Symposium Title: Enhancing Scalability of Clinical Trials in Rare Disorders: Strategies in Remote Assessment and Intervention

Chair: Shafali Jeste MD¹

Discussant: Len Abbeduto PhD²

We are entering an era of targeted therapeutics, both behavioral and pharmacologic, for rare genetic syndromes associated with Intellectual Disability (ID), with key examples being Down Syndrome, Tuberous Sclerosis Complex and Fragile X Syndrome. These therapeutic opportunities, with syndrome-focused interventions and outcome measures, can greatly improve clinical outcomes. However, due to the rarity of these conditions, intervention studies require creativity and flexibility in study design and implementation to ensure adequate sample sizes and to maximize their reach to all affected individuals. In this symposium, we share experiences from three studies that have developed unique strategies in remote assessment and intervention for children with rare genetic conditions, and we use these examples as a platform to discuss key challenges and opportunities in clinical trials in rare conditions, such as participant recruitment, parent participation, validation of remote clinical assessments, reliability and fidelity of remote behavioral intervention, and access to technology. We will begin with a presentation by Bridgette Tonnsen, from Purdue University, who will discuss the development of quantitative, scalable outcome measures that can be collected in the home, such as heart rate monitoring and eye tracking, in children with Down Syndrome. Next, Shafali Jeste will share experiences from a new randomized clinical trial of behavioral intervention for infants and toddlers with TSC, called JETS (Jasper Early Intervention in TSC), in which the JASPER intervention has been modified to be performed remotely. Finally, Len Abbeduto and Elizabeth Berry-Kravis will discuss the NeuroNext trial in Fragile X, which combines pharmacological intervention with a remote language skills intervention. Lessons learned and strategies developed from these innovative studies can greatly inform assessment and intervention studies across neurodevelopmental disorders.

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Paper Title: Parent-Administered Remote Developmental Assessment (PANDA) for Down Syndrome and Other Neurogenetic Syndromes

Authors: Bridgette Tonnsen, Ph.D³, Taylor Halligan, B.S³, Wei Siong Neo, M.A³

Introduction: Adequately measuring treatment responses in children with Down syndrome and other neurogenetic syndromes requires outcome measures that are sensitive to developmental change and can be administered with continuity across a variety of ages and abilities. A number of passive experimental methods – such as eye movement analyses and psychophysiological methods – show promise as outcome measures for neurogenetic groups due to high resolution for detecting individual differences and minimal task demands on participants. However, many of these methods can only be administered in the laboratory or clinic, either due to technical limitations of commercially-available telehealth software or the practical challenges of collecting data without an examiner physically present. Thus, these methods can be difficult to “scale up” for use in clinical trials for children with rare syndromes, who are often geographically dispersed and may not be able to engage in frequent travel to clinical sites. For example, our previous work has shown that heart-rate defined sustained attention, a physiological metric of attentional engagement, predicts clinical outcomes in infants at risk for autism (Tonnsen, Richards, & Roberts, 2018), however commercially-available telehealth platforms are not compatible with high-quality psychophysiological or eye-movement monitoring necessary to replicate this task outside of the laboratory. As a solution to these barriers, we have developed Parent-Administered Neurodevelopmental Assessment (PANDA), a novel parent-facilitated telehealth protocol for assessing early...
developmental skills and psychiatric risks in neurogenetic syndromes. This presentation will provide an initial overview of PANDA, including preliminary feasibility and attention task data from young children with Down syndrome and community controls who completed the PANDA protocol via simulated remote assessment.

Methods and Results: Twenty-three infants (ages 3-24 months) and their mothers completed the PANDA protocol via simulated remote assessment, with an expected final sample of 40 dyads (20 Down syndrome, 20 community controls). PANDA includes a series of child-friendly tasks that are commonly used in studies of infants at high risk for autism and other forms of psychopathology: parent-child interactions, attention tasks, language assessments, psychophysiological monitoring, and autism-specific presses. Parents were provided a kit with all necessary materials, including a computer, manipulatives, and a heart monitor. Parents administered PANDA protocol while an examiner remotely provided online coaching and technological support. Preliminary findings (n=15 dyads) suggest parents are able to implement the PANDA tasks with high-fidelity, with over 90% success for the heart-rate defined sustained attention task. Our final presentation will discuss feasibility data and preliminary attention findings in the full sample. We will also discuss methods for optimizing PANDA for infants and toddlers with diverse developmental, motor, and language abilities common in neurogenetic syndromes.

Discussion: Parent-facilitated remote assessment provides a novel solution to the practical constraints of collecting outcome measures in geographically-dispersed cohorts of children with neurogenetic syndromes. Our preliminary findings suggest that with further refinement, the PANDA battery may provide a naturalistic, low-cost, high-resolution option for characterizing incremental changes in young children with neurogenetic syndromes, including over the course of clinical trials.

References/Citations:

Purdue University

Paper 2 of 3

Paper Title: Jasper Early Intervention in TSC (JETS): Methods to Enhance Study Participation and Scalability

Authors: Shafali Jeste MD1, Nicole McDonald PhD1, Carly Hyde1, Connie Kasari PhD1

Introduction: Tuberous Sclerosis Complex (TSC) is an autosomal dominant disorder caused by mutations in either the TSC1 or TSC2 genes. Inactivation of either gene leads to dysregulation of the MTORC1 pathway, resulting in the widespread growth of hamartomas in multiple organ systems, including the brain, as well as aberrant connectivity across neural circuits. Up to 80% of children with TSC suffer from some level of cognitive impairment, from milder learning disabilities to severe ID, and rates of ASD approach 60% (Jeste, 2014; Jeste, 2016). In a longitudinal study of development in TSC, we found that infants demonstrate delays in nonverbal cognition and social communication skills as early as 9 months of age, and these delays significantly differentiated infants who were later diagnosed with ASD from those that were not diagnosed with ASD. We also found that infants with TSC/ASD demonstrated a significant decline in their nonverbal cognitive abilities from 12-36 months (Jeste, 2014; McDonald, 2017). These early delays necessitate the implementation of early intervention that targets social communication skills in TSC.

Methods: In 2017, we began a randomized, double blind controlled trial of JASTER, a well validated and rigorously studied social communication intervention for autism, in infants with TSC ages 12-36 months (NICHD RO1 HD090138-01A1). This is the first behavioral intervention trial for TSC. By the end of year one, despite investing considerable resources into recruitment, only three participants had enrolled. Parent interviews on barriers to enrollment revealed that the greatest obstacle to participation
was the weekly travel to the sites (UCLA and Boston Children’s Hospital) for the intervention, particularly given their distance from the sites (average distance of families was 164 miles) and the medical complexity of the children. In response, we substantially revised the study design, with remote intervention delivery, assessments and parent communication. In-person JASPER is now delivered monthly, with weekly intervention performed by parent in the home. Parents record videos of their weekly on iPads that the study provides, upload the videos to a common server, and then receive feedback from an interventionist via video conferencing. Weekly check-ins are also performed via text messaging and online surveys.

**Results:** Since this modification was made 7 months ago, enrollment has increased from 3 to 24 participants. The average distance from the testing sites of participants enrolled is 320 miles, with states represented including not only Massachusetts and California, but also Maine, New York, Maryland, Arkansas, North Carolina. There has been no attrition during the study but there is a range in amount of JASPER being practiced by parents during the week (from 30 minutes to 2 hours).

**Discussion:** The tremendous success in enrolling participants through these modifications reinforces the need for innovative research delivery methods in rare populations. In this presentation, we will describe in more detail not only the methods, but also lessons learned through the process that can help guide future clinical trials across neurodevelopmental disorders.

**References/Citations:**

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UCLA Center for Autism Research and Treatment

**Paper title:** Pharmacological Trials with Language Intervention in Fragile X Syndrome

**Authors:** Elizabeth Berry-Kravis MD, Len Abbeduto PhD, Andrea McDuffie PhD

**Introduction:** Enormous progress in basic and translational research in fragile X syndrome (FXS) has allowed identification of neuronal pathway targets for treatment of the underlying disorder (Berry-Kravis, 2018). The most well-studied target has been of these has been reduction of excessive mGluR5 translational pathway signaling, which has been overwhelmingly successful in pre-clinical FXS models. In fact, there are over 60 papers showing both pharmacological (using mGluR5 negative allosteric modulators (NAMs)) and genetic (using crosses with mGluR5 heterozygous mutants) reversal of abnormal synaptic plasticity, dendritic morphology, cellular signaling, electrophysiological, cognitive, social, learning, behavioral and even growth phenotypes in 3 different species (FXS fly, mouse and rat models) and with 4 different mGluR5 NAMs. Human early phase trials of mGluR5 NAMs fenobam (Neuropharm), AFQ056 (Novartis) and RO4917523 (Roche) have suggested possible benefit in FXS, but larger phase IIb studies of AFQ056 and RO4917523 failed to meet primary behavioral outcomes in adolescents and adults. These trials may have failed due to lack of measurement of core FXS phenotypes of cognition and learning in a sufficiently young population over a long enough period of time. This NeuroNEXT trial uses an innovative exploratory design to change the paradigm for translation of targeted treatments in FXS and determine whether AFQ056 can improve language learning in 100 very young (age 3-6 years) children with FXS during participation in an intensive language learning intervention (PILI), as a surrogate for enhanced neural plasticity.

**Methods:** The trial uses a double blind placebo-controlled parallel flexible-dose forced-titration design with a 12 month blinded treatment period with randomization to AFQ056 or placebo and titration to maximum tolerated dose (MTD), 6 months
treatment with AFQ056/placebo combined with a parent-implemented language intervention (PILI) delivered through the parent by Skype, followed by an open-label 8 month open-label extension with re-titration to MTD and ongoing treatment of all participants with PILI and AFQ056, and follow up at the end of the trial. The study will assess effects of AFQ056 versus placebo on language and developmental functioning after language intervention, and on biomarkers that interrogate neural functioning (event-related potentials and eye tracking). The primary outcome is the weighted communication scale (WCS), a standardized videotaped observational measure of communication during play which is synched to the communication and language that will be targeted by PILI.

**Results:** To date 12 sites have been trained and opened, including 20 SLPs brought to fidelity on delivery of the PILI intervention and 20 SLPs or psychologists brought to fidelity on the WCS assessment. Ten have been approved for ERP, with consistent ERP output from the same phantom used for standardization across all sites. All 12 sites have completed eye tracker timing and fidelity assessments. Thus far, 44 FXS participants have enrolled, and 3 have screen failed, with 65% age 5-6 and 35% age 3-4, 92% male, and 85% white. Adverse events have been mild, with sleep and hyperactivity being most frequent. Many lessons have been learned regarding methodology for implementing PILI across sites.

**Discussion:** Processes developed in this trial for cross-site standardization of the WCS and PILI, ERP, and eye tracking, as well as use of Skype and Bluetooth methodology for delivering PILI, will be available for other similar trials in the future. If the design is successful, this novel multi-center trial can serve as a model for future trials of mechanistically-targeted treatments operating on neural plasticity in other NDDs, and can accelerate the process of bringing needed treatments to these disorders with high unmet need.

**References/Citations:**


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2 UC Davis MIND Institute  
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