Rationale
Pathogenic variants in the Cyclin-dependent kinase like 5 (CDKL5) gene cause CDKL5 deficiency disorder (CDD), a severe developmental and epileptic encephalopathy associated with cognitive and motor impairments and cortical visual impairment. While capability for disease-modifying therapies is accelerating, there is a critical barrier for clinical trial readiness that may result in failure of these therapies, not due to lack of efficacy but due to lack of validated clinical outcome measures (COMs) and biomarkers. The measures and biomarkers validated here may be adaptable to other developmental and epileptic encephalopathies. Supported by NINDS U01NS114312 (Benke/PD).

Goals:
1) Refine and validate appropriate quantitative COMS and biomarkers
2) Conduct a multi-site clinical trial readiness study to refine implementation

Methods
Refine, Psychometrically test and Create Training materials for:
• Clinician-CDD Clinical Severity Assessment (C-CCSA)
• Parent-CDD Clinical Severity Assessment (P-CCSA)
• Communication (CSBS-DP)
• Quality of Life (QI-Disability)
• Sleep (Bruni-SDSC)
• Gross Motor Video assessment
• Fine Motor Video Assessment

Correlate with EEG and Evoked Potentials (EEP):
• EEG background
• Auditory evoked potentials
• Visual evoked potentials

Goal: 200 unique, complete data sets by SEP 2022

Preliminary Results
• C-CCSA: Content validated. Think Aloud Consensus (29 items, 2 domains), dynamic range, training videos, training of raters, published.
• P-CCSA: Content validated, Think Aloud Consensus, split into 2 tools (P-CCSA (5 domains, 16-67 questions) and Developmental Questionnaire (3 domains, 30-50 questions) with skip logic for variable number of questions), dynamic range. Submitted.
• CSBS-DP:
  • Initial data collected
  • 1006 cases, 42 domains
  • Social, Speech and Symbolic domains
  • 24 items, takes approx 20 mins
  • Evaluations
    • Structural characteristics
    • Confirmatory factor analysis
    • Goodness of fit
    • Convergent and divergent validity
    • Known-groups validation
  • Next steps
    • Evaluate reliability:
      • Problems with floor effect and test length, considering adapting it for CDD
      • However, use for initial
• QI-Disability: content validated, responsive to change, minimal detectable difference, published.
• SDSC: initial correlation with QI-Disability.
• EEP: responsive to severity with RTT-specific measures. Submitted.

Discussion
• Development of suite of CDD specific COMS that are attentive to family-prioritized functioning.
• Use of responsive biomarker.
• Consent, DUA, network: in place
• External Advisory Committee: in place
• Site initiation visit: completed
• Enrollment: underway
• Next steps: Data review with FDA Fall 2022.

Etc.
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Disclosures: Available upon request from corresponding author *. Tim.benke@cuanschutz.edu.

References: