, Janssen, Merck, Neurocrine, Novartis, Perception Neuroscience, Relmada Therapeutics, Sage Pharmaceuticals, Seelos Pharmaceuticals, Tetricus, Transcend Therapeutics, Usona Institute, and XW Labs and received research contracts from Merck and the Usona Institute over the past 12 months. GS holds equity in Biohaven Pharmaceuticals, Freedom Biosciences, Gilead, Relmada, and Tetricus. He is a co-inventor on a US patent (#8,778,979) held by Yale University and a co-inventor on US Provisional Patent Application No. 047162-7177P1 (00754) filed on August 20, 2018, by Yale University Office of Cooperative Research. Yale University has a financial relationship with Janssen Pharmaceuticals and may receive financial benefits from this relationship. GS does not receive any direct payments through this relationship, and the university has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office.

DPW has served as consultant to Otsuka, Janssen, Boehringer Ingelheim, Biogen, and Lyndra, and has received grant/research support from Novartis, Johnson & Johnson Pharmaceutical Research & Development, Sunovion, Janssen, Cerevel, Pfizer, AbbVie, Alkermes, Allergan, Sage, Takeda, Otsuka, Neurocrine, Noven, Karuna, Indivior, Intra-Cellular, Lyndra, Lupin, Avanir, Lundbeck, Roche, Boehringer Ingelheim, Acadia, and Biogen.

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HR is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG. MS is an employee of main analytics GmbH, working on behalf of Boehringer Ingelheim Pharma GmbH & Co. KG. LA is an employee of Boehringer Ingelheim Pharmaceuticals, Inc. AS, SDS, and FDC are employees of Boehringer Ingelheim International GmbH.

FUNCTIONAL AND SEXUAL DISABILITY AND QUALITY OF LIFE AFTER ONE DOSE OF MM120 (LYSERGIDE) IN ADULTS WITH GENERALIZED ANXIETY DISORDER

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Background/Objective: To determine if single-dose MM120 (lysergide D-tartrate) results in improvements in functional disability (FD), sexual dysfunction (SD), and quality of life (QoL) in participants with generalized anxiety disorder (GAD).

Design: This phase IIb (NCT05407064) multicenter, randomized, double-blind, placebo-controlled study enrolled adults (aged 18–74 years) diagnosed with GAD and moderate-to-severe anxiety as defined by a Hamilton Anxiety Scale (HAM-A) score of 20 or greater. Participants were randomized equally to receive single dose MM120 at 25µg, 50µg, 100µg, or 200µg, or placebo. FD, QoL, and SD were assessed by the Sheehan Disability Scale (SDS), EQ-5D-5L and Pittsburgh Sleep Quality Index (PSQI), and Arizona Sexual Experiences Questionnaire (ASEX), respectively.

Results: Overall, 198 participants were enrolled. MM120 dosing over 100µg demonstrated consistent improvements in FD at Weeks (W) 1 to 12. The optimal primary efficacy dose (100µg MM120) demonstrated placebo-adjusted improvements in EQ-5D-5L utility index of 0.111, 0.081, and 0.116 points and in EQ5 visual analog scale (VAS) of 4.02, 5.41, and 6.04 points at W4, W8, and W12, respectively. Mean PSQI scores improved at W4, W8, and W12 across all groups, including placebo. At W12, there was a considerable decrease from baseline in the proportion of participants who reported SD for male participants with MM120 100µg (29.2% at baseline vs. 10% at W12) versus placebo (15.4% at baseline vs 12.5% at W12) and for female participants with MM120 100µg (75% at baseline vs. 46.2% at W12) versus placebo (50% at baseline vs. 33.3% at W12).

Conclusion: QoL measures demonstrated clinically significant and durable changes in response to single-dose treatment with MM120.

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LUMATEPERONE AS ADJUNCTIVE THERAPY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, PHASE III TRIAL

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Background/Objective: Lumateperone is a United States Food and Drug Administration (FDA)-approved antipsychotic to treat schizophrenia and bipolar depression. This Phase III, randomized, double-blind, placebo-controlled, multicenter, international trial (NCT04985942) investigated adjunctive lumateperone 42mg in patients with major depressive disorder (MDD) with inadequate response to antidepressant therapy (ADT).

Design: Eligible adults met *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for MDD with inadequate response to 1 to 2 courses of prior ADT and had Montgomery–Åsberg Depression Rating Scale (MADRS) total score of 24 or greater, Clinical Global Impression-Severity (CGI-S) score of 4 or greater, and Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) score of 14 or greater. Patients were randomized to outpatient six-week placebo or lumateperone 42mg adjunctive to ADT. Primary and key secondary efficacy endpoints were change from baseline to Day 43 in MADRS total and CGI-S scores, respectively. QIDS-SR-16 total score and safety were evaluated.

Results: Of 484 patients treated (placebo, n=243; lumateperone, n=241), 93 percent completed treatment. Primary and key secondary endpoints were met for adjunctive lumateperone, with significantly greater improvement versus adjunctive placebo from baseline to Day 43 in MADRS total score (least squares mean difference vs. placebo [LSMD]: −4.9; effect size [ES]: −0.61; $p<0.0001$) and CGI-S (LSMD: −0.7; ES: −0.67; $p<0.0001$). Adjunctive lumateperone significantly improved QIDS-SR-16 total score at Day 43 versus adjunctive placebo (LSMD: −2.4; ES: −0.50; $p<0.0001$). Adjunctive lumateperone was generally safe and well tolerated, consistent with prior studies. No serious adverse events occurred with lumateperone during treatment.

Conclusion: Lumateperone 42mg adjunctive to ADT demonstrated robust and clinically meaningful efficacy over placebo adjunctive to ADT and was generally safe and well tolerated, indicating lumateperone as a promising adjunctive therapy to ADT for MDD in adults.

Funding/financial disclosures: SD, WRE, SGK, CC, HL, and MM are full-time employees of Intra-Cellular Therapies, Inc. and may hold equity in the company.

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SS has served as a consultant to Acadia; Alkermes; Allergan; AbbVie; Arbor Pharmaceuticals; Axovant; Axsome; Celgene; Concert; Clearview; EMD Serono; Eisai Pharmaceuticals; Ferring; Impel NeuroPharma; Intra-Cellular Therapies, Inc.; Ironshore Pharmaceuticals; Janssen; Karuna; Lilly; Lundbeck; Merck; Otsuka; Pfizer; Relmada; Sage Therapeutics; Servier; Shire; Sunovion; Takeda; Taliaz; Teva; Tonix; Tris Pharma; and Viforpharma; he is a board member of Genomind; he has served on speakers bureaus for Acadia, Lundbeck, Otsuka, Perrigo, Servier, Sunovion, Takeda, Teva, and Vertex; and he has received research and/or grant support from Acadia; Avanir; Braeburn Pharmaceuticals; Eli Lilly; Intra-Cellular Therapies, Inc.; Ironshore; ISSWSH; Neurocrine; Otsuka; Shire; Sunovion; and TMS NeuroHealth Centers.

PHASE II, RANDOMIZED, DOSE-FINDING STUDIES OF THE NMDA SUBUNIT 2B-SELECTIVE NEGATIVE ALLOSTERIC MODULATOR, BI 1569912, IN PEOPLE LIVING WITH MAJOR DEPRESSIVE DISORDER

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Background/Objective: We describe two Phase II, multicenter, randomized, double-blind, placebo-controlled trials to provide proof of concept and dose selection for BI 1569912 for the treatment of major depressive disorder (MDD).

Design: In the current, ongoing, dose-finding adjunctive trial (1447-0005, NCT06280235), 204 adults (aged 18–65 years old) with an established MDD diagnosis and insufficient treatment response (<50% response to ≤4 antidepressants) in their current episode are randomized to six weeks' treatment with BI 1569912 (5mg, 10mg, or 20mg) or placebo once daily in addition to their existing antidepressant. Assessments include the Montgomery–Åsberg Depression Rating Scale (MADRS), Symptoms of Major Depressive Disorder Scale, safety, and tolerability. Primary endpoint is change from baseline in MADRS total score at Day 8.

The planned dose-finding monotherapy trial (1447-0012) will randomize 222 adults (aged 18–65 years old) with an established MDD diagnosis to six weeks' treatment with one of the three doses of BI 1569912 or placebo once daily. Assessments will include the MADRS, safety, and tolerability. Primary endpoint will be change from baseline in MADRS total score at Week 6.

Results: The BI 1569912 adjunctive therapy trial started recruitment in March 2024 and is expected to complete in October 2025. The BI 1569912 monotherapy trial is expected to start in October 2024. The poster will present a status update on screening and recruitment of the adjunctive trial and further methodology for the monotherapy trial.

Conclusion: These trials will explore efficacy and safety of BI 1569912 in people with MDD.

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Pharmaceuticals, Minerva, Merck, Teva, and Denovo Biopharma.

GS has served as consultant to Aptinyx, Atai, Biogen, Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Clexio, Cowen, Denovo Biopharma, ECR1, EMA Wellness, Embark, Daiichi Sankyo, Freedom Biosciences, Gilgamesh, Janssen, Merck, Neurocrine, Perception Neuroscience, Relmada Therapeutics, Sage Pharmaceuticals, Seelos Pharmaceuticals, Tetricus, Transcend Therapeutics, Usona Institute, and XW Labs and received research contracts from Merck and the Usona Institute over the past 12 months. GS holds equity in Biohaven Pharmaceuticals, Freedom Biosciences, Gilead, Relmada, and Tetricus. GS is a co-inventor on a US patent (#8,778,979) held by Yale University and a co-inventor on US Provisional Patent Application No. 047162-7177P1 (00754) filed on August 20, 2018, by Yale University Office of Cooperative Research. Yale University has a financial relationship with Janssen Pharmaceuticals and may receive financial benefits from this relationship. GS does not receive any direct payments through this relationship, and the university has put multiple measures in place to mitigate this institutional conflict of interest.

KW has served as consultant of Boehringer Ingelheim, Daiichi Sankyo, Eisai, Eli Lilly, Janssen Pharmaceutical, Kyowa Pharmaceutical, Lundbeck Japan, Luye Pharma, Mitsubishi Tanabe Pharma, Otsuka Pharmaceutical, Pfizer, Sumitomo Dainippon Pharma, Taisho Toyama Pharmaceutical, and Takeda Pharmaceutical.

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FDC, SDS, BS, RM, and AS are employees of Boehringer Ingelheim International GmbH. R-GG is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG.

PRELIMINARY DATA FROM THE CONNEX-X EXTENSION TRIAL EXAMINING THE LONG-TERM SAFETY OF ICLEPERTIN (BI 425809) IN PATIENTS WITH SCHIZOPHRENIA WHO COMPLETED PHASE III CONNEX TRIALS

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Background/Objective: Iclepertin (BI 425809), a glycine transporter-1 inhibitor, has improved cognitive impairment associated with schizophrenia (CIAS) in Phase II trials, with Phase III trials underway. The CONNEX-X extension study aims to examine the long-term safety of iclepertin to treat CIAS.

Design: CONNEX-X is a multinational, multicenter, open-label, single-arm extension study in patients with CIAS who completed treatment (26 weeks, iclepertin 10mg or placebo) in one of three Phase III CONNEX parent trials. Approximately 1,400 clinically stable outpatients will be treated (1 year, iclepertin 10mg daily). Patients are excluded if any of the following occurred up to Visit 1 of CONNEX-X: suicidal behavior/ideation, diagnosis with moderate/severe substance use disorder, diagnosis other than schizophrenia, development of any condition preventing participation, hemoglobin level decrease (>25% or <100g/L from CONNEX baseline), or hemoglobinopathies. Primary endpoint is occurrence of treatment-emergent adverse events. Secondary endpoints include change from baseline (CfB) in Clinical Global Impressions-Severity and hemoglobin. Further efficacy endpoints include CfB in MATRICS Consensus Cognitive Battery overall composite T-score, Schizophrenia Cognition Rating Scale total score, and Virtual Reality Functional Capacity Assessment Tool total times.

Results: A total of 460 patients have been enrolled and randomized from CONNEX with zero percent screening failures (~82% rollover rate, April 29, 2024). Current study status, including recruitment, screening failures, and data collection experiences, are presented.

Conclusion: Patient enrollment rates from CONNEX to CONNEX-X are stable. CONNEX-X will explore long-term safety and descriptive analyses of cognitive and functional endpoints of iclepertin in CIAS treatment.

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RAPID AND DURABLE RESPONSE TO A SINGLE DOSE OF MM120 (LYSERGIDE) IN GENERALIZED ANXIETY DISORDER: A DOSE-OPTIMIZATION STUDY

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Background/Objective: To evaluate the dose-response relationship of efficacy, safety, and tolerability for single-dose MM120 (lysergide D-tartrate) in participants with generalized anxiety disorder (GAD).

Design: This Phase IIb (NCT05407064) multicenter, randomized, double-blind, placebo-

controlled study enrolled adults (aged 18–74 years) diagnosed with GAD and moderate-to-severe anxiety as defined by a Hamilton Anxiety Scale (HAM-A) score of 20 or greater. Participants were randomized equally to receive single-dose MM120 at 25µg, 50µg, 100µg, or 200µg, or placebo. The primary objective assessed change in HAM-A from baseline to Week (W) 4. Secondary endpoints included improvements in other efficacy measures, quality of life, and safety and tolerability.

Results: Overall, 198 participants were enrolled. MM120 at 100µg and 200µg doses demonstrated clinically and statistically significant efficacy. The 100µg dose achieved the highest level of clinical activity, with a 7.6-point greater change in HAM-A score compared to placebo at W4 (–21.34 MM-120 vs. –13.75 placebo; p=0.0004). At W4, 77.5 percent of participants treated with MM120 100µg showed a clinical response (≥50% improvement in HAM-A vs. 30.8% with placebo). Clinical Global Impressions-Severity (CGI-S) scores improved by 1.8 points with MM120 100µg versus 0.7 points with placebo (p=0.0001) on Day 2, which persisted through W4 (p<0.01). Treatment-emergent adverse events occurred in 97.5 percent of participants in the MM120 100µg group versus 56.4 percent in the placebo group. Most adverse events were mild-to-moderate, occurred on the dosing day, and were consistent with the expected effects of MM120.

Conclusion: These findings suggest a rapid and durable clinical response to MM120 with no identified safety concerns among participants with moderate-to-severe GAD.

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ReST THERAPEUTICS NEUROPSYCHIATRY PLATFORM: SELECTIVE NMDAR MODULATION OF NEUROINFLAMMATION AND NEUROPLASTICITY

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Background/Objective: ReST Therapeutics is a biotechnology company developing breakthrough therapies to treat complex central nervous system disorders. Our lead candidate, RST-01, selectively modulates N-methyl-D-aspartate receptor (NMDAR)–controlled neuroplasticity, and ReST is preparing to file its Investigational New Drug Application (IND) for early intervention in post-traumatic stress disorder (PTSD).

Design: RST-01 is a novel and proprietary chemical entity specifically targeting certain NMDAR subtypes involved in synaptic plasticity. It facilitates stress extinction and neuroprotection without triggering the adverse side effects classically encountered with less selective NMDA targeting drugs. It is through a chronic model of neurodegeneration induced by the inoculation of Aβ25-35 into the cerebral ventricles that a selection of the new drugs was made possible. The model was designed in a robust, reproducible, and versatile manner, testing various routes of administration and pharmacokinetics. Furthermore, the model proved to be translational in the sense that memantine, a well-established symptomatic treatment of Alzheimer's disease (AD) whose efficacy disappears over time, also displays a transient efficacy in the model. This results in the ability to set a simple endpoint and straightforward study duration for disease modifier candidates. Animals are treated daily, and their spatial working memory evaluated once a week throughout the whole experiment. Brain tissue can be further analyzed to identify specific biomarkers linked with neurodegenerative diseases, such as neuroinflammation, and refine the specific mode of action.

Results: Seven chemical variations of RST-01 were designed to develop a better understanding of the structure-activity relationship and potentially extend ReST Therapeutics' portfolio of drug candidates. Out of the seven molecules, three resulted in performances either equal or superior to RST-01 and are currently being investigated in AD, amyotrophic lateral sclerosis, Huntington's disease.

Conclusion: Through breakthrough discoveries, proprietary technologies, and unique expertise, ReST proposes a platform based on a robust, reproductible, and easy-to-handle approach targeting neurodegenerative disorders.

Funding/financial disclosures: AC, AF, and GR are employees of ReST. GR and AF are inventors in patents supporting the ReST technology platform.

SAFETY DATA OF ICLEPERTIN (BI 425809) FROM PHASE I HEALTHY VOLUNTEERS AND PHASE II PATIENTS WITH COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA (CIAS)

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Background/Objective: To assess the safety of iclepertin (BI 425809), a glycine transporter-1 inhibitor in Phase III development for cognitivie impairment associated with schizophrenia (CIAS), in Phase I (N=391 healthy volunteers [HV]; 339 iclepertin-treated, 52 placebo-controlled) and Phase II trials (N=709 patients with CIAS; 438 iclepertin-treated, 271 placebo-controlled).

Design: Descriptive statistics.

Results: In Phase I, 198 (58.4%) iclepertin-treated and 17 (32.7%) placebo-controlled HVs reported adverse events (AEs), four (1.2%) severe and 125 (36.9%) defined as drug-related. Ten (2.9%) AEs led to treatment discontinuation. No AEs of special interest (AESI) or serious AEs (SAE) were reported. No suicidal ideation or behavior was reported.

In Phase II, 204 (46.6%) iclepertin-treated patients with CIAS versus 131 (48.3%) placebo-treated participants reported any AEs. Ten (2.3%) treated participants versus three (1.1%) placebo-controlled patients reported AEs of severe intensity, and 76 (17.4 %) versus 50 (18.5%) were drug-related. Fourteen (3.2%) versus eight (3.0%) patients discontinued treatment due to an AE. One (0.2%) AESI occurred on iclepertin (0 on placebo). Thirteen (3.0%) versus six (2.2%) SAEs have been reported. The most common preferred terms were headache (40 [9.1%] vs. 20 [7.4%]), somnolence (17 [3.9%] vs. 7 [2.6%]), dizziness (17 [3.9%] vs. 6 [2.2%]), and nasopharyngitis (29 [6.6%] vs. 14 [5.2%]). Suicidal ideation was reported in one (0.2%) iclepertin-treated and three (1.1%) placebo-controlled patients.

Conclusion: Iclepertin was well tolerated by both populations. No dose-dependent trends were observed for the overall number of AEs. No meaningful changes were observed in the analyzed ocular safety and hemoglobin parameters versus placebo.

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TerXT, A NOVEL PRODRUG APPROACH TO A LONG-ACTING INJECTABLE COMBINATION OF XANOMELINE AND TROSPIUM, SHOWS IMPROVED PHARMACOKINETICS IN ANIMAL MODELS

Authors: Sam Clark, MD, PhD[1]

Affiliations: [1]Founder and CEO, Terran Biosciences

Background/Objective: A twice-daily combination of xanomeline and trospium has demonstrated robust clinical efficacy and safety in recent schizophrenia trials. However, chemical properties of xanomeline and trospium have limited the feasibility of improved dosing forms, such as once-daily oral and long-acting injectable (LAI) formulations. We sought to apply a prodrug strategy to xanomeline and trospium to develop a fixed-dose combination of two new prodrugs to enable once-daily oral and LAI administration.

Design: Using a structure activity approach, we synthesized over 500 examples of xanomeline and trospium prodrugs, which were tested in rodent pharmacological models using oral, subcutaneous, and intramuscular administration compared to the original parent compounds. The prodrugs underwent *in vitro* testing, including stability in plasma and S9 liver fraction and binding to liability receptors (e.g., hERG). Based on the results, we further modified lead candidates to optimize for stability in formulation while simultaneously optimizing the half-life of the circulating prodrug.

Results: We identified the prodrugs that outperformed the parent compounds on both oral and intramuscular metrics and demonstrated increased stability in formulation studies. The lead prodrugs showed optimized area under the curve (AUC) and C_{max} compared to the parent compounds, improved solubility in lipids, lacked hERG liability, and improved stability in a wide range of pH buffered solutions.

Conclusion: Our study showed that both xanomeline and trospium could be optimized through a prodrug approach for once-daily oral administration and long-acting injection. These results support the further development of these prodrugs in trials for patients with schizophrenia.

Funding/financial disclosures: SC is a full-time employee and stockholder of Terran Biosciences.

VRAYLAR VS. PLACEBO IN SOCIAL ANXIETY DISORDER

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Background/Objective: To assess the efficacy and tolerability of Vraylar (cariprazine) monotherapy as a treatment for social anxiety disorder (SAD).

Design: This was a 12-week, double-blind, placebo-controlled, randomized trial of cariprazine 1.5 to 3mg per day versus placebo. Primary outcome measure was change in Liebowitz Social Anxiety Scale (LSAS) total score from baseline to endpoint. Planned study sample was 40 subjects meeting *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for SAD, with a minimum LSAS score of 70 and maximum Hamilton Depression Rating Scale (HAM-D) score of 15.

Results: Cariprazine was statistically superior to placebo beginning at Week 1 and at almost every measurement point of the trial. Cariprazine exceeded placebo at primary endpoint (p=0.021). At endpoint, mean change with cariprazine was more than 15 points greater than with placebo on total LSAS. Cariprazine was generally well tolerated, but many subjects experienced mild akathisia.

Conclusion: Cariprazine may be a new option for treating SAD, as severely affected individuals appear to benefit from it.

Funding/financial disclosures: AbbVie supported this investigator-initiated trial that was conducted at the Medical Research Network LLC. ML holds the copyright for the LSAS.

TREATMENT DEVICES AND TOOLS

EFFICACY OF A VIRTUAL REALITY (VR) DIGITAL THERAPEUTIC FOR THE TREATMENT OF SOCIAL ANXIETY DISORDER: A RANDOMIZED SHAM-CONTROLLED TRIAL

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Background/Objective: Only a minority of patients with social anxiety disorder (SAD) receive appropriate treatment. BVR-100, a novel virtual reality (VR)-based digital therapeutic for SAD, delivers cognitive behavioral therapy (CBT), including exposure therapy. This study aimed to evaluate the credibility, efficacy, and safety of BVR-100, compared to a VR sham intervention.

Design: Fifty-six patients with SAD were randomly assigned to receive BVR-100 or the sham for eight weeks. Primary endpoints were treatment credibility as measured with the Credibility/Expectancy Questionnaire (CEQ), retention, and time-on-task. Exploratory endpoints were the change in SAD symptoms measured with the Liebowitz Social Anxiety Scale (LSAS) and symptom response measured with the Clinical Global Impressions-Improvement (CGI-I).

Results: There were no significant differences in CEQ scores, time-on-task (8.2 vs. 7.9 active days), or retention (100% vs. 96%) between groups. The BVR-100 group showed a greater reduction in LSAS total score compared to sham

at Week 8 (mean difference: –27.9 vs. –20.2). Additionally, 48 percent of patients in the BVR-100 group were classified as responders (CGI-I score of 1 or 2) versus 26 percent in the sham group. Both interventions were well tolerated.

Conclusion: Our findings indicate that the VR sham intervention is an appropriate control and provide preliminary evidence of the therapeutic effects of BVR-100, as evidenced by greater reductions in LSAS scores and higher response rates compared to the sham intervention. Both interventions were well tolerated and pose minimal health risks to subjects.

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TRIAL METHODOLOGY

A SURVEY OF OUTCOMES SELECTION CHALLENGES IN EARLY-TO-LATE-PHASE NEUROSCIENCE DRUG DEVELOPMENT

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Background/Objective: Despite major advances in neuroscience, clinical trials for neurological and psychiatric conditions continue to have notoriously high failure rates. The use of innovative clinical outcome assessments (COAs) grounded in translational research is key to maximize the likelihood of identifying promising new treatments in early-phase clinical trials. However, the field has lacked standardized practice guidelines for optimal selection of COAs and also faces a low acceptance of innovative outcomes by regulators or health agencies. For the recently developed seven-step standard process for COA selection, we wanted to explore the existing challenges for its implementation by pharmaceuticals and biotechnology.

Design: A survey was distributed to experts on outcomes research to solicit feedback on the proposed seven-step process, including level of agreement, endorsement, and expected challenges when implementing the standards.

Results: Twenty-six participants, 46 percent from the pharmaceutical industry, 19 percent from clinical research organizations (CROs), and 18 percent from academia, among others, were collected. The majority (81%) had experience working on setting strategies for COA in clinical trials, with 60 percent over 10 years. The seven-step process was accepted by all, with 30 percent suggesting additional activities. Opinions regarding how much the industry is currently using standards varied widely. Suggestions to encourage its adoption included to conduct dissemination/educational activities, to proof the method, to review the alignment with existing regulatory guidance, and to promote the advantages to pharma industry in terms of time and cost-effectiveness.

Conclusion: The consensus-based seven-step method for setting COAs strategy in neuroscience clinical trials is a key reference for any type of research in drug development. Feedback obtained from experts supports its adoption. It is worth mitigating the risks of failure and facilitating the interaction with regulatory agencies. The answers indicate several additional actions to improve the process.

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A NOVEL ASYNCHRONOUS VIDEO TECHNOLOGY AND SERVICE TO SECURE PROTOCOL MEDICATION COMPLIANCE AND REDUCE RISK OF ABUSE, MISUSE, AND DIVERSION OF CLE-100 IN SOLEO: A PHASE II, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY IN PARTICIPANTS WITH MAJOR DEPRESSIVE DISORDER (MDD)

Authors: Morad Elmi,[1] Jorge Aquino,[1] Hedi Kim,[1] Linor Haimson,[2] Yifat Ronen-Protas,[2] Oren Berkowitz,[2] Esther Lukasiewicz-Hagai[2]

Affiliations: [1]Scene Health (Scene); [2]Clexio Biosciences (sponsor)

Background/Objective: Clexio Biosciences is continuing its use of Scene's (formerly emocha) video platform services to monitor compliance to trial protocol and to mitigate risk of misuse/abuse/diversion of CLE-100 (oral esketamine).

Design: Scene's United States Centers for Disease Control and Prevention (CDC)-endorsed asynchronous video technology and service is expected to enhance protocol and medication adherence rates. Adherence is measured as the number of doses confirmed over the number of expected doses. The ongoing trial (SOLEO) is designed to assess CLE-100 added to an ongoing antidepressant for the treatment of MDD. Scene was previously used in a similar trial, CLEO, where mean adherence was 97.39 percent. Participants use Scene's smartphone application at home every day to video-record taking every dose and show the number of tablets remaining. Scene's Adherence Review team personally reviews each video and immediately escalates any issues observed to trial sites for patient-specific interventions as appropriate.

Results: SOLEO began enrollment in April 2024 and is ongoing. Participants (n=~90) are treated for 28 days in the double-blind, placebo-controlled phase and for 24 weeks in the open-label phase. We hypothesize participants will demonstrate high medication adherence rates and have low levels of drug accountability issues or abuse/misuse/diversion due to early detection.

Conclusion: Pending results, Scene's technology-enabled adherence service helps obtain accurate pill counts, secure high rates of medication adherence, and mitigate misuse/abuse/diversion. Timely human review of each video submission by Scene is allowing trial sites to correct participant protocol issues early and in near real-time. In the ongoing SOLEO trial,

participants have successfully engaged with the Scene smartphone application.

Funding/financial disclosures: HK, JA, and ME are employees of Scene Health.

ACCELERATING MEDICINES PARTNERSHIP® SCHIZOPHRENIA (AMP® SCZ)

Authors: Yael Mandelblat-Cerf,[1]* Linda Brady,[2] Carlos Larrauri,[3] Suzanne Garcia,[4] Loni Ajagbe,[5]

*Presenting author

Affiliations: [1]Branch Chief, National Institute of Mental Health; [2]Director of the Division of Neuroscience & Basic Behavioral Science, National Institute of Mental Health; [3]National Alliance on Mental Illness; [4]Project Manager, National Institute of Mental Health; [5]Project Manager, Foundation for the National Institutes of Health

Background/Objective: The Accelerating Medicines Partnership® for Schizophrenia (AMP® SCZ), launched in 2020, is the first AMP initiative directed toward a neuropsychiatric disorder.

Design: AMP SCZ will recruit a large cohort (n=1,977) of individuals between the ages of 12 and 30 years who meet the criteria for being clinical high risk for psychosis (CHR) and healthy controls (n=640) across 43 sites from 14 countries. This public-private partnership is focused on developing and implementing a set of biomarkers combined with clinical and cognitive assessments to create algorithms that reliably distinguish course types in CHR individuals. Employing a comprehensive deep phenotyping approach, including neurocognitive imaging, electrophysiology, fluid biomarkers, digital measures, and speech sampling, the observational study aims to create multimodal algorithms that distinguish trajectories and outcomes (conversion, remission, and unremitted symptoms) in CHR individuals. The proof-of-principle (PoP) trial will determine if a pharmacological treatment can produce a detectable signal on the same biological, digital, cognitive, and clinical outcomes measures as used in the observational study within a 12-week period of study.

Results: Data from the observational study and PoP trial will be uploaded to the National Institute of Mental Health (NIMH) Data Archive (NDA) and made available to the broader research community with approved NDA Data Use Certifications. The AMP-SCZ Data Release 2.0 contains quality-controlled screening and baseline data from 1,048 subjects, including behavioral and clinical measures, electroencephalography, imaging data, and associated data. Every six months, new curated data sets will be shared through the NDA until the data from 2,617 participants are made available.

Funding/financial disclosures: None.

BRAIN NETWORK BIOMARKERS AND NEUROTRANSMITTER CONTRIBUTION TO DRUG EFFECTS USING EEG TOMOGRAPHY IN NONHUMAN PRIMATES AND HUMANS

Authors: Monica Metea,[1] Lucas Crum,[1] Mark Jahnke,[1] Ernesto Soler[1]

Affiliations: [1]Preclinical Electrophysiology Consulting, MA, US

Synopsis: We show streamlined platform-based heuristics for generating cross-species preclinical-to-clinic translatable biomarkers of drug effect on brain network function using nonhuman primate (NHP) and human electroencephalogram (EEG) tomography and artifical intelligence (AI)-informed methods for predicting neurotransmitter contribution to drug-induced oscillatory changes.

Background/Objective: EEG is widely used in drug development due to its low cost and high sensitivity to pharmacological modulation, yet EEG methods investigating network function or predicting receptor contribution to drug-induced changes in oscillatory activity are underused both preclinically and in the clinic. To close this gap, we developed platform-integrated heuristics for generating EEG tomography-derived biomarkers across species (cynomolgus monkey and human), aligned with AI-informed methods predicting neurotransmitter contribution to the drug's effect on brain function.

Design: Cynomolgus and human brain models were developed using the MEBRAINS Multilevel Macaque Atlas and Julich Probabilistic Human Atlas. Source localization and functional connectivity algorithms were developed using swLORETA. AI algorithms, including multiple linear regression models and dominance analyses, were developed to predict the source power distribution of each frequency band from normative neurotransmitter positron emission tomography (PET)-derived densities, and to compare pre-post drug neurotransmitter dominance change.

Results: The heuristics for obtaining predictions of neurotransmitter contribution to a drug's effect and alignment with drug effects on brain networks are presented stepwise using side-by-side preclinical cynomolgus EEG and patient EEG. We include examples of network metrics identifying the presence and localization of drug-induced synaptic modulation and dominance analyses showing specific neurotransmitter contribution to respective drug effects.

Conclusion: In conclusion, we show streamlined translational tools for understanding target-specific drug effects targeting the central nervous system (CNS) across species with profound practical implications for the development of CNS-active compounds, enabling low-cost, rapid, hypothesis-driven decision-making using functional metrics of brain network function.

Funding/financial disclosures: Not provided.

COMPLIANCE WITH 2017 FDA GUIDANCE FOR EVALUATING DRUG-IMPAIRED DRIVING

Authors: Gary Kay, PhD;[1] Thomas Hochadel, PharmD;[1] Brandy Isaacks[1]

Affiliations: [1]Cognitive Research Corporation, St. Petersburg, FL

Background/Objective: The United States Food and Drug Administration (FDA) issued final guidance, entitled, "Evaluating Drug Effects on the Ability to Operate a Motor Vehicle," in November 2017. The purpose of this presentation is to report on how this guidance has been applied to drugs subsequently approved by the FDA (January 2018–July 2024).

Design: The FDA website (www.fda.gov) served as the source of information. A listing was generated of all novel drug approvals from January 2018 to July 2024. For each drug, the listing included sponsor, drug name, active ingredient, approval date, approved use, adult use, and driving studies conducted. In addition, information was recorded regarding central nervous system (CNS)-relevant adverse events (AEs). Authors, utilizing FDA criteria, judged whether each of the drugs warranted a dedicated driving study.

Results: Of the 377 FDA-approved drugs from January 2018 to July 2024, four drugs underwent a dedicated driving study. Based upon conservative application of FDA criteria, 35 drugs were identified that met criteria for a dedicated driving study, and 40 others were identified as

having CNS AEs of concern for potential effects on driving.

Conclusion: Dedicated driving studies are not routinely being performed for drugs that might affect driving ability. We found multiple instances of drugs being approved without a driving study in spite of the drug being clearly impairing when used chronically on an outpatient basis by adults.

Funding/financial disclosures: GK and TH are employees and shareholders of Cognitive Research Corporation. BI is an employee of Cognitive Research Corporation.

DEMONSTRATING THE VALUE OF A COLLABORATIVE ELIGIBILITY REVIEW FOR THE ENROLLMENT OF APPROPRIATE TRIAL PARTICIPANTS WITH MAJOR DEPRESSIVE DISORDER

Authors: Melissa A. Carbo, MS; Kenneth Williams, MD; Madelyn Moberg, BA; Rolana Avrumson, MS

Background/Objective: A collaborative approach toward review of patient eligibility can serve to mitigate negative impacts on data quality. Enrollment of ineligible participants can adversely influence study outcomes, including an increase in incomplete data due to confounding variables, which can contribute to a high rate of early discontinuation, thus impacting the overall cost to run the trial, investment of resources, and time (Fogel 2018).

Design: This analysis examines the benefits of implementing an independent central collaborative review of major depressive disorder (MDD) participant eligibility in a United States-based, Phase II, proof-of-concept trial. Completion of the eligibility review was required for each participant (n=364) across 46 sites prior to randomization and was based on medical history, concomitant medication, laboratory results, and diagnostic psychiatric evaluation through identified screening assessments.

Results: The central collaborative review identified 79 participants as ineligible, resulting in a screen failure rate of 22 percent based on the sample reviewed. Further analysis revealed the largest reason for screen failure was due to the presence of exclusionary medical or psychiatric conditions prior to randomization, not determined by the site(s) and classified accordingly. Clinically significant abnormalities in laboratory values, exclusionary electrocardiogram (ECG) abnormalities, and a positive urine drug screen followed, contributing to a sizable percentage of the overall screen fail count.

Conclusion: Incorporating collaboration among functional groups through a central review can further support MDD clinical trials, contributing to greater success in signal detection. The eligibility review in this study successfully prevented a significant percentage of the screened population from being inappropriately randomized into the trial.

Funding/financial disclosures: Not provided.

DEVELOPMENT OF THE SUBJECT-RATED COMPREHENSIVE DRUG WITHDRAWAL SCALE (CDWS) TO EVALUATE THE PHYSICAL DEPENDENCE POTENTIAL OF INVESTIGATIONAL DRUGS

Authors: Beatrice Setnik, Denise Milovan

Background/Objective: Novel drugs with abuse potential are assessed for physical dependency as part of the approval process under the Controlled Substances Act. Several drug class-specific withdrawal scales are available; however, these are mostly clinician-rated, challenging to administer frequently in late-stage clinical trials, and contain questions specific to drug use disorders. The objective was to develop a comprehensive subject-rated scale that can be frequently administered in a clinical investigational drug trial to identify potential signs of physical dependence and withdrawal.

Design: The published literature and scales of drug withdrawal were reviewed for various classes of drugs. A collective list of symptoms was identified, and each term was evaluated for comprehension and ease of administration using Simple Measure of Gobbledygook (SMOG) and Flesch Kincaid Readability scoring. Questions were modified for comprehension and past tense suitable to evaluate symptoms (current/24 hours).

Results: Following a thorough literature review, 62 drug withdrawal symptoms associated with scheduled and unscheduled drug classes were identified. A standard Likert 0-to-3-point rating scale was selected, ranging from no symptoms to severe. The SMOG Readability measure confirmed comprehension at a sixth grade reading level or lower (easy to read). The Flesch Kincaid Readability scoring identified some terms (e.g., diarrhea, constipation) at greater than an eight grade level. Validation of the scale for content, comprehension, and appropriateness of recall period is ongoing.

Conclusion: A reliable, self-reported scale is needed to effectively identify potential signs and symptoms of drug discontinuation in clinical trials evaluating novel drugs. The Comprehensive Drug Withdrawal Scale (CDWS) is a promising tool to address these issues.

Funding/financial disclosures: BS and DM are employees of Altasciences.

DIGITAL OUTREACH CONTRIBUTES TO EQUITABLE ACCESS: RETHINKING THE STEREOTYPES ABOUT "WHO'S ONLINE?"

Authors: Dan Brenner,[1] Steve Wimmer,[1] Katie Rodammer[1]

Affiliations: [1]1nHealth, Orlando, FL, US

Background/Objective: To demonstrate through demographic data and multiple case studies that direct-to-patient digital outreach enhances diversity in clinical research.

Design: Despite widespread internet access, we still have a stark discrepancy between those with in-home broadband and those without it. The differences emerge along demographic lines that mirror those in clinical research participation. This has led to the perception that recruiting patients through digital channels would serve to exacerbate the issue of limited diversity in clinical trials, and on the surface, this seems true. A deeper analysis reveals the contrary when digital channels are deployed with the specific intent of reaching those historically underrepresented in research. Another dataset, focusing on access to mobile data stands in stark contrast to in-home broadband; digital channels could be seen as one of the most equitable pathways available to reach patients of diverse backgrounds. In 1nHealth's data analysis, over 99 percent of patients who participated in research after interacting with a recruitment advertisement came from mobile devices, not desktops.

Results: Three case studies showcase the impact of digital recruitment on diversity:

1. Achieved diversity targets
2. Met target race/ethnicity cohorts
3. National Institutes of Health (NIH) All of Us: Enrolled underrepresented patients

Conclusion: United States Food and Drug Administration (FDA) guidance has spurred global collaboration among study teams. Sponsors are actively engaging advocacy

groups and community events and rethinking site selection. 1nHealth proves all communities are online, receptive to research, and willing to participate. While a multitiered approach remains essential, our data confirms the potency of digital platforms as the clear solution.

Funding/financial disclosures: Not provided.

EFFECTS OF INCORPORATING A HIGH-PERFORMING ALZHEIMER'S DISEASE BLOOD BIOMARKER TEST BEFORE OR AFTER TRADITIONAL PET SCAN SCREENING IN CLINICAL TRIALS

Authors: Venky Venkatesh, PhD, PMP;[1] John Bui, PharmD;[1] Cassandra Cox, BS;[1] Justine Coppinger, MS;[1] Tim West, PhD;[1]

Affiliations: [1]C2N Diagnostics LLC, St. Louis, MO, US

Background/Objective: The objective of this study was to examine the impact of incorporating the high-performing, clinically validated PrecivityAD2™ blood test for Alzheimer's disease (AD) pathology into clinical trial designs.

Design: Trial enrollment was divided into three steps: 1) initial phone call, 2) screening visit, and 3) amyloid positron emission tomography (PET) scan. Time and cost to reach 100 PET-positive patients at the end of the screening funnel was modeled using base assumptions for costs and time for four different trial scenarios: A) no blood test, B) blood test after screening visit, C) blood test before screening visit, and D) blood test before screening visit and no confirmatory PET scan. The PrecivityAD2™ blood test details, including 88-percent sensitivity, 89-percent specificity, and list price, were included in the model.

Results: Model A required phone calls to 222 participants at a cost of $1.7 million (M) for a duration of 623 days. Model B increased the number of phone calls to 253 participants but reduced cost ($1.4M) and time to enrollment (393 days). Model C had similar enrollment time compared to B (403 days) but offered further cost reduction ($1.2M). Model D, which eliminated the cost and time for PET scan, reduced the cost to $0.52M and the time to enrollment to 259 days.

Conclusion: Inclusion of the high-performing and scalable PrecivityAD2™ blood test showed significant reductions in cost and time to enrollment, demonstrating increased enrollment efficiency in clinical trials.

Funding/financial disclosures: VV, JB, CC, JC, and TW are employees of C2N Diagnostics, LLC, and receive compensation from the company in the form of salary or equity.

ENHANCING ACCESS AND DIVERSITY WITH PURPOSE-BUILT STUDY SITES

Authors: Ricky de Lemos[1]

Affiliations: [1]Alliance Clinical Network

Background/Objective: Increasing clinical trial diversity is critical for enhancing representation and ensuring the generalizability of study results. However, effective diversification strategies remain elusive, and meaningful strides must still be made. Alliance Clinical Network's decade-long initiative sought to evaluate whether establishing *de novo* study sites in communities with underrepresented populations would impact clinical trial diversity.

Design: Seven clinical research sites were established in California, Nevada, and Texas. Site locations were specifically selected to maximize racial, ethnic, and age diversity and were designed to increase clinical trial awareness and access among underrepresented groups. All sites were staffed to reflect the diversity of the patient population. These sites were utilized for recruiting, enrolling, and conducting clinical trials across an expanding range of therapeutic areas, including metabolics, dermatology, immunology, and central nervous system (CNS) conditions.

Results: The database across the seven clinical research sites includes more than 250,000 consented and prescreened participants, more than 85 percent of whom are from underrepresented populations. In large vaccine studies conducted at these sites, the racial demographic breakdown among enrolled participants was 50 percent African American, 30 percent Hispanic/Latino, 15 percent Caucasian, and five percent other races.

Conclusion: Clinical trial participation remains relatively low among racial and ethnic minority groups, yet these groups carry a disproportionately high burden of the chronic diseases that garner the most drug development interest. In the wake of the United States Food and Drug Administration's recent draft guidance on diversity action plans, intentionally establishing sites in strategic locations with underrepresented populations may help improve the strength and generalizability of clinical trial evidence.

Funding/financial disclosures: RdL is the Chief Operating Officer at Alliance Clinical Network.

ENHANCING PATIENT RECRUITMENT STRATEGIES FOR CNS CLINICAL TRIALS: INNOVATIVE SOLUTIONS TO OVERCOME BARRIERS

Authors: Thibaud Belleface, BA, BS; Jeffrey T. Apter, MD

Background/Objective: This poster presentation aimed to address the significant challenges encountered in patient recruitment for central nervous system (CNS) clinical trials. We identified effective strategies and proposed innovative solutions to overcome these barriers.

Design: Our study involved a comprehensive analysis of obstacles to patient recruitment, including issues such as no-shows, low awareness of clinical trials, and declining interest due to delayed response times.

Results: Through our analysis, we identified a personalized implementation of an online CRM platform as a key solution. This platform includes immediate online phone screening and self-scheduling capabilities to address delayed responses and cater to immediate participant interest. Automated communication through text messages, calls, and emails allowed for reminders and effectively reduced no-show rates. Additionally, we found that email campaigns providing educational initiatives significantly enhanced participant understanding and comfort with the clinical trial process. An artificial intelligence (AI)-powered chatbot was implemented to sustain participant interest and engagement, particularly addressing issues of dwindling interest over time and the possibility to accurately achieve every one of the above tasks autonomously.

Conclusion: These innovative solutions demonstrated promising outcomes in overcoming the challenges of patient recruitment for CNS clinical trials. By leveraging technology and enhancing participant engagement through personalized approaches, we aim to substantially improve recruitment rates. Our findings suggest that integrating these advanced technological solutions not only streamlines the recruitment process but also enhances participant retention and overall trial efficiency. Moving forward, continued innovation in patient engagement strategies is crucial for achieving successful outcomes in CNS clinical

trials, ultimately benefiting patients, sites, sponsors, and contract research organizations.

Funding/financial disclosures: Not provided.

FUNCTIONAL UNBLINDING EVALUATION OF CENTRAL RATERS IN A LARGE PSYCHEDELIC CLINICAL TRIAL

Authors: Sarah M. Karas, PsyD;[1] Adam Kolar, PhD;[1] Todd M. Solomon, PhD;[1] Daniel R. Karlin, MD, MA[1]

Affiliations: [1]Mind Medicine, Inc., New York, NY

Background/Objective: To examine if central raters (CRs) in psychedelic clinical research trials experience functional unblinding to treatment allocation while assessing key endpoints due to spontaneous participant responses.

Design: Data were collected during a Phase IIb (NCT05407064) multicenter, randomized, double-blind, placebo-controlled, dose-finding study of MM120 (lysergide D-tartrate) in adults (aged 18–74 years) diagnosed with generalized anxiety disorder (GAD). For each study visit, CRs were assigned to rate the Hamilton Anxiety Rating Scale (HAM-A) and Montgomery–Åsberg Depression Rating Scale (MADRS) for participants based on availability. CRs were blinded to all study information, including the study visit, subject information (rated via telephone), and treatment type. Following conclusion of rating both assessments, CRs completed "rater blinding questionnaires" (5-point Likert scale: 1. I am certain the subject received the active drug; 2. I believe that the subject received the active drug; 3. I am unable to discern whether the subject received the active drug or placebo; 4. I believe the subject received placebo; 5. I am certain the subject received placebo).

Results: The study collected over 1,500 unique assessments of subjective CR blinding from 198 participants from screening out to 12 weeks postadministration. Data supported CRs remaining blinded, with over 80 percent indicating they were largely unable to discern drug versus placebo.

Conclusion: This is the first large psychedelic randomized, controlled trial to collect data on CR unblinding. Results support the use of CRs as a viable method to reduce functional unblinding, as the majority of the CRs were unable to discern drug versus placebo.

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HEARING OUR GLOBAL PSYCHOMETRIC RATERS' STRESSORS: IMPACT TO DATA QUALITY AND RECOMMENDATIONS OF CHANGE FOR THE INDUSTRY

Authors: Cassie L. Blanchard,[1] Elan A. Cohen,[1] Judith Montero,[2] Vera M. Grindell,[3] Katarzyna Wyka,[4] Howard A. Hassman,[1] David P. Walling,[3] Mark G. Opler,[5] David Mischoulon,[6] Larry Ereshefsky[2,7]

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Background/Objective: At CNS Summit 2023, we presented descriptive data on how work distress/burnout impacted the work performance of 529 global psychometric raters. We now focus on raters from countries other than the United States (US) and continue to delve into correlational and differential analyses for this group. Our findings, not located in a thorough review of the literature, are important, as they describe which raters in countries other than the US might be prone to negative work functioning.

Design: Three rater training and surveillance companies in our industry emailed a 39-item Site Rater Stressors Survey (SRSS) link to the raters whom they have trained in previous clinical trials to obtain raters' demographics and perceptions of job stress, burnout, and work impact.

Results: Of the 209 global raters who completed the SRSS, a one-way ANOVA indicated significantly more distress among raters with master's degrees versus those with doctoral degrees ($p<0.05$), while raters with doctoral degrees had significantly lower stress than those with medical doctoral degrees ($p<0.05$). Additionally, a Pearson correlation coefficient indicated a positive correlation between a rater's self-reported work stress and how frequently these same raters reported being "negatively impacted" by feeling busy ($r=0.47$, $p=0.001$). Relatedly, there was a positive correlation between the amount of job stress raters reported with how often raters experienced burnout on the job ($r=0.63$, $p=0.001$).

Conclusion: Recommendations will be provided in the poster, such as increasing support and training to raters with less practical training.

Funding/financial disclosures: All authors have no conflicts of interest or bias in the conclusions of the current investigation or promotion of the current study results.

IN SILICO FRAMEWORK FOR DOSE SELECTION AND DESIGN OF A PHASE II STUDY IN PATIENTS WITH ALS TREATED WITH NX210c

Authors: Giuseppe Pasculli,[1] Annette Janus,[2] Fianne Sips,[3] Pauline Bambury,[1] Sebastien Marie,[2] Juliette LeDouce,[2] Mario Torchia,[1] Emilien Bernard,[4] Yann Godfrin,[2,5] Daniel Röshammar[1]

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Background/Objective: NX210c, developed by Axoltis Pharma, is a promising drug candidate for treating neurodegenerative diseases, especially when the blood–brain barrier is impaired. This study aims to support the design of an upcoming Phase II clinical trial in patients with amyotrophic lateral sclerosis (ALS) by analyzing NX210c pharmacokinetics (PK) and pharmacodynamics (PD) from a 29-patient Phase Ib, placebo-controlled, multiple ascending dose (MAD) study in healthy elderly volunteers.

Design: A nonlinear mixed effects modeling framework was used to analyze NX210c PK and PD data. The Wagner Target-Mediated Drug Disposition (TMDD) model, which describes drug binding to its biological target, combined with an indirect response model best captured NX210c time-concentration profiles and its impact on neurofilament light chain (NfL) levels, a relevant biomarker in ALS.

Results: PK/PD modeling results, particularly the exposure-response relationship between NX210c PK and biomarker PD, supported the selection of doses of 5mg/kg and 10mg/kg for the Phase II ALS trial (SEALS, NCT06365216). The planned study, including 30 patients for each dose and 20 patients in the placebo group,

will be enhanced by virtual subjects with ALS created using machine learning models. External datasets of patients with ALS will be used to generate disease progression responses based on actual patients' baseline characteristics, enhancing statistical analyses with synthetic placebo outcomes.

Conclusion: The *in silico* approach provides a robust foundation for the Phase II ALS trial design, offering potential to derisk NX210c development, increase the likelihood of success in subsequent phases, and enhance statistical power to minimize patient burden.

Funding/financial disclosures: GP, FS, PB, MT, and DR are employees of InSilicoTrials Technologies. AJ is an advisor for Axoltis Pharma. SM and JL are employees of Axoltis Pharma. YG is an employee and shareholder of Axoltis Pharma. EB has no conflict of interest to disclose; he will be the coordinating investigator of the Phase II SEALS study

IN THE WAKE OF THE PRESIDENTIAL ELECTION, ADVOCATING FOR NEW BIPARTISAN RESEARCH-PATIENT-CENTRIC LEGISLATION MAY BOLSTER YOUR BELIEF IN THE POLITICAL PROCESS!

Authors: Charles S. Wilcox, PhD, MPA, MBA[1,2,3]

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Background/Objective: To identify additional opportunities for the clinical research community to make substantive improvements in, and contributions toward, patient-centricity that simultaneously enhance diversity, equity and inclusion in all phases of clinical trials. Additionally, we need to keep our focus on actionable, not just aspirational, goals.

Design: We conducted an informal survey of central nervous system (CNS) sites along with a literature search to identify actionable opportunities to strengthen and/or streamline the clinical research process. Increasing the rate of patient enrollment, in tandem with enhancing the overall diversity of study participants, remains at the top of most decision-makers goals, objectives, and priorities.

Results: In harmony with prior advocacy for plain language summaries (PLS) as a comparatively low-cost, patient-centric initiative, the newest and arguably most patient-centric goal yet is the late-2023 and early-2024 call for legislative action to make clinical trial participant compensation exempt from federal and state income tax. While managing tax-related responsibilities pertaining to patient stipends can be burdensome for sponsors, sites, and clinical research organizations (CROs), the stakeholder facing the greatest impact is clearly the study participant. A recent survey reflected that 75 percent of sites and 63 percent of sponsors and CROs advocated that tax on clinical trial stipends of $600.00 (or more) should either be eliminated or increased to more than $1,000.00.

Conclusion: We will highlight and advocate for the recently introduced bipartisan legislation to make trial participant income tax exempt and provide a link for conference attendees to register their support of this critically important legislation.

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LEARNINGS FROM COGNITIVE DEBRIEFING AND USABILITY TESTING STUDIES ON NEUROSCIENCE ASSESSMENTS: A QUALITATIVE SYNTHESIS

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Background/Objective: Incorporating the patient voice into neuroscience clinical programs is essential and often achieved via use of patient-reported (PRO) or observer-reported (ObsRO) outcomes measuring events or psychological symptoms (e.g, seizures, pain, depression). Cognitive debriefing (CD) measuring respondent understanding is often recommended for ensuring high-quality measures, but access to CD findings is limited. We performed a qualitative synthesis of CD and usability testing (UT) studies to determine common issues identified by patients and caregivers to inform good electronic clinical outcome assessment (eCOA) design.

Design: A retrospective analysis was performed of 20 neuroscience CD/UT studies conducted from 2013 to 2022 using Clario devices. Findings were pooled to make recommendations on eCOA design best practices.

Results: A total of 20 studies (53 assessments) were included in the analysis. Data were collected from 386 participants, of whom 24 percent were children/adolescents and 23 percent were caregivers. Indications included, but were not limited to, migraine, headache, impulsive aggression, multiple sclerosis, Parkinson's disease, and depression. Interpretation issues included interpretation of response options/scale (e.g., markedly, faces pain scale), recall period (e.g., 24-hour clock, since yesterday), and symptoms (e.g., aura, predominant status). Recommendations for improving understanding included adding definitions or rewording, with 50 percent of studies recommending participant training. Some led to recommendations for caregiver reports in addition to or instead of child self-reports.

Conclusion: Identifying common issues with respondent understanding helps in recognizing areas of focus for developing appropriate neuroscience assessments for the population under study. Findings highlight the need for participant training on completing PROs/ObsROs to help clarify clinical terms.

Funding/financial disclosures: All authors are employees of Clario.

LEVERAGING A LEARNING HEALTH SYSTEM TO IMPLEMENT THE DSM-5-TR LEVEL 1 CROSS-CUTTING MEASURE IN REAL-WORLD MENTAL HEALTH PRACTICES

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Background/Objective: To assess if a learning health system (LHS) can promote adoption of the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (DSM-5-TR) Level 1 Cross-Cutting (DSM-XC) measure in independent mental health practices over three months, examine its value, and support data-driven care aligned with precision psychiatry.

Design: The APA and Osmind, a LHS with an electronic health record optimized for real-world evidence generation, deployed the DSM-XC using knowledge-to-action principles. The primary endpoint was overall DSM-XC use. Secondary endpoints included clinician satisfaction and use cases.

Results: Eighty-eight practices adopted the measure within three months, with 74 percent using it multiple times. Use increased from 143 (Month 1) to 1,028 (Month 3). Average uses per practice were 11.5 (standard deviation: 19.98). Clinicians rated usefulness at 6.6 out of 10 (95% confidence interval: [4.81, 8.31]); 63 percent used it for initial visits, 31 percent for follow-ups, and six percent did not use it regularly. Values included comprehensive screening and improved treatment planning. Drawbacks included lack of detailed score interpretation and initial feature constraints.

Conclusion: Phased LHS implementation promoted adoption of the DSM-XC, supporting precision psychiatry advancements. Widespread adoption of measurement-informed care depends on clinician awareness, perceived value, and ease of use. This study addressed these factors using a knowledge-to-action strategy within a LHS, suggesting a stepped approach might accelerate utilization of novel measures. Future potential includes validating composite endpoints for clinical trials that focus increasingly on symptoms rather than syndromes.

Funding/financial disclosures: CM, LAM, MW, and JQ are all employees of Osmind. DG and NG are employees of the American Psychiatric Association.

LEVERAGING MOBILE TECHNOLOGY TO ENHANCE SITE EFFICIENCY

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Affiliations: [1]Director of Product, StudyKIK, a Syneos Health Company; [2]Product Marketing Manager, StudyKIK, a Syneos Health Company; [3]Project Manager, StudyKIK, a Syneos Health Company

Background/Objective: This case study demonstrated the impact of mobile applications to reduce the burden on clinical research sites. It demonstrated the value of incorporating technology in early study design and strategy, which can greatly enhance support for research sites.

Design: In a Phase IV trial designed to monitor serious major adverse cardiovascular events (MACEs), the sponsor contracted StudyKIK to develop a custom patient engagement application (app) to be included in the study protocol. The app was designed to identify potential MACE and serious AE (SAE) occurrences over a one-year treatment period. It served multiple functions: logging SAEs, such as emergency room visits and hospitalizations; monitoring medication usage; providing real-time medication updates; and acting as an eDiary.

The study was extensive, involving 95 sites and approximately 8,600 patients. To manage this vast scale and the critical need for daily monitoring of SAEs, StudyKIK developed tailored reporting tools. These tools allowed for effortless identification of events across the extensive participant pool. Key features included downloadable reports that provided a detailed history of each subject from onboarding to the present, automated daily reports sent directly to the primary site user, and a daily digest report for the contract research organization (CRO) to help with study oversight.

Results: There was a dramatic reduction in site workload through automation compared to manual methods. It enhanced participant engagement with 84.7 percent WAU. Positive feedback indicated that site staff valued the app's reduction in manual tasks. The use of mobile technology replaced the need for daily manual data reviews with automated reporting, reducing site burden and improving efficiency.

Conclusion: While patient apps are commonly viewed as tools for enhancing participant engagement, this study demonstrated they can also enhance research site efficiency and reduce burden, demonstrating their broader value beyond participant engagement.

Funding/financial disclosures: Not provided.

METHODOLOGICAL OVERVIEW OF COA DEVELOPMENT: LITERATURE REVIEW OF BEST PRACTICES

Authors: J. Lynsey Psimas, PhD;[1] Katrina Bengtson[1]

Affiliations: [1]Pearson Clinical Assessments

Background/Objective: This poster provides a comprehensive, methodological review of best practices in the development and standardization of clinical outcome assessments (COAs). Using the Vineland-3 as an exemplar, we analyzed normative data to illustrate how sample size and validation on diverse populations ensure validity, reliability, sensitivity, clinical utility, and generalizability of COAs. Employing a sample representative of the target population is critical to accurately measuring longitudinal changes. Data will demonstrate potential consequences of utilizing poorly developed COAs. A graphic will also depict methodological best practices in COA development and its alignment with Vineland-3 development.

Design: Using proprietary, nonpublished Vineland-3 data, we analyzed the validation process, focusing on demographic distribution and its congruence with the United States population and specific subpopulations. We will demonstrate how sample size during validation impacts statistical parameters, such as means and standard deviations (SDs), affecting overall reliability and validity.

Results: Findings indicate that larger representative samples (Vineland-3, n=2,560) enhanced the precision of mean estimates and SD compared to smaller samples (10% of Vineland-3 sample, n=256), resulting in increased clinical sensitivity. Graphs demonstrate how frequency distributions vary with sample size. Sensitivity and the ability to track change over time are illustrated through Growth Scale Values (GSV) scores.

Conclusion: Validated and reliable COAs are pivotal to the success of clinical trials, as they significantly mitigate the high failure rate in central nervous system trials, which often depend on COAs to measure primary endpoints. This poster underscores the importance of rigorously validated COAs on diverse populations to ensure reliable and generalizable clinical trial outcomes.

Funding/financial disclosures: Authors are employees of Pearson Clinical Assessments.

MOTOR DISABILITIES LINKED TO INCREASED ABNORMAL EYE MOVEMENTS IN MULTIPLE SCLEROSIS: FINDINGS FROM AN EYE-TRACKING STUDY

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Affiliations: [1]Multiple Sclerosis University Center (CUEM), Ramos Mejía Hospital, Buenos Aires, Argentina; [2]View Mind, Inc., New York, NY, US

Background/Objective: Abnormal eye movements can indicate brain dysfunction and highlight the presence of motor impairments in patients with multiple sclerosis (PwMS). This study aimed to investigate eye movement

metrics as proxy indicators of standard clinical assessments of motor impairments in PwMS.

Design: Conducted as a cross-sectional study at Ramos Mejía Hospital, a specialized center for demyelinating diseases in Buenos Aires, Argentina. This research included 65 patients with relapsing-remitting MS (RRMS) and five with secondary progressive MS (SPMS). An eye-tracking virtual device was used to record eye movements during the n-back test. Motor function was evaluated using the Expanded Disability Status Scale (EDSS), Nine-Hole Peg Test (NHPT), and Timed 25-Foot Walk (T25FW).

Results: Significant correlations were observed between eye movement metrics, such as gaze duration, fixation count, and saccade amplitude, and motor impairments measured by the EDSS, NHPT, and T25FW. All correlations had significant *p*-values.

Conclusion: The study demonstrated significant associations between eye movement patterns and motor disabilities in PwMS. These findings support the potential of eye movement metrics as surrogate biomarkers for monitoring MS progression.

Funding/financial disclosures: GF, ME, and DV are employed by View Mind, Inc.

NEURONAL PLASTICITY MARKERS IN iPSC-DERIVED NEURONS AS A PLATFORM FOR DRUG RESPONSE MODELS IN ALZHEIMER'S DISEASE

Authors: Daphna Laifenfeld, PhD;[1] David Pattison;[1] Orit Goldman, PhD;[1] Shiran Zimri, PhD;[2] Nitai Kerem[2]

Affiliations: [1]NeuroKaire; [2]NeuroSense Therapeutics

Background/Objective: To demonstrate the novel potential of patient-derived neurons from well-characterized Alzheimer's disease (AD) patients to support advanced drug development strategies, we are utilizing induced pluripotent stem cell (iPSC)-derived neurons to profile the drug response induced *in vitro* by the ciprofloxacin and celecoxib combination (i.e., PrimeC).

Design: Peripheral blood mononuclear cells (PBMCs) are extracted from patients' blood, reprogrammed into iPSCs and differentiated into cortical neurons as part of the ongoing Phase IIa RoAD clinical trial. Patient-derived neurons are exposed to the PrimeC combination including each of its components and are evaluated for changes in neuronal and synaptic plasticity features utilizing a consolidation of both trained and clinical data.

Results: Analysis utilizing the first patient sample demonstrated successful differentiation of neurons, with robust quantities and the presence of cortical neuron-specific markers. This effect supports the viability of this technology for AD drug development. Preliminary findings suggest this approach can help provide mechanistic insights and identify patient phenotypes, potentially aiding in patient stratification and biomarker development. Treating cells with PrimeC is planned to evaluate its effects on neuronal plasticity.

Conclusion: This study demonstrates the utility of iPSC-derived neurons for modeling drug responses in AD and highlights PrimeC's therapeutic effects for AD based on the synergistic impact of the combination. The successful creation of cortical neurons from patient-derived iPSCs highlights the potential of this approach for exploring novel therapeutic mechanisms. Anticipated outcomes include identifying drug response markers and developing patient-specific therapeutic strategies. Further research will focus on evaluating neuronal plasticity changes and developing predictive models for treatment response, advancing precision medicine in neurodegenerative diseases.

Funding/financial disclosures: All authors are employees of either NeuroKaire or Neurosense Therapeutics.

ONLINE ADVERTISING RESULTED IN MORE EDUCATED PARTICIPANTS AND NONINFERIOR SCREEN FAIL RATES WHEN COMPARED TO OFFLINE METHODS IN AN ALZHEIMER'S DISEASE CLINICAL TRIAL

Authors: Yu-Jay Huoh, PhD;[1] Ralph Lee;[1] Colin Sholes;[1] Brenda Martinez;[1] Sydney Hopkins;[1] Jennifer Mitolo, PsyD;[1] Tara Parnitvithikul, PhD;[1] Edward Zamrini, MD;[1] Elly Lee, MD[1]

Affiliations: [1]Irvine Clinical Research, Irvine, CA

Background/Objective: Alzheimer's disease (AD) drug trials are slow and difficult to recruit for, so sites have turned to online advertising to find participants outside of traditional offline methods. In this study, we investigated if the recruitment method, online versus offline, affected the education levels or the screening failure rate of study participants in industry-sponsored AD drug trials.

Design: In 2023, 208 participants screened at a commercial site for a clinical trial of an investigational, early, symptomatic AD treatment. The mean duration of education was 15.28 years (standard deviation [SD]: 2.99 years). A total of 75.5 percent of participants (n=157) were recruited through online advertising and 24.5 percent (n=51) through offline means. Forty-eight of the participants screened successfully and enrolled into the study.

Results: The average duration of education for someone recruited through online advertising was 15.57 years; through offline channels, it was 14.35 years. This difference of 1.22 years was statistically significant (p=0.015). The screening failure rate of persons recruited through online advertising was 76.4 percent (120 of 157); through offline methods, it was 78.4 percent (40 of 51). This two-percent difference was not statistically significant (t=–0.29, p=0.77).

Conclusion: Recruitment channel having no impact on a participant's ability to pass screening and enroll in an AD study is unsurprising, since screen failures are typically due to clinical reasons, which should be uncorrelated with recruitment channel. The significant effect for duration of education could be a byproduct of the wider reach of online advertising. There is no obvious explanation for the observed directionality, and additional investigation would be required to identify one.

Funding/financial disclosures: All presenters are employees of Irvine Clinical Research, an independent central nervous system research site that conducts industry-sponsored pharmaceutical trials

OPTIMIZED CALL CENTER ACCELERATES STUDY ENROLLMENT

Authors: Dan Brenner,[1] Steve Wimmer,[1] Katie Rodammer[1]

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Background/Objective: The objective of this poster was to demonstrate the effectiveness of leveraging trained, nonmedical patient coordinators to increase enrollment rates.

Design: The burden of calling a high volume of potential patients referred from online sources creates extra work for an already overstretched staff, and patients who respond to these campaigns often disqualify to participate.

Results: 1nHealth examined the efficacy of using centralized resources to provide the first touchpoint for patients responding to centralized

campaigns and documented positive outcomes for the study and the patient. 1nHealth compared the enrollment results of medical (e.g., nurses, crisis counselors) versus nonaccredited, but highly trained, patient coordinator representatives. The results of this comparison showed increases in patients referred, with 220 percent more patients enrolled when using a nonmedical professional for this resource.

Conclusion: *Better outcomes:* Patient coordinators who did not have advanced degrees excelled in ensuring patients were experiencing less time waiting for a response due to lower average call durations; patients were more likely to get the information they need and less likely to disqualify.

Sites love quality and quantity: Engaged patients were validated to be seen on-site; medically accredited staff tended to have longer conversations and lower flow through, which meant fewer patients referred to sites proportionally and fewer patients in total.

Sponsors win when patients and sites win: By drastically reducing site burden, improving patient education, and reducing screen fail rates (by 40% in some studies), the sponsor's trial reached LPI faster, cheaper, and with better site dynamics.

Funding/financial disclosures: Not applicable.

OPTIMIZED EEG/ERP TEST BATTERY AND ANALYTICAL PIPELINE FOR USE IN EARLY-PHASE CNS INTERVENTIONAL TRIALS

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Affiliations: [1]Cognision, US; [2]Follow the Molecule LLC, US; [3]CenExel Research, US

Background/Objective: The ERP Biomarker Qualification Consortium has developed standardized methods and operating procedures for an electroencephalogram (EEG)/event-related potential (ERP) test battery and a fully automated data analysis pipeline for use in early-phase central nervous system (CNS) interventional trials.

Design: Testing and analysis methods were validated in a Consortium-sponsored trial with healthy participants versus patients with schizophrenia and in a ketamine-challenge trial. These trials optimized standardized EEG/ERP protocols that can be practically performed during a one-hour testing session and validated a fully automated data analysis pipeline that cleans, analyzes, and extracts predefined EEG/ERP features from a complete study cohort.

Results: In both Consortium studies, results closely matched published findings from top academic labs. Standardized ERP/EEG equipment and methods ensured few test failures, and test-retest reliability was fair-to-excellent for most outcome measures. The fully automated data analysis pipeline provided near real-time visibility of results. Recent pharmaceutical-sponsored trials that leveraged these methods showed significant effects on EEG/ERP measures for an investigational nicotinic agonist and a Na+ channel blocker in small cohorts of participants, providing valuable information on target engagement and dose selection for later-phase trials.

Conclusion: With standardized equipment and protocols, a comprehensive battery of EEG/ERP tests can be practically performed in early-phase trials, and results can be analyzed in near real-time to produce quality data with high test-retest reliability and few test failures. This test battery can be used to probe various brain networks and neurotransmitter pathways and is sensitive to pharmacological manipulation by drugs with diverse targets and mechanisms of action.

Funding/financial disclosures: Not provided.

PRAGMATIC CONSIDERATIONS OF PHYSICAL WITHDRAWAL ASSESSMENTS IN PATIENT STUDIES

Authors: Denise Milovan,[1] Thomas Sciascia,[2] Megan Shram,[3] Cynthia Arons,[4] Thomas J. Hudzik,[5] Michael Klein,[6] Joseph Grieco,[7] Beatrice Setnik[1]

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Background/Objective: The evaluation of physical dependence (PD) is an important aspect of the clinical safety profile of investigational products, including the potential need for tapering upon discontinuation and its abuse potential under the Controlled Substances Act. Therefore, a sound methodological framework for evaluating drug withdrawal is needed.

Design: For most novel drugs in development, PD will be evaluated by documenting disease-specific rebound symptoms, vital signs, and adverse events (AEs); by administering drug class-specific withdrawal scales, physiological measures, and daily participant diaries; and by assessing the association of PK with withdrawal signs/symptoms. As PD evaluations are generally conducted during outpatient Phase II/III clinical trials, pragmatic challenges include the feasibility of completing frequent, in-clinic, clinician-driven assessments; suitability of traditional measures, such as the Clinical Opiate Withdrawal Scale, developed for drug-abusing populations, for patients; and insufficient sampling timepoints resulting in partial characterization of withdrawal.

Results: Leveraging nonclinical data and recognizing potential withdrawal effects early in drug development enhances Phase II/III evaluations. Use of self-administered scales and questionnaires via electronic devices, along with home blood sampling kits for drug concentration analysis, can reduce in-clinic burdens. Developing validated, self-administered withdrawal scales for various drug classes and diseases can address the specificity limitations of scales targeting drug-abusing populations, especially for drugs with novel mechanisms. A holistic assessment of behavioral, physiological, and PK data is crucial for identifying serious AEs related to withdrawal.

Conclusion: A comprehensive approach to the assessment of PD will be presented.

Funding/financial disclosures: BS and DM are employed by Altasciences. TS is an employee of Trevi Therapeutics. CA is an employee of Pfizer. JG is an employee of Tris Pharma. MS (Altreos Research Partners), TJH (ALAC Group), and MK are independent consultants to pharmaceutical and biotechnology companies.

PRECISION PSYCHIATRY WITH CODEVELOPMENT OF GENETIC COMPANION DIAGNOSTICS: A NOVEL APPROACH FOR CLINICAL DEVELOPMENT

Authors: Daniel Gehrlach,[1] Bertram Müller-Myhsok,[1] Hans Eriksson[1]

Affiliations: [1]HMNC Holding GmbH

Background/Objective: HMNC aims to codevelop novel psychiatric medications with predictive companion diagnostics (CDx). Despite the significant role of the stress-axis in major depressive disorder (MDD), broad-spectrum use of stress-axis modulators has yielded inconsistent results. Thus, pairing them with predictive selection tools might be necessary to achieve their full potential.

Design: Our approach centers on deoxyribonucleic acid (DNA) analysis for its rapid, cost-effective, and globally accessible nature. Single nucleotide polymorphisms offer insights into genetic predispositions, while methylation analysis provides information on environmental impacts. Machine learning algorithms are employed to train multimodal predictive models efficiently, with the vision to incorporate real-world data postapproval for continuous improvement.

Results: A *post hoc* analysis of our prototype CRHR1-CDx demonstrated over 80 percent sensitivity and specificity in predicting treatment response, with a large effect size and high response rates. Furthermore, the V1b-CDx, which is based on the Dex/CRH test, is developed to predict the response to a vasopressin 1b receptor antagonist. These efforts may provide the first CDx to selectively treat patients with MDD with a dysregulated stress-axis. Therefore, it would rejuvenate interest in stress-axis modulation and serve as a prototype for reviving shelved but promising compounds that are not suited for one-size-fits-all application.

Conclusion: The integration of genetic CDx offers a precision psychiatry framework that personalizes treatment for MDD. This methodology has substantial potential in improving therapeutic efficacy and patient safety, signifying a major advancement in the field of psychiatric drug development.

Funding/financial disclosures: The authors declare no conflicts of interest related to this study.

PREDICTING PATIENT DROPOUT IN CLINICAL TRIALS: A FIRST STEP TOWARD PERSONALIZED ENGAGEMENT STRATEGIES

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Affiliations: [1]Cognivia

Background/Objective: Patient nonadherence and dropout significantly extend the duration and cost of clinical trials. A predictive tool identifying patients likely to drop out could enhance clinical trial management through targeted and personalized engagement strategies. We aimed to develop such a tool using predictive modeling on data from two studies on schizophrenia and dry eye.

Design: In these studies, early termination events were categorized as informed consent withdrawal, nonadherence, adverse events, and lost to follow-up, focusing on the first two due to their association with lack of engagement. The timing of these events was also important, as early dropouts indicate lower engagement levels. We modeled dropout due to informed consent withdrawal or nonadherence as a survival endpoint (time to dropout) using a multivariate Cox's model. Baseline predictors of patient engagement, such as study site perception, belief in medicine, and health literacy, were collected via the Compl-AI questionnaire.

Results: Separate models were constructed for each study and validated on out-of-sample patients from the other trial. The predictive performance was robust, with C-indices of 0.73 and 0.87 (both $p<0.001$) demonstrating a strong association between the predicted engagement score and dropout.

Conclusion: Informed consent withdrawal and nonadherence can be predicted at baseline, identifying patients at higher risk of dropping out. These patients are prime candidates for targeted engagement strategies to improve retention rates and optimize the efficiency of clinical trials.

Funding/financial disclosures: Not provided.

PRESCREEN USE OF A SUBJECT REGISTRY IN A LARGE SITE NETWORK: ANALYSIS OF THE FIRST 20,000 SUBJECTS PRESCREENED

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Background/Objective: To identify and examine the use of a subject registry on the identification of duplicate, professional, or otherwise inappropriate subjects at the prescreening visit for CenExel, the largest therapeutically focused site network.

Design: We looked at pooled study data for all subjects that prescreened at a site within the CenExel site network from January 2023 to July 2024. The number of matches (subjects who presented to a unique site) found within 30 or 90 days was collected. Matches between "sister sites" (i.e., those where prescreening might take place at more than one location) were not included in the analysis. The subject registry used was CTSdatabase, one of several commercially available subject databases.

Results: Of 19,307 CenExel network subjects prescreened using CTSdatabase from January 2023 to July 2024, 618 unique site matches (3.2%) were found for these subjects within 30 days of the prescreening visit and 1,569 unique site matches (8.1%) within 90 days of the prescreening visit.

Conclusion: Use of a subject registry during the prescreening process can eliminate duplicate and professional subjects from a large site network before they are ever screened for a study. These numbers have remained relatively stable over the 18 months of this analysis and highlight that many subjects (8.1% in this sample) present to other sites within a 90-day period. Such an effort requires a commitment on the part of the site network to integrate such a system at prescreen; however, this will likely reduce screen failures and improve the quality of screened subjects.

Note: Data was updated through September 2024, prior to CNS Summit.

Funding/financial disclosures: Not provided.

PROFILING OF DRUG RESPONSE MECHANISMS AND PATIENT SUBPOPULATIONS THROUGH READOUTS FROM A BIOBANK OF PATIENT-DERIVED NEURONS

Authors: Daphna Laifenfeld, PhD;[1*] Tal Birnberg, PhD;[2*] David Pattison;[1**] Claudia Albeldas;[1] Elena Kagan[2]

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Affiliations: [1]NeuroKaire; [2]Clexio BioSciences

Background/Objective: To profile the antidepressant response induced by esketamine and its major metabolites (S-norketamine and hydroxynorketamine) and the effects of CLE-901-M, a Clexio pipeline compound, in induced pluripotent stem cell (iPSC)-derived neurons from patients with a known response profile to citalopram. This approach leverages a validated artificial intelligence (AI) model for antidepressant response, a biobank of patient samples, and associated clinical data to characterize drug activity and response mechanisms in defined patient populations.

Design: iPSC-derived neurons from eight patients with depression (3 citalopram responders and 5 nonresponders) were exposed to esketamine with and without its two major metabolites, CLE-901-M, and citalopram.

Imaging-based features reflecting aspects of synaptic connectivity were captured, and an AI-model for antidepressant response was applied.

Results: Esketamine induced an antidepressant profile in derived neurons in responders and nonresponders to citalopram. Esketamine's major metabolites significantly contributed to the response. CLE-901-M induced a synaptic plasticity profile higher than citalopram and similar to esketamine with metabolites, demonstrating its potential for further development in depression treatment. Individual patient analysis indicated that some citalopram nonresponders will respond to both esketamine and CLE-901-M. Neurons from citalopram responders showed a higher predicted response to esketamine than nonresponders, and their response was of a higher magnitude compared to citalopram.

Conclusion: The potential of esketamine and CLE-901-M to induce a stronger antidepressant effect than citalopram in citalopram responders, and to drive response in citalopram nonresponders, can be used in support of the clinical development strategies. The results demonstrate the utility and importance of biomarkers in well-profiled iPSC-derived neurons for drug development from screening through to companion diagnostics.

Funding/financial disclosures: All authors are employees of either NeuroKaire or Clexio Biosciences.

REAL-WORLD DATA INSIGHTS FROM MoCA Xpress0, A SELF-ADMINISTERED DIGITAL COGNITIVE PRESCREENING TOOL

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Affiliations: [1]MoCA Cognition, Montreal, Quebec, Canada

Background/Objective: Xpress0 from Montreal Cognitive Assessment (MoCA) is a self-administered, digital cognitive screening test recently released in the United States (US). It can be used to support large-scale cognitive screening campaigns required for both drug development and clinical adoption. Xpress0 was recently validated to predict MoCA score with an area under the curve (AUC) of 0.85. The aim of this study was to characterize user demographics and determine whether the real-world evidence (RWE) Xpress0 scores are reflective of the prevalence of mild cognitive impairment (MCI) in the US.

Design: The study included 1,880 distinct users between February to May 2024; multiple attempts increased the total tests to 3,273. Exclusion criteria included all incomplete sessions and age inputted as over 120 years. Demographic characteristics were described using means, standard deviations, frequencies, and percentages. The frequency distribution of Xpress0 scores was graphically represented in a histogram. The Xpress0 scores were compared to US prevalence data of MCI across various age groups.

Results: The histogram of Xpress0 scores was highly skewed toward the right, suggesting most users' scores indicated a high probability of intact cognition. The results aligned with expected scores, as most users in the general population were anticipated to have normal cognition. Additionally, the occurrence of low Xpress0 scores (≤42) in the real-world data mirrored the prevalence of MCI in the US across various age groups between 60 to 84 years of age.

Conclusion: Xpress0 is emerging as an important tool in cognitive prescreening. RWE supports that Xpress0 scores are reflective of MCI prevalence data in the general population.

Funding/financial disclosures: This study was funded by MoCA Test Inc.

RELIABILITY OF BRAIN METRICS DERIVED FROM A TIME-DOMAIN FUNCTIONAL NEAR-INFRARED SPECTROSCOPY SYSTEM

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Affiliations: [1]Kernel, Culver City, CA

Background/Objective: Validation of novel brain measurement systems is essential to assess their potential to contribute to clinical trials. The objective of this study was to quantify the reliability of Kernel's Flow2 time-domain functional near-infrared spectroscopy (TD-fNIRS) system.

Design: A repeated measures design was used to compare brain activation patterns for the same tasks on two separate days and with two separate devices. Healthy participants (n=49, 18 female, age [mean±standard deviation]: 43.9±14.6 years) completed two study visits as follows: 1) resting state session (abstract movie watching) followed by an auditory task (interleaved story blocks and noise blocks); 2) short break with headset removed; and 3) resting state session. Neural recordings were done during Stages 1 and 3 either using the same Flow2 device or a different device. Oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) concentrations were calculated from brain data. Resting state neural features, including absolute HbO/HbR, fractional amplitude of low frequency fluctuations, and functional connectivity, were computed. Brain activation patterns were quantified with a generalized linear model.

Results: All participant-level resting state features demonstrated moderate-to-strong correlations both within and across visits. Participant-level correlations of the magnitude of auditory activations across visits were strong (e.g., left temporal cortex: $\rho=0.56$, $p<0.001$; right temporal cortex: $\rho=0.61$, $p<0.001$).

Conclusion: We report reliable measurements across several neural metrics extracted from both tasks. The reliability demonstrated in brain metrics over time and with different devices can fill a need for scalable multidevice and multisite neuroimaging for clinical trials.

Funding/financial disclosures: All authors of the study are employed by Kernel.

SMART-UPLOADER: AN AUTOMATIC TOOL FOR MEDICAL IMAGE DATA CLASSIFICATION AND QUALITY PROTOCOL ADHERENCE

Authors: Óscar Peña-Nogales,[1] Evie Neylon,[1] Marc Ramos,[1] Tommy Boshkovski,[1] Paulo Rodrigues,[1] Vesna Prčkovska,[1] Kire Trivodaliev[1]

Affiliations: [1]QMENTA, Inc., Boston, MA, US

Background/Objective: Imaging biomarkers are vital in large trials, offering objective measures of biological processes. Various magnetic resonance imaging (MRI) acquisitions (T1, T2 weighted, etc.) generate multiple imaging biomarkers aiding diagnosis, disease understanding, progression evaluation, and treatment efficacy. However, the complexity and lack of standardization of advanced MRI acquisitions pose challenges for large trials. Complicated MRI consoles and inadequate operator training lead to protocol deviations, necessitating data disqualification and/or rescans, thus increasing costs. Moreover, diverse MRI modalities complicate archival systems, such as PACS and cloud solutions. Thus, we introduce *Smart-Uploader*, a tool for automatic classification of medical imaging data and quality protocol adherence.

Design: Coded in Python and integrated into a cloud-based platform, *Smart-Uploader* removes protected health information, extracts DICOM header metadata, and groups files post-MRI acquisition. *Smart-Uploader* employs a few-shot learning classifier based on triplet ranking networks for image modality classification and a deterministic heuristic on DICOM headers. It tags and classifies files, then assesses protocol adherence via predefined rules.

Results: *Smart-Uploader* processes an MRI session (T1, T2, functional MRI, diffusion tensor imaging [DTI]) in about three minutes, classifying 20 MRI modalities. It applies up to 50 rules for protocol adherence, facilitating data harmonization and minimizing human error. In a Phase II Alzheimer's disease trial (100 patients, 13 institutions), it reduced manual assessment time by 88 percent, improving data collection to 95 percent of the target.

Conclusion: This tool enhances MRI data management, ensuring accurate classification and protocol compliance, boosting imaging quality, operational efficiency, and reducing trial costs. Future work includes extending classification to other modalities and automatically assessing image quality.

Funding/financial disclosures: The presenters are employed and own stocks or hold options of QMENTA.

STREAMLINING SITE ACTIVATION TO ACCELERATE ENROLLMENT

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Affiliations: [1]ArcheMedX, Inc.

Background/Objective: To demonstrate that use of innovations in learning and behavioral science by trial sponsors reduces site training and initiation timelines, accelerates enrollment, mitigates risk, and improves study quality.

Design: This study aimed to apply cutting-edge innovations in learning and behavioral science to accelerate site start up and analyze the completion rates, training outcomes and timelines, and evaluation data for clinical trial sites participating in study training programs powered by the Ready platform.

Results: Analysis of trials supported in 2023 and 2024 demonstrated that 80 percent of sites completed training and activation using the Ready platform in less than two weeks, with 90 percent of sites completing training within three weeks. Training outcomes data in protocol-specific training activities demonstrated that site personnel increased their knowledge and confidence in effectively applying the protocol by an average of 179 percent. For context, most study training conducted outside of the Ready platform only tracks whether or not the training was completed, not how much or how little a primary investigator (PI) or study coordinator understood the material and either achieved or failed to meet the learning objectives. The Ready platform analyzes thousands of learning behaviors to measure each clinical professional's knowledge and confidence in conducting the study. This novel data is utilized to automatically upskill and remediate each learner and to more accurately analyze and report on training outcomes. Evaluation data also revealed that 96 percent of site personnel reported they were better prepared to screen and enroll patients sooner after completing training on the Ready platform. These results are consistent across study design and therapeutic areas.

Conclusion: Delivering study training as a more tailored, on-demand experience streamlines site activation, increases site preparation to conduct the study, and can accelerate enrollment, mitigate risk, and improve study quality.

Funding/financial disclosures: Data was provided by ArcheMedX, Inc.

THE BENEFITS OF REAL-WORLD MONITORING: A COMPARATIVE ANALYSIS OF REMOTE WALKING USING PATIENT-REPORTED OUTCOMES

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Background/Objective: Symptoms of multiple sclerosis (MS) are highly variable and include impaired senses, instability, and fatigue, making persons with MS (PwMS) ill suited for the traditional six-month office visit paradigm. Instead, PwMS are well suited for remote monitoring to capture their true impairment. The objective of this work is to investigate the value of free-living data compared to prescribed walking tasks.

Design: Wearable sensor data were utilized from six-weeks of data from 24 PwMS. Participants completed a daily one-minute walk and surveys of balance confidence (Activities-Specific Balance Confidence Scale [ABC]), fatigue (Modified Fatigue Impact Scale [MFIS]), and walking impairment (Multiple Sclerosis Walking Scale [MSWS]). Temporal, stability, and complexity measures of gait were computed from free-living bouts in addition to the one-minute daily walk. We then compared gait features from three domains, the prescribed walk, all free-living walking (all-free), and free-living walking bouts 30 seconds or longer (long-free), to each other, as well as correlated them to patient-reported outcomes (PROs). Lastly, we used a regression to determine the variance of the PRO explained by different gait domains.

Results: All-free bouts were most different from the prescribed walk. All-free gait established the most and strongest significant correlations with ABC. The strongest association was found with prescribed walking for MSWS; however, all-free was stronger on average. No correlations were found with MFIS. Finally, all-free gait explained the most variance in ABC and MSWS, followed by long-free, which explained the most variance in MFIS.

Conclusion: These findings demonstrate that free-living data are more reflective of patient state and highlight the importance of free-living analysis in future studies.

Funding/financial disclosures: Not provided.

THE STRATEGIC APPLICATION OF GAMIFICATION IN CLINICAL STUDIES AT REGENERON

Authors: Roland Barge

Background/Objective: To bring our patients' voices into clinical studies through user experience research and design thinking to influence the collaborative development of innovative digital health technologies (DHTs), improving the clinical study journey for all.

Design:

- Literature reviews of existing implementations of gamification in clinical studies.
- United States (US) adult survey on perspectives of gamification in clinical studies.
- Regeneron sites survey on perspectives of gamification in clinical studies.
- FOP pediatric patient voice feedback through focus groups.
- Strategic integration of gamification into DHT development and operations by building empathy and understanding

of our patients' lived experiences and employing design thinking to improve those experiences.

Results:

- Education, health outcomes measures, and patient engagement were key areas identified by the literature review.
- US adults stated a preference for trials that included gamified applications, although they were concerned about the impact on human behavior and performance.
- Sites also preferred clinical studies that include gamified applications. Notifications, education, and training were most important for sites.
- Caregivers demonstrated that appointments, note taking, rewards, and community were key considerations.
- FOP children demonstrated that personalization, education, and socialization were important and provided feedback on desired additional functionality.
- When implemented in an adult POTs/nOH exploratory study, some negative feedback was received, proving that the application of gamification cannot be applied across all contexts and audiences (e.g., pediatric populations are more suited).

Conclusion:

- Advantages of gamification include increased engagement, education, adherence, and enjoyment.
- Research was conducted to understand our target patient pediatric populations specific unmet needs.
- Considered operationalization of gamification is required to understand the potential impact on how patients feel or function and the impact on their clinical study experiences.

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WILLINGNESS TO COLLABORATE: PROGRESS IN BUILDING A SINGLE HOME FOR SITES PROVIDES EVIDENCE OF AN INDUSTRY READY TO SOLVE LARGE-SCALE CHALLENGES

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Background/Objective: To reduce the burden of technology overload by developing a single platform where all trial-related systems, regardless of competitive positioning, can be accessed by sites.

Design: In the early 2020s, IQVIA Technologies was working to connect more than 20 software products it had developed or acquired. Single sign-on for site users was the minimum design objective. As site capacity challenges grew post-COVID-19, IQVIA Technologies' product strategists saw the need to link the entire clinical ecosystem, not just their own products. They began developing a single home for sites that would relieve staff of the significant burden they experienced from using hundreds of software products required by multiple sponsors to conduct studies.

As initial prototypes were shared with sites, technology vendors, and sponsors, feedback was incorporated into deeper design and development. All stakeholders were overwhelmingly positive and open to a vendor-neutral, sponsor-neutral platform that would finally solve the problem of site technology overload. A partner program was formalized in the early months of 2024, but questions remained about competitors' willingness to work together.

Results: As of October 2024, the platform now known as One Home for Sites has seven technology partners' products live in production in its SSO System Library (Medidata Rave, Clario Portal, Greenphire, ClinCard, TruLab, Signant SmartSignals, and Zelta by Merative) alongside seven IQVIA Technologies products (Feasibility, Safety Notifications, Site Activation, IRT, Clinical Trial Payments, and GrantPlan). Six more vendors will most likely be live in Q4 2024, along with six additional IQVIA Technologies products.

Conclusion: The industry is ready to collaborate and forego competitive discourse for the benefit of sites and patients.

Funding/financial disclosures: AA is an employee of IQVIA. ICNS

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