Multi-Site Validation of Biomarkers and Core Clinical Outcome Measures for Clinical Trials Readiness in CDKL5 Deficiency Disorder
NIH/NINDS U01NS114312

Tim Benke, Peter Jacoby, Eric Marsh, Scott Demarest, Joni Saby, Jacinta Saldaris, Lauren Mitchell, Helen Leonard, Jenny Downs and the ICCRN network: Heather Olson, Raj Rajaraman, Dana Price, Bernhard Suter, Judy Weisenberg & Elia Pestana-Knight

Baylor College of Medicine
Boston Children's Hospital
Children's Hospital Colorado
Children's Hospital of Philadelphia
Cleveland Clinic
NYU Langone Health
TELETHON KIDS INSTITUTE Discover. Prevent. Cure.
UCLA
Washington University in St. Louis School of Medicine

Introduction

Tim Benke

Grant Aims

Aim 1

- Develop, refine, and validate appropriate fit-for-purpose quantitative
  - clinical outcome measures (ClinROs)
  - parent reported outcome measures (ObsROs)
  - biomarkers

Aim 2

- Conduct a multi-site clinical trial readiness study to ensure that they can be successfully implemented in disease-modifying clinical trials of therapeutic interventions for CDD

Methods

Jenny Downs

How to make clinical outcome measures

1. Know what an outcome measure is (FDA guidance documents)

A clinical outcome measure is a tool used to assess how a patient feels, functions, or survives as a result of medical care or treatment.

2. Find out what is important to caregivers (Knight 2024, Neul 2023, PFDD)

3. Write a grant. Go back to caregivers for input. Repeat…

4. Work as a team

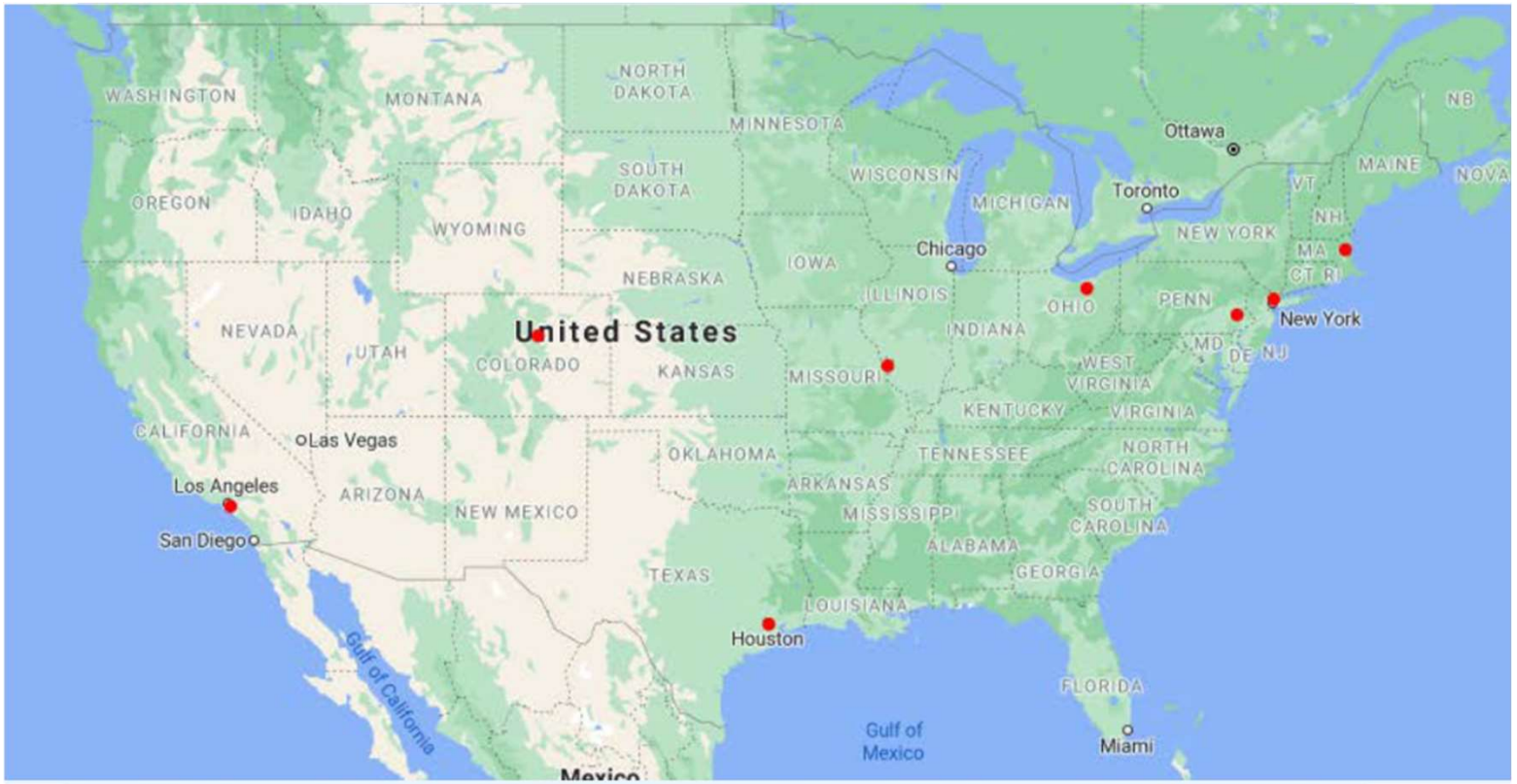
5. Work closely with a patient advisory group who can fund you and keep going until you get an NIH grant.

6. Create a multidisciplinary clinic that serves your people's needs.

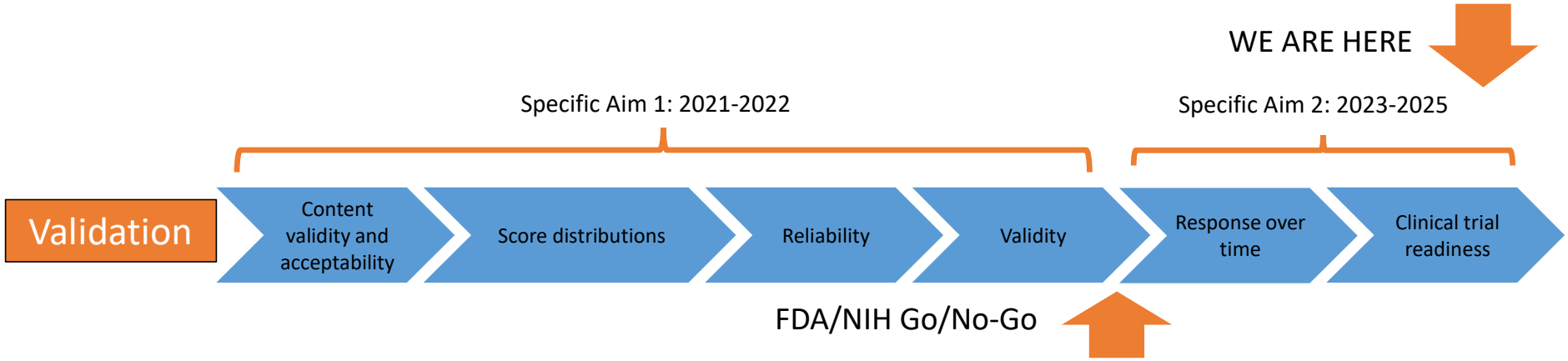
7. Work hard. Write a bunch of papers. Work closely with your patient advisory group. Enroll a bunch of families. Collaborate. Bother a bunch of people for advice. Keep being nice. Repeat.

Community is the critical component

Who are we?


WASHINGTON
MONTANA
NORTH DAKOTA
MINNESOTA
Ottawa
NB
MAINE
NOVA
SOUTH DAKOTA
WISCONSIN
VT
OREGON
IDAHO
WYOMING
MICHIGAN
Toronto
NH
NEW YORK
Chicago
MA
IOWA
CT RI
NEBRASKA
ILLINOIS
OHIO
PENN
New York
NEVADA
United States
INDIANA
MD
DE NJ
UTAH
COLORADO
KANSAS
MISSOURI
WEST VIRGINIA
KENTUCKY
VIRGINIA
CALIFORNIA
Las Vegas
OKLAHOMA
TENNESSEE
NORTH CAROLINA
Los Angeles
ARIZONA
NEW MEXICO
ARKANSAS
MISSISSIPPI
SOUTH CAROLINA
San Diego
ALABAMA
GEORGIA
TEXAS
LOUISIANA
Houston
Gulf of California
FLORIDA
Gulf of Mexico
Miami
Mexico

UO1 Contribution to Clinical Trial Readiness for CDD



COAs

Clinical Severity
- Clinician-CDD Clinical Severity Assessment
- Parent-CDD Clinical Severity Assessment
- Parent-CDD Developmental Questionnaire

Biomarkers
qEEG
VEPs
AEPs

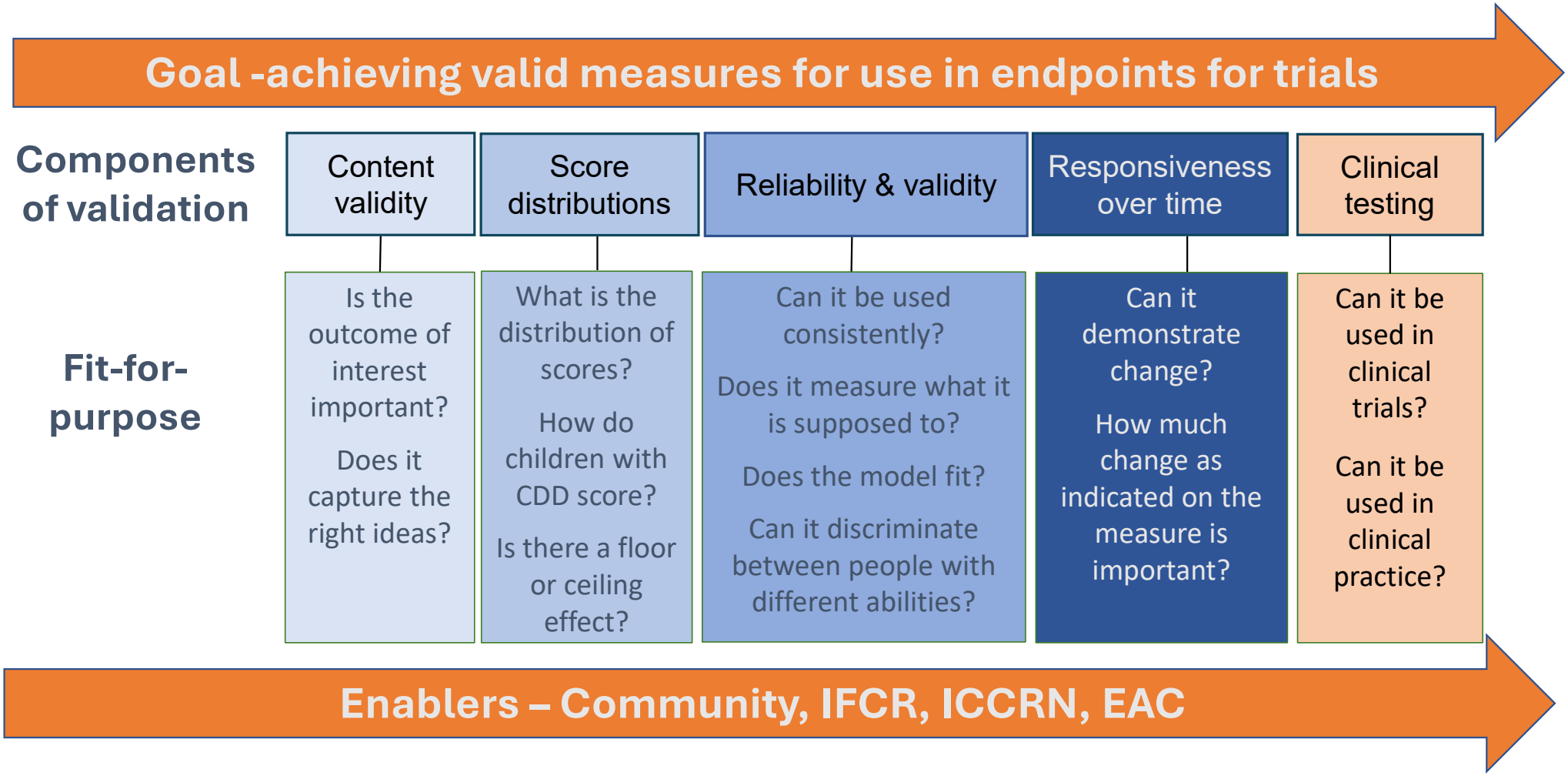
Video
- Gross Motor
- Hand Function

Parent-report
Communication
Sleep
Quality of Life

Goal

Valid COAs for CDD that could be suitable to trials

Measure development and validation plan



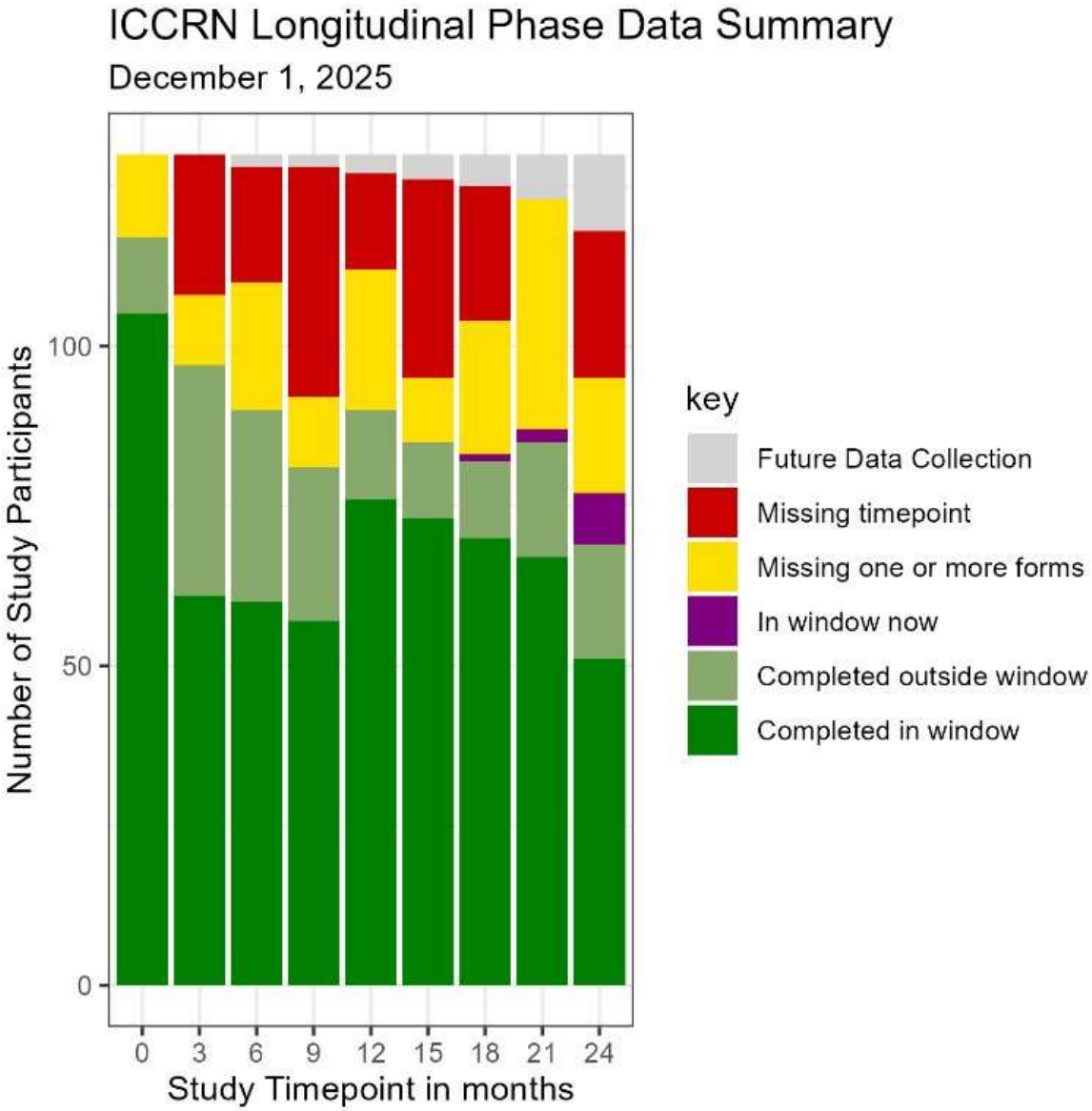
Cross sectional validation

Eric Marsh

Study Population

n = 159

	Male	Female
Sex	30	129
Race		
Asian	0	6
Black or African-American	1	5
White	24	105
More than one race	2	8
Unknown/not reported	3	5
Ethnicity		
Hispanic or Latino	8	17
Not Hispanic or Latino	21	109
Unknown/not reported	1	3


ICCRN Longitudinal Phase Data Summary
December 1, 2025
Number of Study Participants
100
50
0
0
3
6
9
12
15
18
21
24
Study Timepoint in months
key
Future Data Collection
Missing timepoint
Missing one or more forms
In window now
Completed outside window
Completed in window

Measures

Clinician-CDD Clinical Severity Assessment — Clinician-reported COM

Parent-CDD Clinical Severity Assessment
Parent-CDD Developmental Questionnaire
Communication (CSBS-DP). NOW CI-DOR!
Quality of Life (QI-Disability)
Sleep (Bruni-SDSC)
Social Determinants of Health
— Parent-reported COMs

Gross Motor Video assessment
Fine Motor Video Assessment
— At-home, parent uploaded, video COMs

Correlate with EEG and Evoked Potentials:

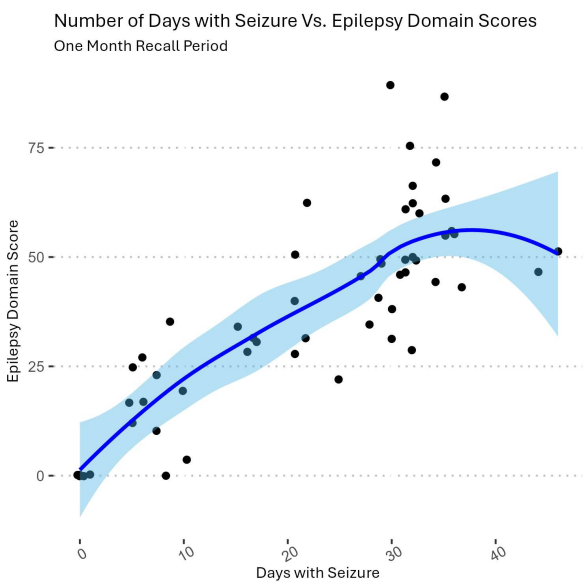
- EEG background
- Auditory and Visual evoked potentials

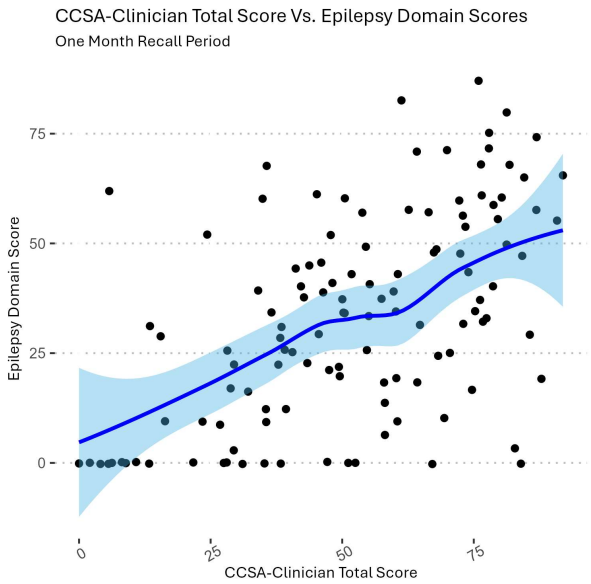
Measure	Number of items	Time to complete (min)	Number completed
Clinician-CCSA	29	30-45	617
Caregiver CCSA	27	30	1407
Caregiver DQ	65	30	670
CID-OR	34	20	371
CSBS	24	10	959
Bruni-sleep	26	10	1320
QI-Disability	32	10	TNTC

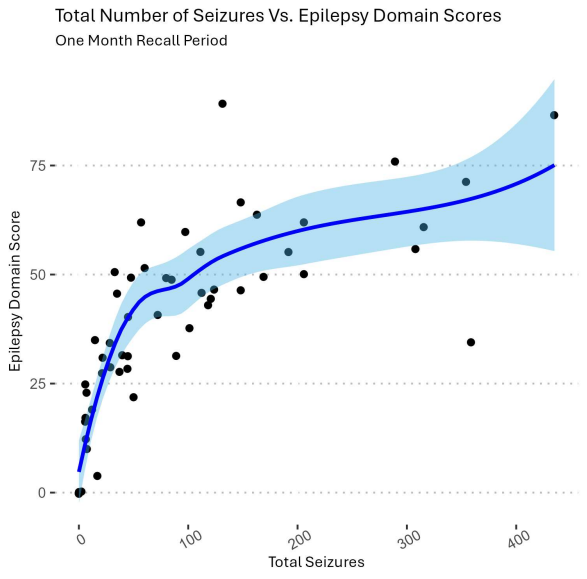
Specific Aim 1 - Validation summary and publications

Measure	Content validity	Factor Loadings	Factor analysis – model fit	Internal consistency	Average variance extracted	Divergent validity	Reliability	Known groups validity	PMID
CCSA-Clinician	✓	✓	±	✓	✓	±	✓	✓	34378447 37751639 39190322
CCSA-Caregiver	✓	✓	✓	✓	✓	✓	✓	✓	
Gross Motor – Complex Disability	✓			✓			✓	✓	38237219
CDD-Hand	✓						✓	✓	35422141
CSBS		✓	✓	✓	✓		✓	✓	37184758 39141588
CID-OR	✓	✓	✓	✓	✓		✓	✓	38425131 39141588 40900005
SDSC		✓	±	✓	±	✓			38963064
Development Questionnaire	✓	✓	✓	✓	✓		✓	✓	
QI-Disability	✓	✓	✓	✓	✓	±	✓		36634535 35415902

Epilepsy Domain Scores







Mega model

Peter Jacoby

Brain and Behavior

WILEY

Brain and Behavior
Open Access

ORIGINAL ARTICLE OPEN ACCESS

Beyond Seizures as an Outcome Measure: A Global Severity Scoring System for CDKL5 Deficiency Disorder

Peter Jacoby[1] | Eric D. Marsh[2] | Scott Demarest[3] | Jacinta M. Saldaris[1] | Helen Leonard[1] | Heather E. Olson[4] | Joni N. Saby[2] | Elia Pestana-Knight[5] | Rajsekar Rajaraman[6] | Dana Price[7] | Judith Weisenberg[8] | Bernhard Suter[9] | Jenny Downs[1] | Tim A. Benke[3]

"Regardless of how symptoms combine, there is a sense from treating physicians, other healthcare providers, and, most importantly, caregivers that an overall concept of severity exists.

Being able to quantify this overall severity.....has merit for understanding aspects of the underlying biology and quality of life, and as a measure for disease modifying therapies."

Beyond Seizures

Combining COAs to measure clinical severity in CDD

Research questions

- Do the measures relate to each other via a latent construct of severity in CDD?
- Can we use our measures data to estimate an individual's global clinical severity?

Analytic methods

- Structural Equation Model (the "Mega-Model) was fitted
- Data available for 208 patients

CDD Clinical Outcome Assessments (COAs)
All validated

CCSA-Clinician Motor, Vision and Communication domain scores	CCSA-Caregiver Seizures, Alertness, Behavior and Feeding domain scores	CSBS-DP ITC total communication scores
SDSC -DIMS (Insomnia) and DOES (Daytime Sleepiness) domain scores	GM-CD video score	CDD-Hand video score

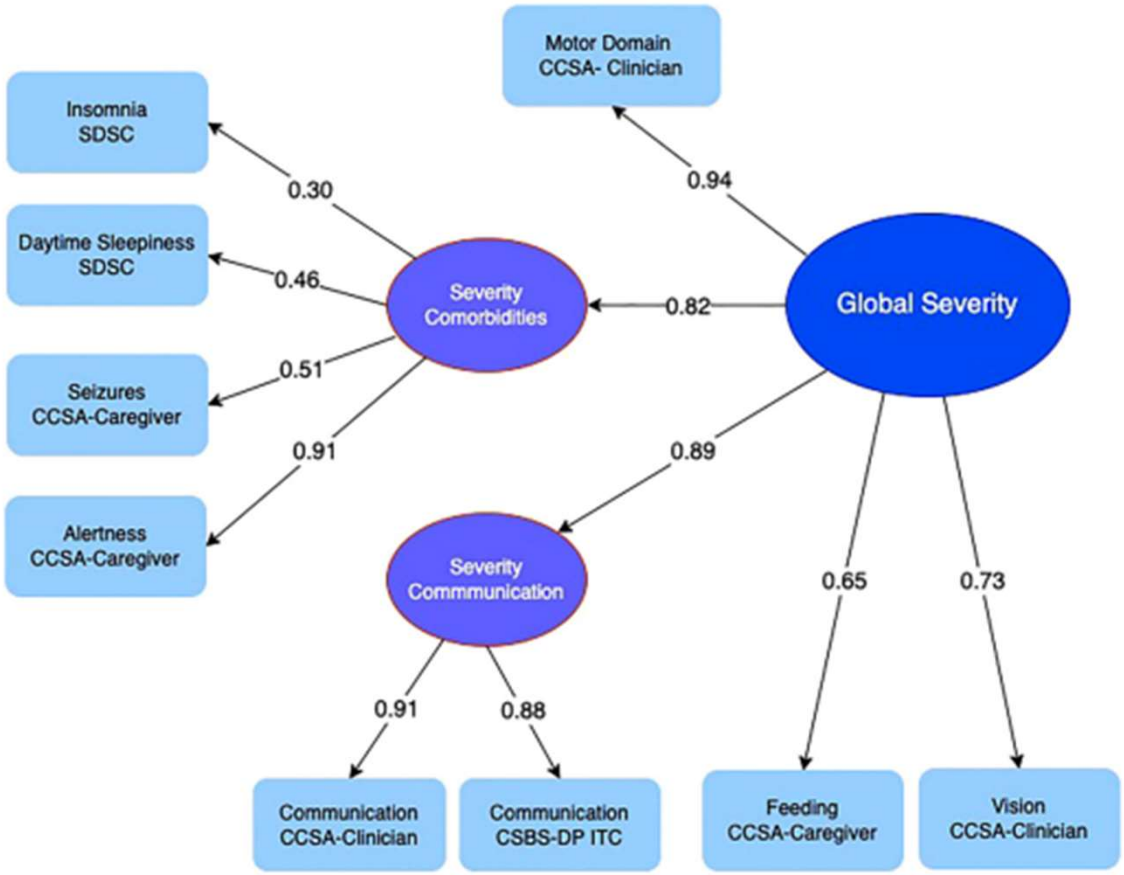
Is Behavior a component of severity in CDD?

- Problematic behavior is a feature of the disease

  BUT

- Our CCSA-caregiver Behavior domain does not correlate with other COAs
  In fact……patients with higher functional ability tend to exhibit 'worse' behavior

The Mega-model



Validation (1)

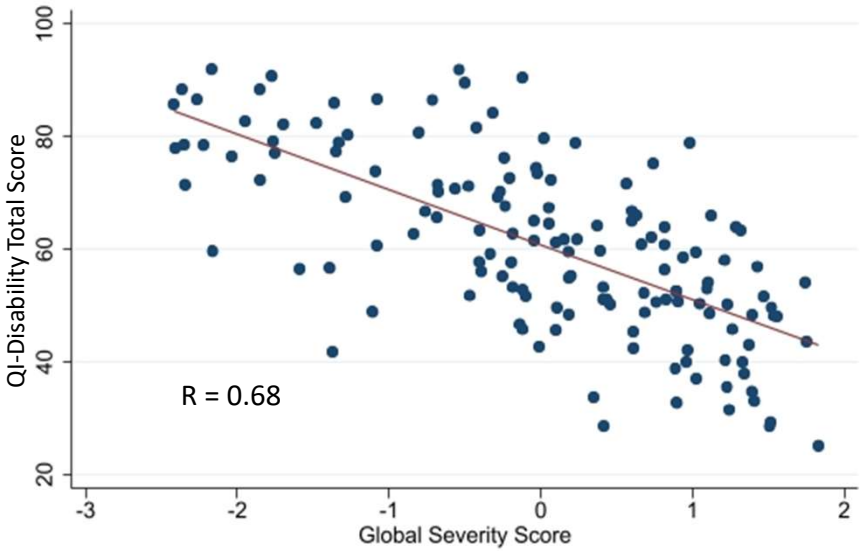
Structural Equation Model fit statistics

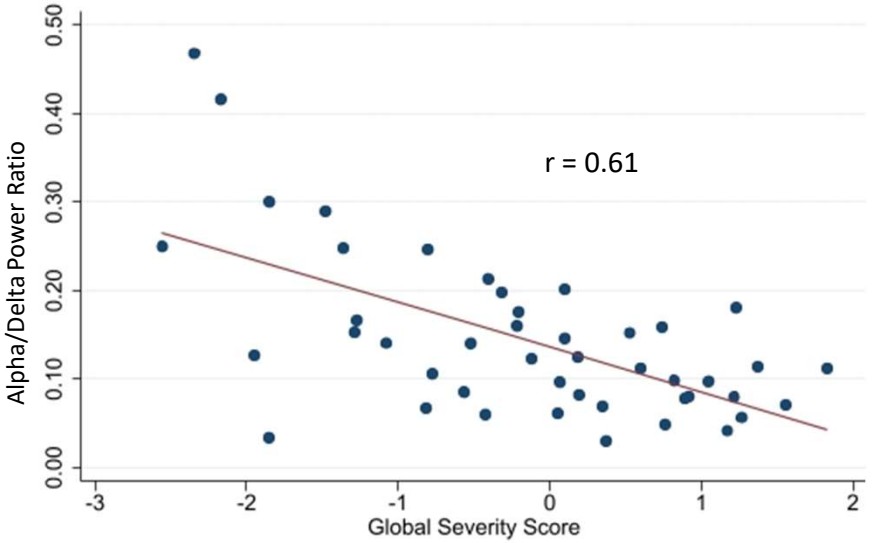
Chi-square(df)	30.02(25)
Chi-square/df	1.21
Root Mean Square Error of Approximation (RMSEA)	0.031
Comparative Fit Index (CFI)	0.992
Tucker-Lewis Index (TLI)	0.998

Commonly used criteria for acceptable model fit are Chi-square/df<3, RMSEA<0.08, CFI>0.9, TLI>0.9

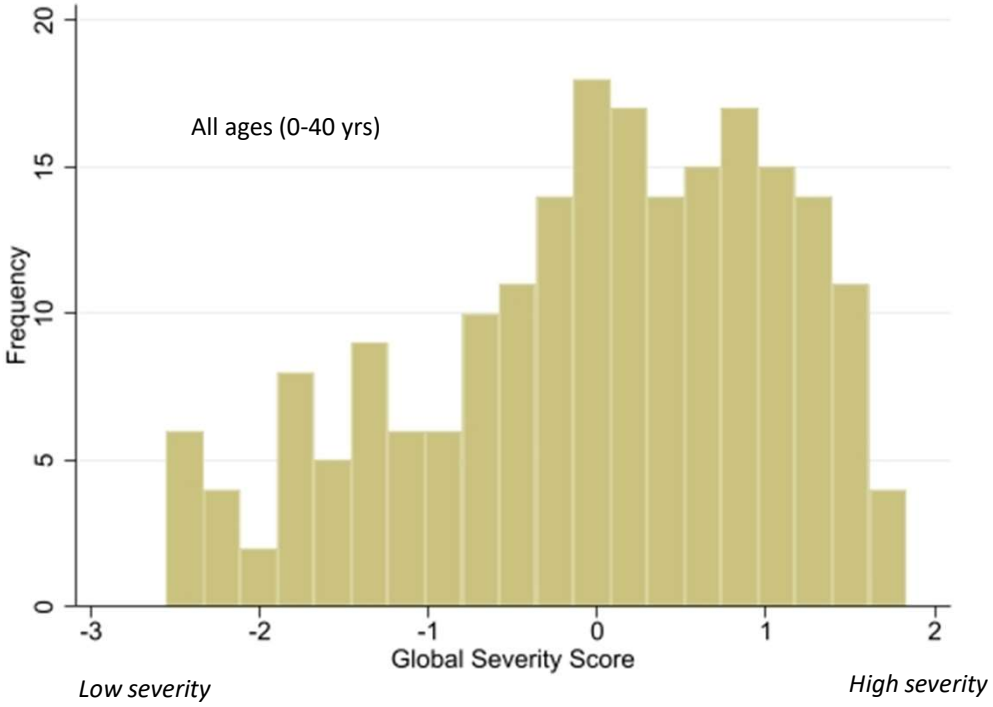
Validation (2)

Evidence for convergent validity of the global severity score



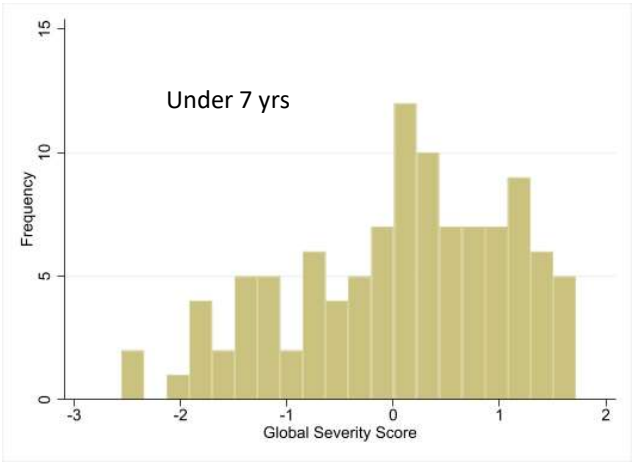


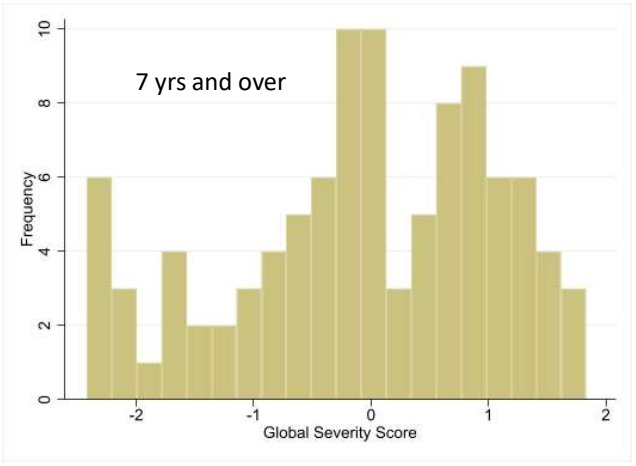
The Mega-Model automatically calculated a global severity score for each of the 206 participants



Low severity *High severity*

Normalized:
Mean=0 StandardDeviation=1





We can use the Mega-model to estimate a global severity score for ANY individual with a set of COA scores

- We constructed a multiple regression model with global severity as dependent variable and COA scores as independent variables
- Regression coefficients (normalized to sum to one) form a set of weights which can be applied to any set of COA scores

Clinical Outcome Assessment/Domain		Weights
Motor	Motor domain – Clinician CCSA	0.467
Comorbidities	Insomnia - SDSC	0.007
	Daytime Sleepiness - SDSC	0.012
	Seizures – Caregiver CCSA	0.012
	Alertness – Caregiver CCSA	0.111
Communication	Communication – Clinician CCSA	0.105
	Communication – CSBS-DP	0.142
Vision	Vision domain – Clinician CCSA	0.091
Feeding	Feeding Domain – Caregiver CCSA	0.052

Motor & communication domains are the most important independent contributors to global severity

Epilepsy is NOT a major contributor

Assumes that all scores are normalized to the same scale

“Mega-Model” – Summary

- Estimates overall severity
- Severity = weighted sum of all measured outcomes using weighting coefficients derived from the model
- Highly correlated measures have higher weightings than poorly correlated measures such as sleep and epilepsy
- A more nuanced estimate of severity than a simple average of outcome scores
- Methodology could be used for other conditions

- *Do we recommend the Mega-Model severity score be used as a clinical trial endpoint? ("Yes")*

Stability, MDDs and Trajectories

Peter Jacoby, Tim Benke

Stability of Clinical Outcome Assessments

We are collecting longitudinal data at 0, 6, 12, 18 and 24 months

A subset of patients (~30) also completed questionnaires/assessments at 13 months

What is a REAL change in score? i.e after eliminating measurement error (noise)

- *Estimated by Minimal Detectable Difference (MDD)*
- *We can be 95% confident that any change > MDD is a REAL change*
- *MDD is calculated using test-retest data (12 and 13 months)*
- *Retest after a short interval when "real" change should be minimal.*

Minimum Detectable Change Values

	Domain	MDD (95%)
CCSA - Clinician	Communication	18.75
	Motor	21.15
	Vision	29.22
CCSA - Caregiver	Seizures	20.80
	Alertness	19.60
	Behavior	16.62
	Feeding	15.95
SDSC	Insomnia	23.84
	Daytime Sleepiness	20.69
Communication	CSBS	9.93
	CID-OR	11.21
Mega-model	Global Severity	9.01

U01 – 6-month change score analysis

Research Questions:

For all domains and global severity:

1. Do change scores vary around an overall mean of zero?

2. Are change scores influenced by
a) Age
b) Sex
c) Baseline score

3. Does the magnitude of 6-month change scores (in either direction) exceed measurement error (noise)?

Are the U01 longitudinal data suitable as historical trial controls? ("Yes")

6-month change scores

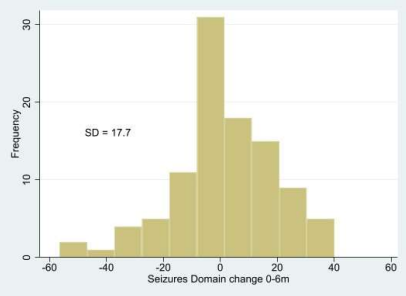
	Domain	Mean Change Score	Significant Predictors
CCSA - Clinician	Communication	-0.39 (-1.38 – 0.60)	Baseline score
	Motor	0.21 (-0.63 – 1.06)	None
	Vision	-0.68 (-2.04 – 0.67)	Baseline score
CCSA - Caregiver	Seizures	-0.46 (-1.60 – 0.68)	Baseline score
	Alertness	0.01 (-1.06 – 1.07)	Baseline score
	Behaviour	-0.46 (-1.47 – 0.55)	Baseline score
	Feeding	0.50 (-0.69 – 1.68)	Baseline score
SDSC	Insomnia	-1.37 (-2.58 - -0.15)*	Baseline score
	Daytime Sleepiness	1.78 (0.23 – 3.33)*	Baseline score
Communication	CSBS	-0.53 (-1.30 – 0.230)	None
	CID-OR	1.33 (0.06 – 2.62)*	Age (-ve effect
Mega-model	Global Severity	0.05 (-0.58 – 0.67)	None

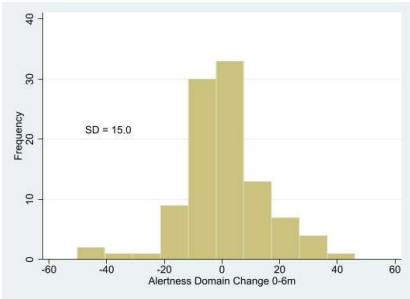
Stability (Absolute change over 6 months)

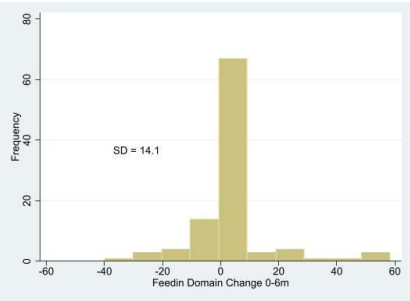
	Domain	Mean Absolute Change	MDD (95%)	% within MDD
CCSA - Clinician	Communication	9.10	18.75	90.6
	Motor	8.14	21.15	93.8
	Vision	11.84	29.22	92.7
CCSA - Caregiver	Seizures	9.94	20.80	85.1
	Alertness	8.86	19.60	89.2
	Behavior	7.58	16.62	87.2
	Feeding	5.37	15.95	90.9
SDSC	Insomnia	11.06	23.84	89.3
	Daytime Sleepiness	12.15	20.69	82.2
Communication	CSBS	4.54	9.93	89.6
	CID-OR	4.99	11.21	88.8
Mega-model	Global Severity	4.80	9.01	87.1

Longitudinal Phase - Stability of measures from baseline to 6-month assessment

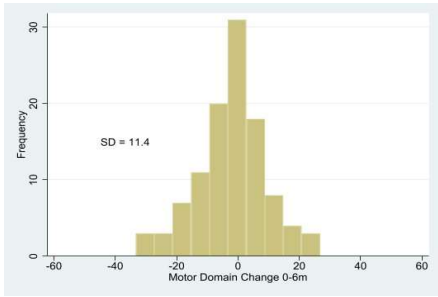
CCSA - Caregiver

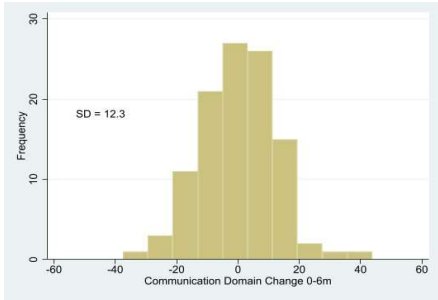


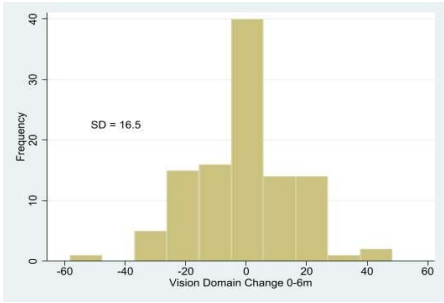


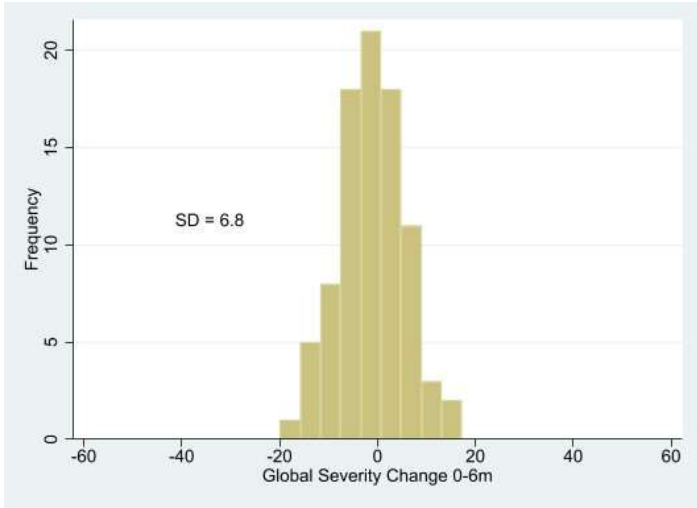


CCSA - Clinician

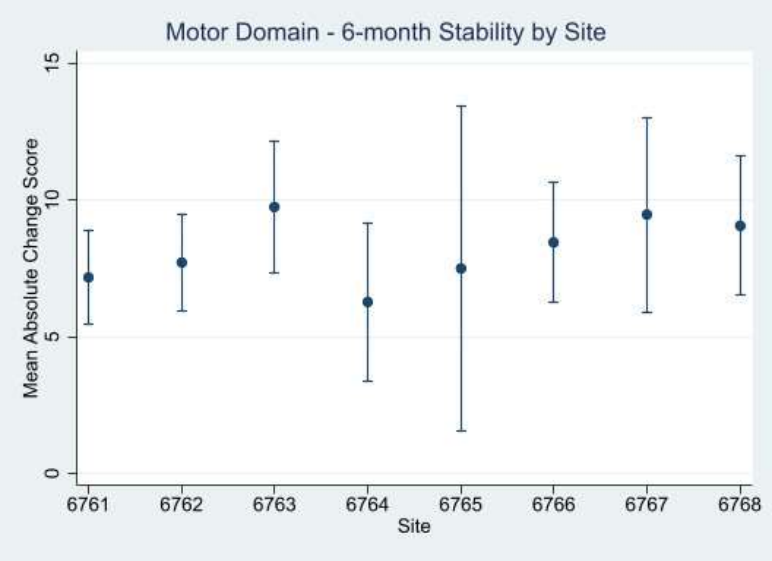


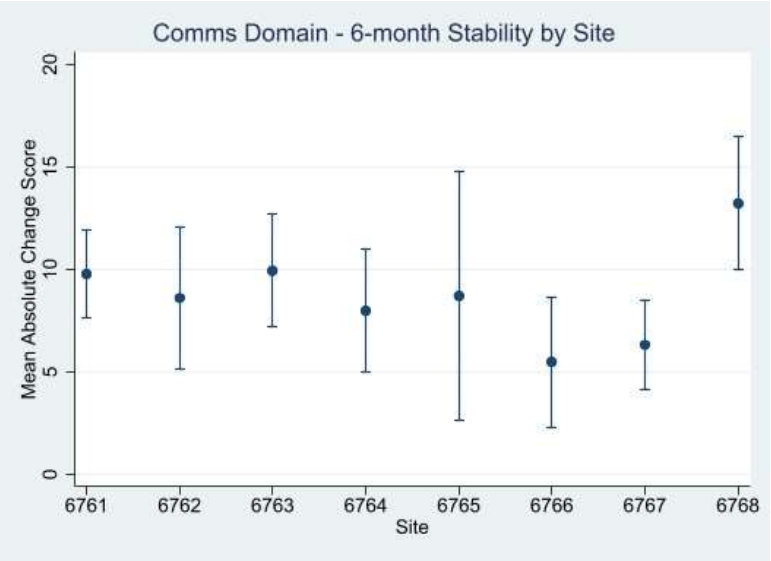


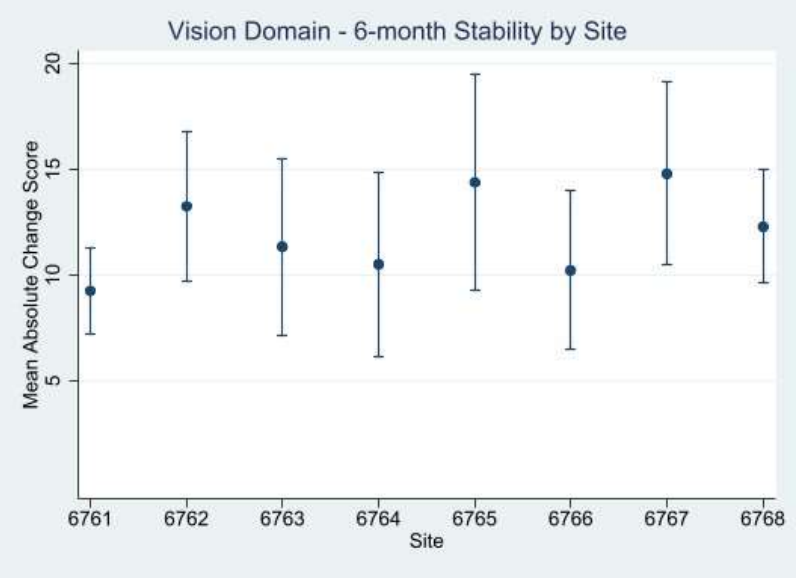




- *Poor stability of individual COAs mostly consists of measurement error ("noise")*
- *Noise is substantially eliminated by (weighted) averaging of Global Severity Index*



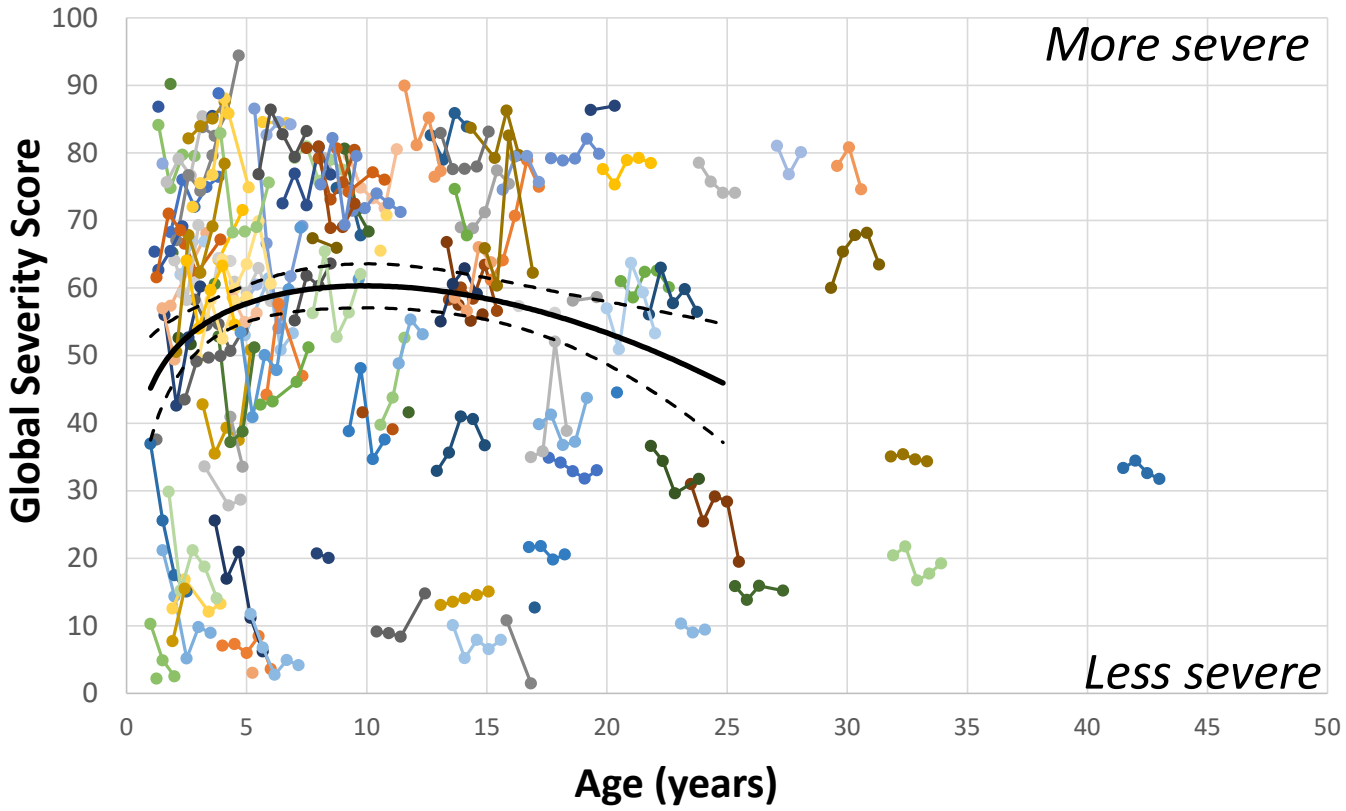




6761 - CHCO
6762 – Boston
6763 – CHOP
6764 – Washington
6765 – Baylor
6766 – NYU
6767 – UCLA
6768 - Cleveland

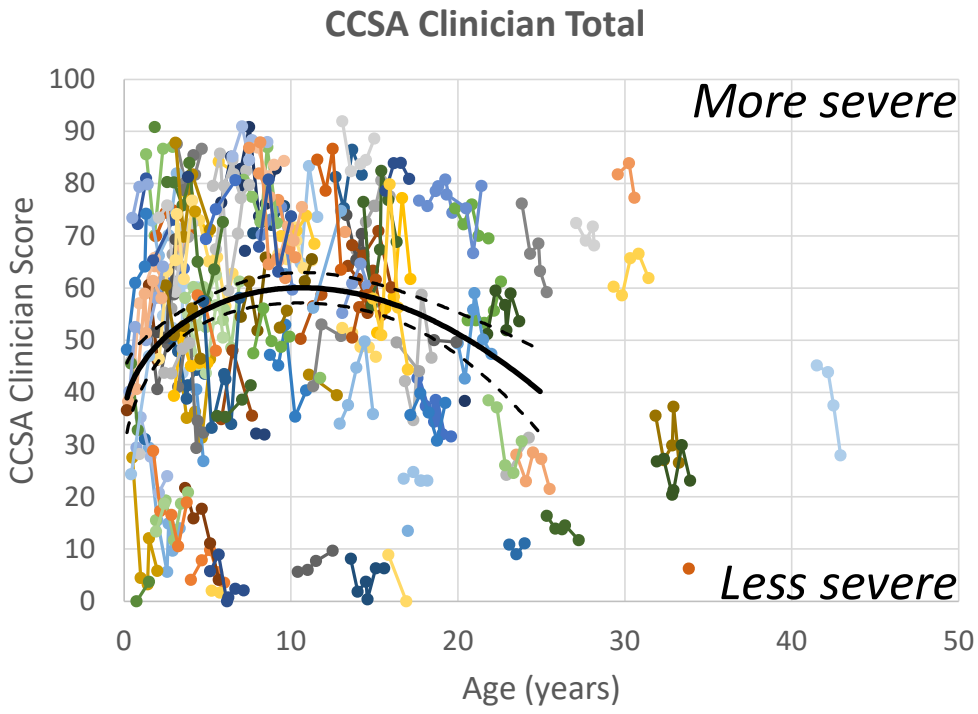
Conclusions

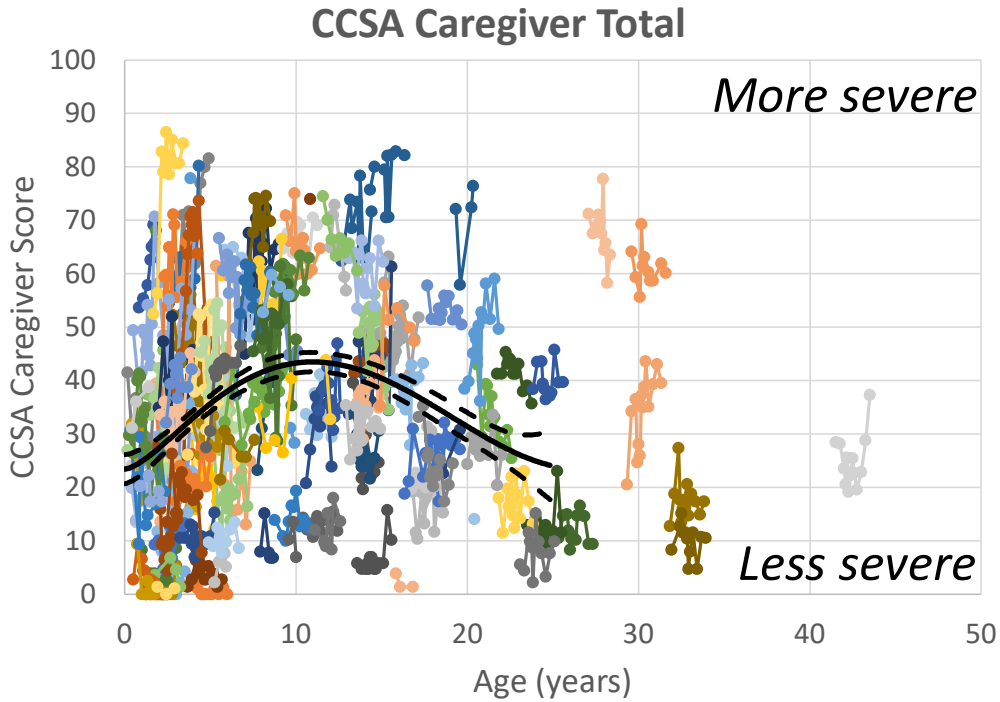
- *Over a 6-month period most of the instability in COA scores comprises of noise*
- *A control group should display only small systematic changes in functioning etc*
- *BUT noise is substantial…….less so for global severity*
- *Noise will be reduced when comparing average changes between treatment and control groups*



<u>Population trends</u> (worse with age) VERSUS <u>Individual trends</u> (mostly stable)

P Jacoby, et al, unpublished





The CCSA-Clinician and CCSA-Caregiver Total scores
Are averages ACROSS Domains
(Motor, Vision, Communication) (Seizures, Alertness, Behavior, Feeding)

The GLOBAL Severity Score effectively removes "noise" across the different measures

P Jacoby, et al, unpublished

Communication Inventory Disability – Observer Reported (CID-OR)

Jenny Downs

The gap

Content validity	Score distributions
Is the outcome of interest important? Does it capture the right ideas?	What is the distribution of scores? How do children with DEEs score? Is there a floor or ceiling effect?

- The target group is CDD
  - Concepts in the CSBS-DP are not all relevant to CDD
  - Not been checked for content validation
  - Floor effect in our cross-sectional data
- Other parent report measures
  - Six with validation data for rare diseases
    - Vineland, most frequently used
    - ABAS, CSBS-DP, Communication Matrix, ORCA, MPSS
  - Incomplete validation

Saldaris 2024
PMID: 39141588

What we have done?

Planning

Consumer Reference group

Communication experts

Keeley 2024
PMID: 38425131

Concept Elicitation

Interviews with caregivers of people with CDD (*n* = 23)

Mapped parent data with literature to draft a measure

Draft of Items

35 items

1. Demonstrating preferences
2. Indicating understanding
3. Expressing emotions
4. Social connections
5. Two-way exchanges

Initial Evaluation

Face validity
(*n* = 2)
Content validity interviews
(*n* = 21)
Expert review
(*n* = 6)

Keeley 2025
PMID: 40900005

Field-testing

Psychometric analyses
N=184

Downs in press

IFCR
International Foundation for CDKL5 Research

Novel scoring method

- What is communicated?
  - Rate consistency
  - If not currently, score is 0
- How is the message communicated?
  - If any level of consistency, bands of scores reflect the mode – non-symbolic and symbolic

Scoring Guide						
Mode		Purpose/Consistency				
		Not currently	Hardly ever	Sometimes	Often	Consistently
Non-symbolic*	-Moving limbs -Moving whole body and/or head -Facial expressions or movements -Eye movements -Vocalisations	0	1	10	19	28
		0	2	11	20	29
		0	3	12	21	30
		0	4	13	22	31
		0	5	14	23	32
Symbolic communication (aided communication, sing language, spoken words)**	Communicates using single words/icons/signs	0	6	15	24	33
	Communicates using 2 words/icons/signs in combination	0	7	16	25	34
	Communicates using 3 or 4 words/icons/sign in combination	0	8	17	26	35
	Communicates multiple sentences	0	9	18	27	36

Consistently					28 to 36
Often				19 to 27	
Sometimes			10 to 18		
Hardly ever		1 to 9			
Not currently	0				

Item scores are summed and scaled to a 100-point scale

Field testing

Analysis

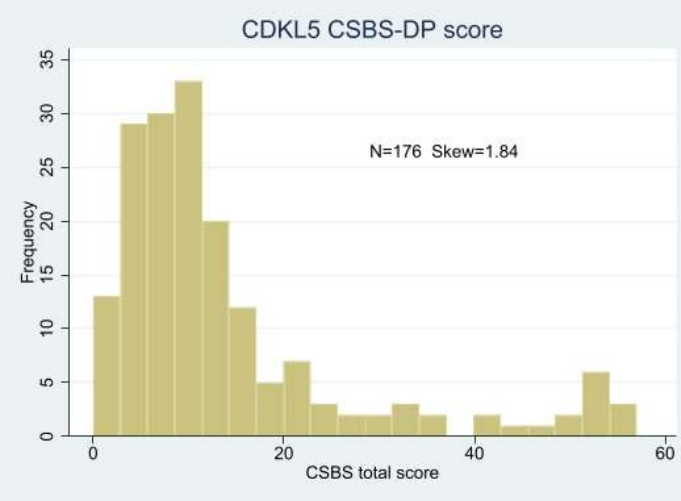
- Visual comparison
  - CID-OR and CSBS scores
- Confirmatory factor analysis
- Internal consistency
- Test-retest reliability
  - ICCs and MDD
- Known groups validity
- Convergent validity

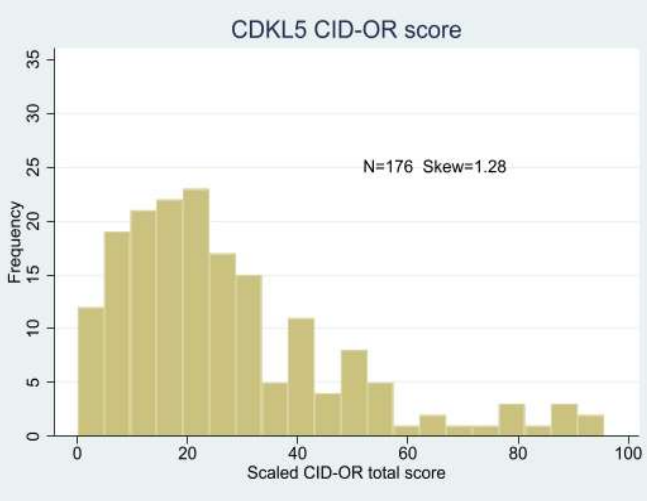
Participants

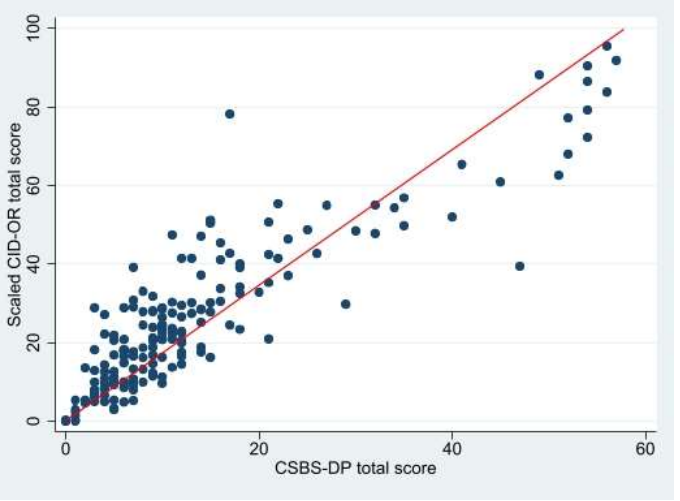
- N = 184
- Median (range) age
  - 9.8 (1-43) years
- Most were female (81.5%)
- 25% able to walk independently and 63% took all food orally

CID-OR reduced the floor effect

- 34 items, single domain
- Median (IQR) score – 22.5 (12.4-38.2), range 0.1-95.6







- Reduced skew of total scores in CID-OR
- Low range of scores – more dots above the red line of unity for CID-OR

CSBS-DP ITC – Communication and Symbolic Behavior – Developmental Profile
CID-OR – Communication Inventory Disability – Observer Reported

Validity and reliability

CID-OR – cross-sectional evaluation (n=184)

Content validity	Score distributions	Reliability		Validity				
		Internal consistency	Test retest	Factor loadings	Model fit	Divergent validity	Convergent validity	Known groups validity
✓	Improved	✓	✓	✓	✓	X	✓	✓

MDD - 10.53, corresponding to score change where there is 95% confidence that the change is greater than measurement error.
MDD corresponding to 90% confidence is ~10.

Downs, in press

Ready for use

- Get fundamentals right with the right content
- Materials prepared to support end users
  - Manual
  - REDCap files, excel scoring tool, paper questionnaire
- Clinical trials – Aim to avoid a trial failing by selecting a unsuitable COA
  - Bespoke – e.g., CID-OR
  - Standardised- e.g., Vineland

EEG Biomarker

Joni Saby

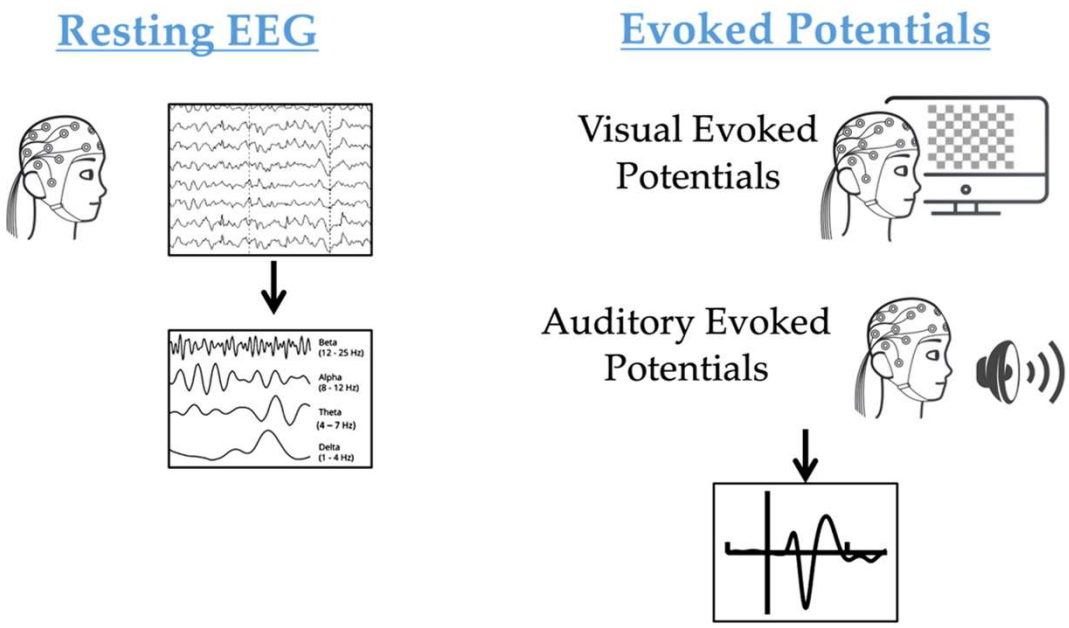
Why EEG?

- Currently, there are no biomarkers to complement COAs and provide an objective measure of treatment response for CDD.

- **Electrophysiological biomarkers** provide direct, real-time insights into brain electrical activity. Key advantages include:
  - Real-time monitoring
  - Non-invasive assessment
  - High temporal resolution
  - Insight into brain networks
  - Scalable across multiple sites

Electrophysiological methods

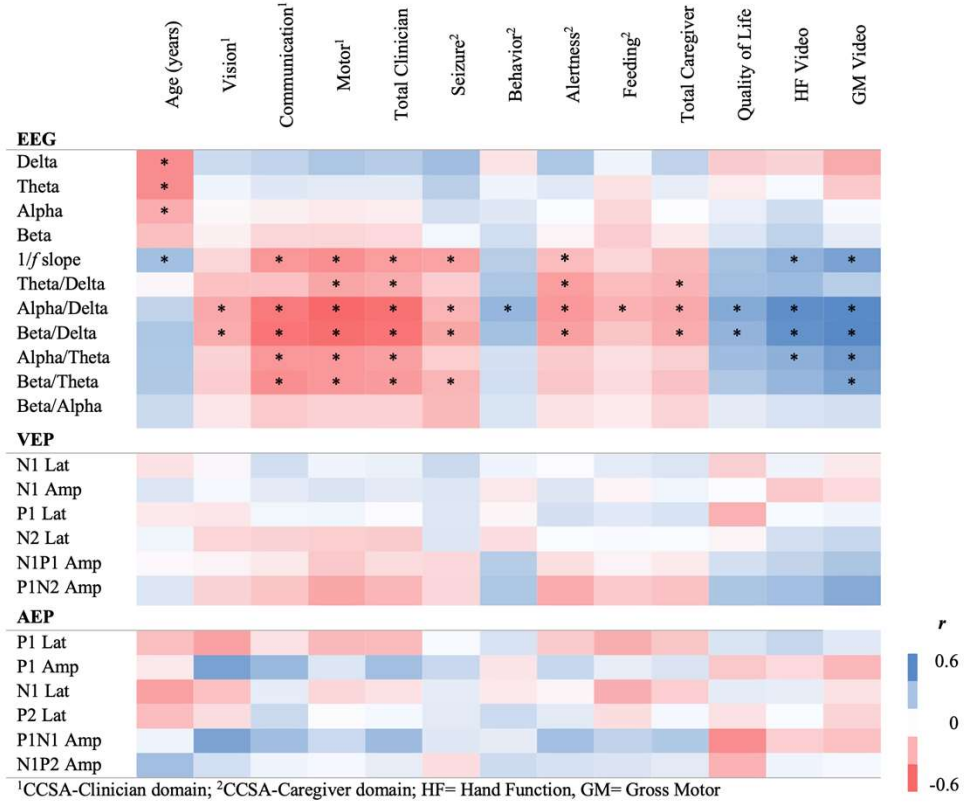
Data collection at 4 locations: Baylor, Colorado, Boston, and CHOP



ICCRN: Baseline EEG acquisitions

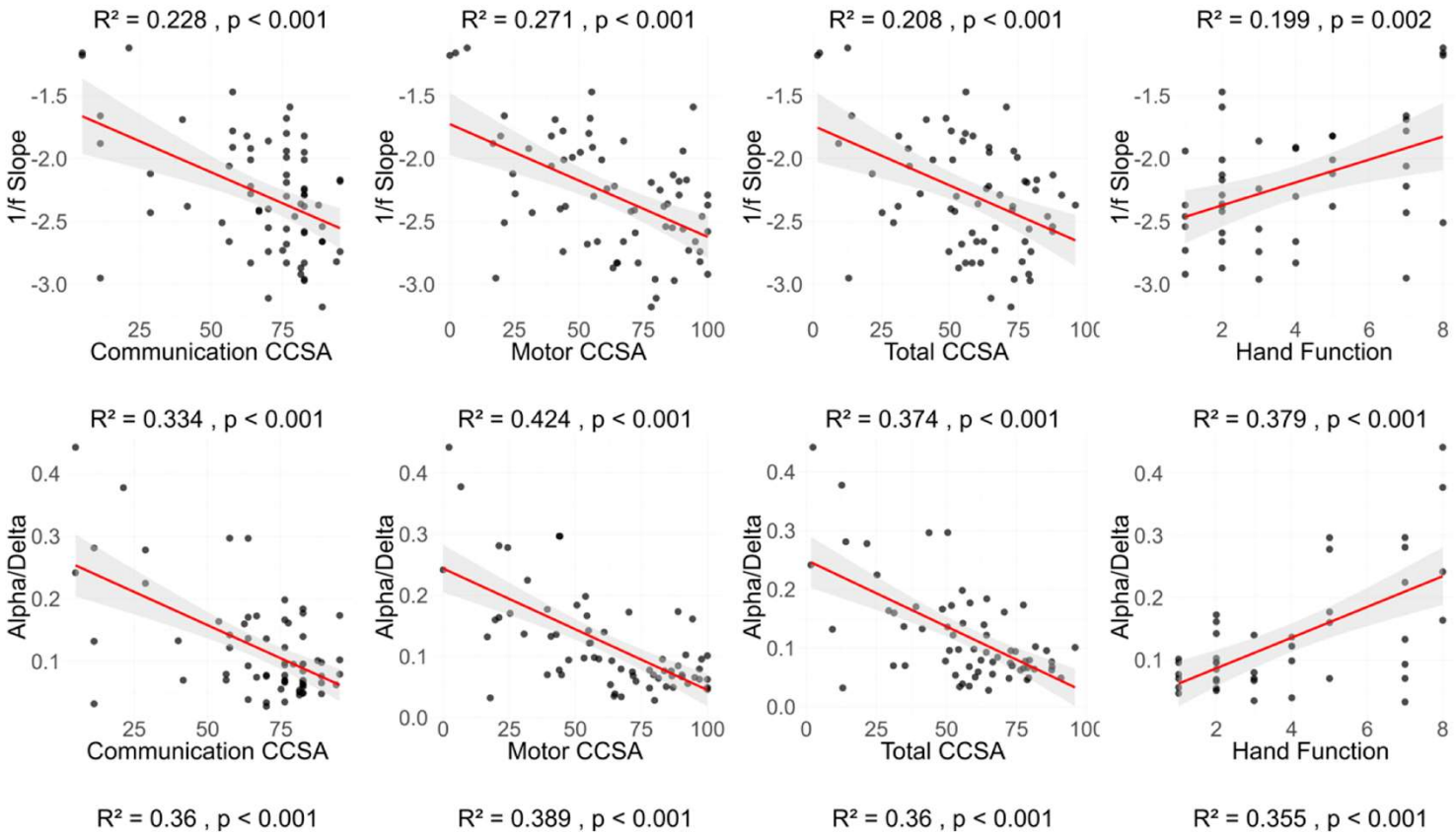
Participant exclusions and characteristics			
Total participants n = 77	**Resting**	**VEP**	**AEP**
% excluded for <1 year of age	5%	5%	5%
% excluded for Insufficient artifact-free data or absence of EP peaks	8%	34%	56%
% excluded for sleeping during EPs	-	6%	10%
% excluded for technical error with EP stimuli	-	4%	4%
Final Group, n	**67**	**39**	**19**
Age, years, median	5.8	3.4	6.3
% female	83%	82%	84%
% with seizures	77%	77%	74%
% walking with or without assistance	35%	33%	57%
% with purposeful communication or speech	17%	18%	36%

Correlations between EEG/EPs and COAs



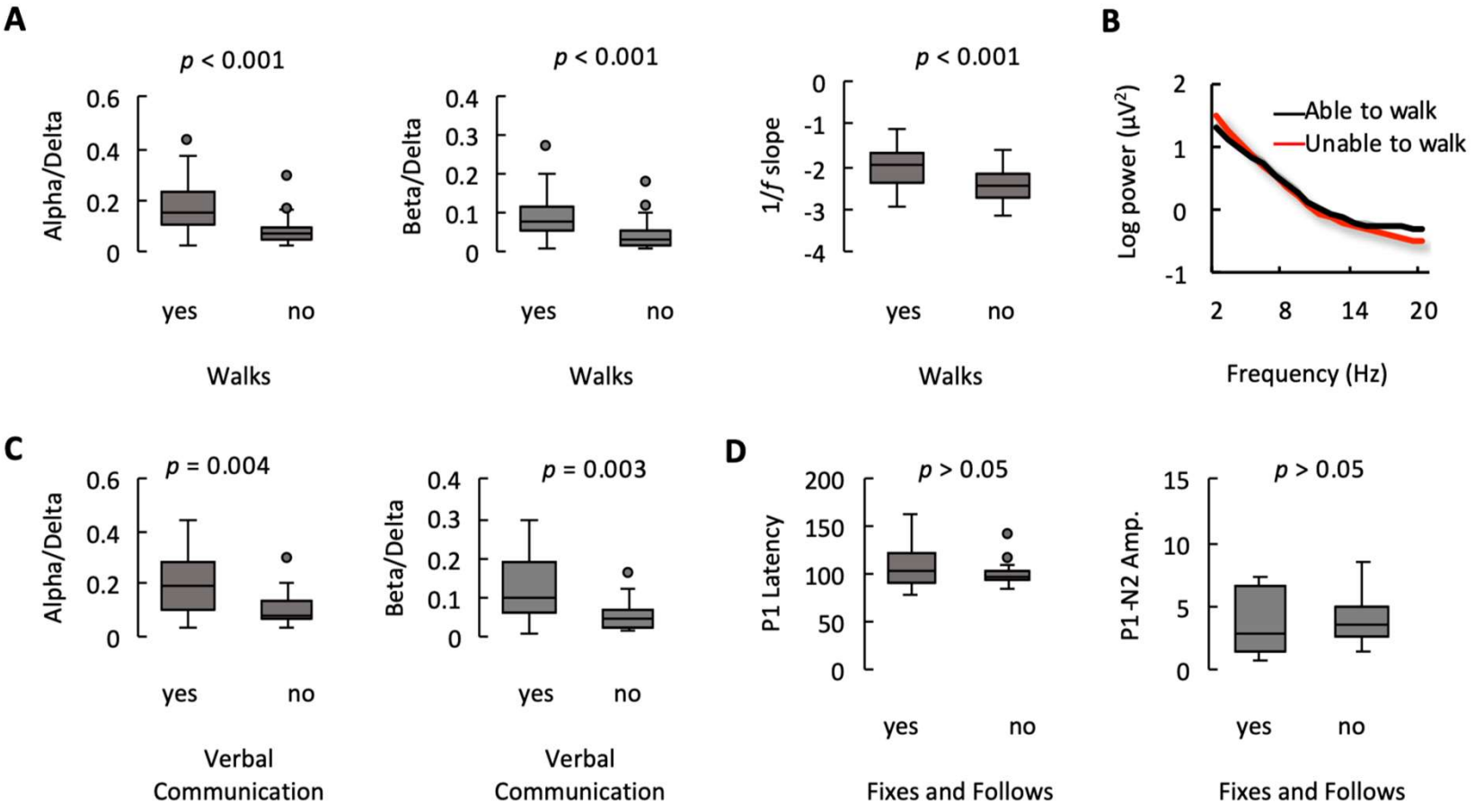
Saby et al., submitted

Correlations between EEG and COAs



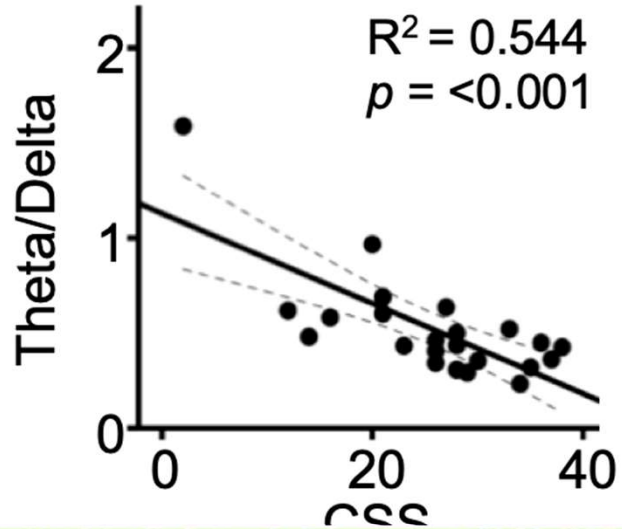
Saby et al., submitted

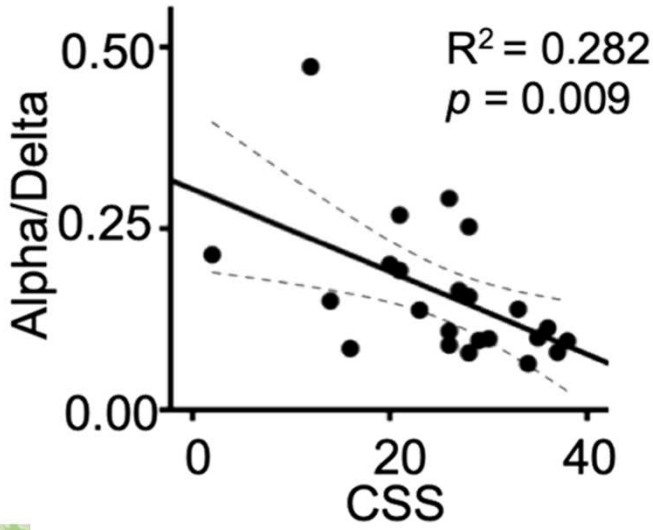
More EEG results: Core functional domains



Saby et al., submitted

Consistency between ICCRN and NHS





BRAIN COMMUNICATIONS

Electrophysiological biomarkers of brain function in CDKL5 deficiency disorder

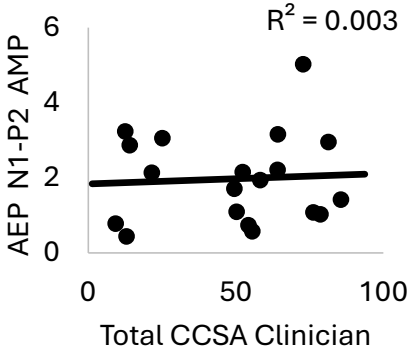
Joni N. Saby,[1,*] Patrick J. Mulcahey,[2,*] Alexis E. Zavez,[3] Sarika U. Peters,[4] Shannon M. Standridge,[5] Lindsay C. Swanson,[6] David N. Lieberman,[6] Heather E. Olson,[6] Alexandra P. Key,[7] Alan K. Percy,[8] Jeffrey L. Neul,[4] Charles A. Nelson,[9,10,11] Timothy P. L. Roberts,[1] Timothy A. Benke[12,13,14,15] and Eric D. Marsh[2,3,16]

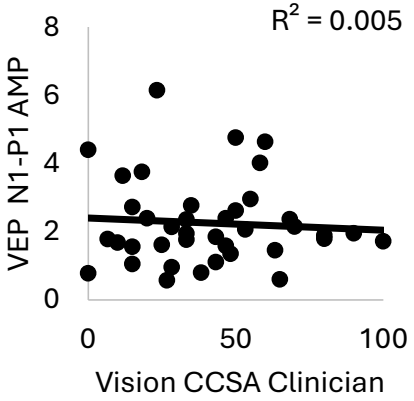
Natural History Study (**NHS**): 2017-2021

28 participants with CDD across 5 sites

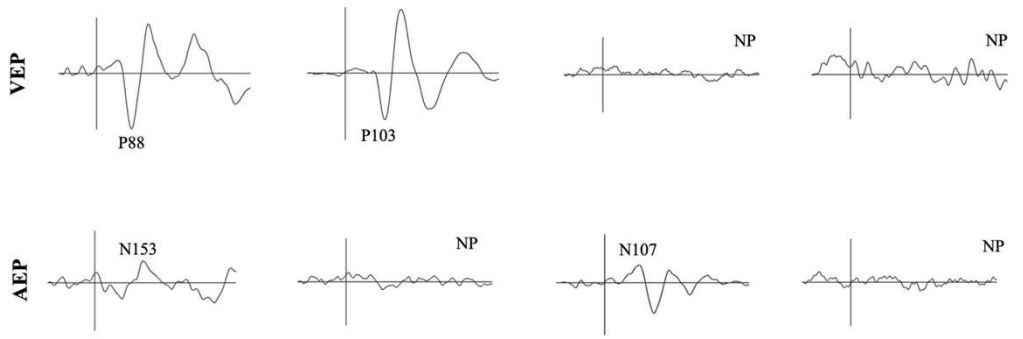
CSS = Clinical Severity Scale

VEPs and AEPs did not correlate with severity





A high % of participants also had to be excluded due to floor effects/absence of VEP and/or AEP peaks



EEG biomarkers - Summary

- EEG has good validity as a biomarker of severity for CDD
- Demonstrated reproducibility
  - Both between studies and across time
- Methodological developments will provide improved potential biomarkers for future trials
- Ultimately need to show it moves with treatment

Video: Gross motor/Hand function

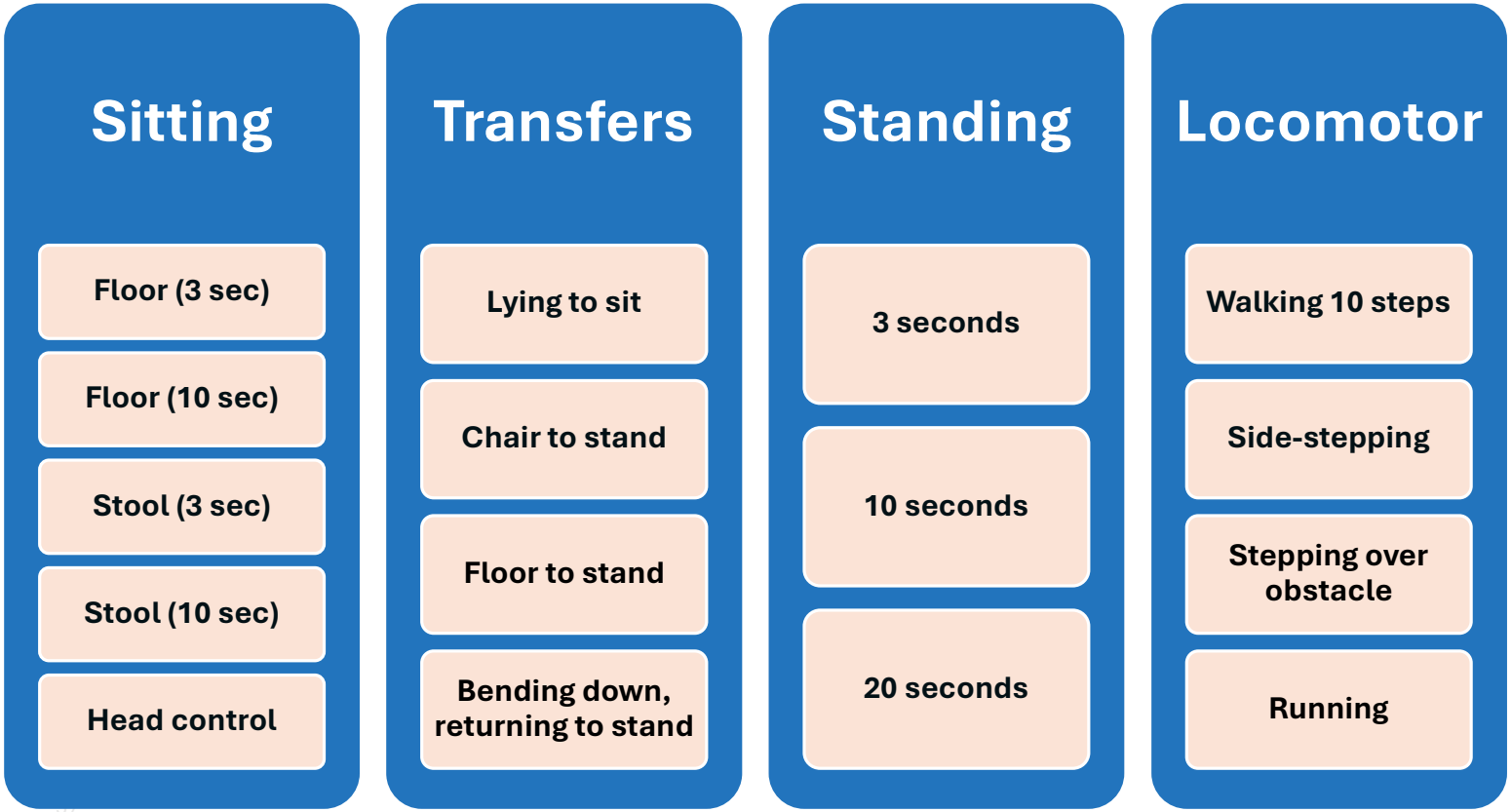
Jenny Downs/Helen Leonard/Jacinta Saldaris

ClinRO motor measures - video provided remotely by parents that is scored remotely

Administration

1. Recruit if 12/18 months or older, telephone, explain study
2. Send instructions and a link for parents to upload video clips from their phone to our server
3. Takes parents 15 to 20 minutes to collect video for the hand function measure and 30 to 40 minutes for gross motor
4. Follow up
5. Check videos and give feedback

1. Gross Motor – Complex Disability (GM-CD)



- Modification of the RSGMS
- 16 or 17 final item set – feasibility, consumer driven and data driven
- Data are centrally coded

Head control

No head raise
0

Any head raise (<5 sec)
1

Head raised >5 sec not vertical or <10 sec vertical - 2

Head raised vertical and still for ≥10 sec
3

Walking

Unable - 0

Moderate assist - 1

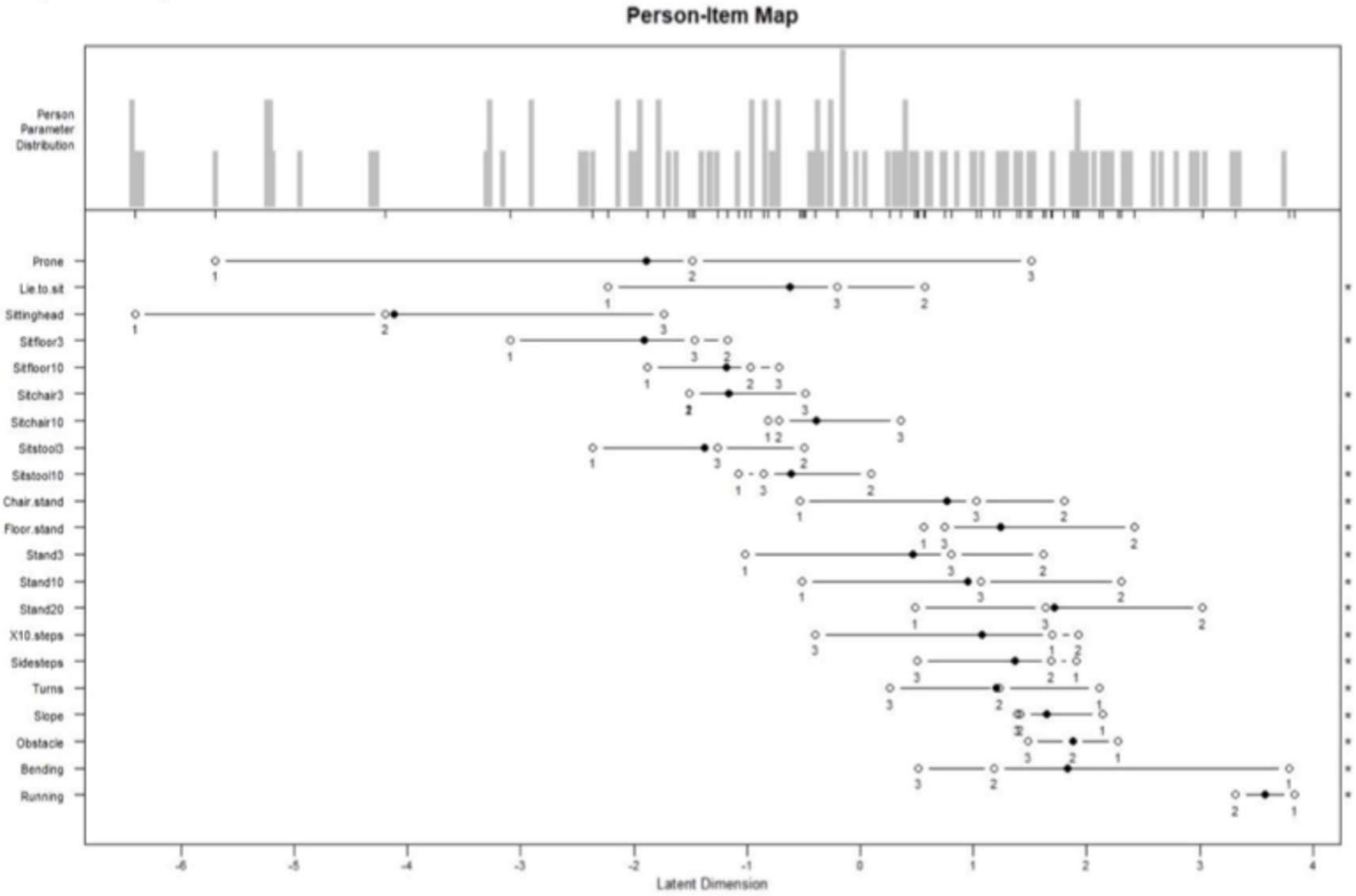
Minimal assist - 2

No assist - 3

Measurement properties ⟶ 17 item scale

Rasch Model (n=137)

- Some item redundancy
  - Several overlapping higher skill items
  - Some items dropped – now 16 or 17 items
- Some items with disordered category thresholds
  - Clinical decision to keep the levels of support for granularity



Score distribution, reliability, known groups validity

Score distribution (n=109)	
Mean (SD)	22 (14.9)
Median (range)	20 (0-48)
Skew	0.29

Rater reliability (n=50)	
Inter-rater	Kappa >0.8 for most and >0.6 for all
Intra-rater	Kappa >0.8 for all
ICC	0.98

Test-retest reliability (n=26)	
ICC	0.994
MDD	3.46 (/48)

	Category	Mean (95% CI)	P value
Biological sex	Male	16.3 (6.4,26.1)	
	Female	22.9 (20.1, 25.8)	P=0.01
Communication *	Non-verbal	18.4 (15.7, 21.1)	
	Verbal	35.4 (30.1, 40.7)	P<0.001
Hand function*	Unable to grasp objects	7.1 (2.2, 12.0)	
	Can grasp large objects	18.9 (15.9, 21.9)	
	Grasps large and small objects	32.5 (29.2, 35.9)	P<0.001

* Adjusted for age

2. Hand grasping skills – CDD-Hand

1. Observe grasping of everyday objects

	Type of grasp	Object
Power	Cylindrical	Drinking cup
		Bottle
	Palmer	Spoon or fork
	Spherical	Small ball
	Various	Favorite toys (small enough to be held)
Precision	Raking, scissors, inferior pincer, pincer, fine pincer	Pieces of food approx. 2cm across

2. Code to 1 of 8 levels

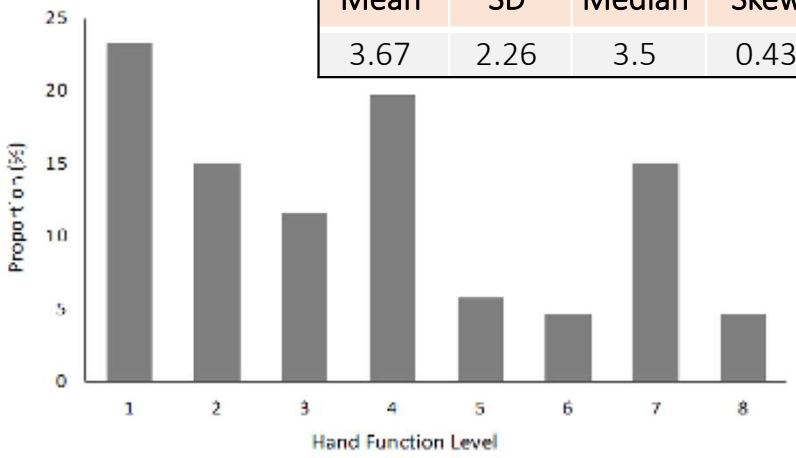
Level	Observed skill
1	No observed grasping
2	Can hold if helped to grasp
3	Can hold and pick up if helped to grasp
4	Grasps, picks up and holds
5	Raking grasp with small piece of food
6	Radial grasp with small piece of food
7	Can also transfer
8	Good hand orientation and size recognition

Small objects (e.g . small pieces of food)	**Coded as level 8** Child pre-shaping, using *radial grasp* to pick up small piece of food and transferring small toy between hands	
	Coded as level 5 Child using a *raking grasp* to pick up small piece of food	
Large objects (e.g. small toy, spoon, cup)	**Coded as level 4** grasping (spherical grasp) and holding small toy for >2s	
	Coded as level 1 Child has no ability to grasp large objects even when provided with assistance	

Measurement properties – CDD-Hand

Distribution of Scores (n=86)

Mean	SD	Median	Skew
3.67	2.26	3.5	0.43



Reliability (n=28)

Test-retest (n=28)	MDD
ICC – 0.986	0.84

Reliability (n=54)

Inter-rater reliability (2 raters)	Intra-rater reliability
K=0.90	K=0.97

Known groups validity (n=86)

- Females had higher scores than males
  - 3.94 vs 2.40, p=0.015
- Non-verbal children had lower scores than verbal
  - 3.37 vs 5.25, p=0.006
- Children able to walk had higher scores than children unable to walk
  - 5.59 vs 2.52, p<0.001

Motor video scales summary

Feasibility / acceptability	Content validity	Score distribution	Reliability			Validity				
			Person Separation	Rater	Test-retest	Factor loadings	Model fit	Divergent	Convergent	Known groups
Gross Motor – Complex Disability (GM-CD)										
+/-	✓	✓	✓	✓	✓	✓	✓		✓	✓
CDD-Hand										
+/-	+/-	✓		✓	✓					✓

Discussion points

Everyone

Discussion point: *Ongoing Projects*

Tim Benke

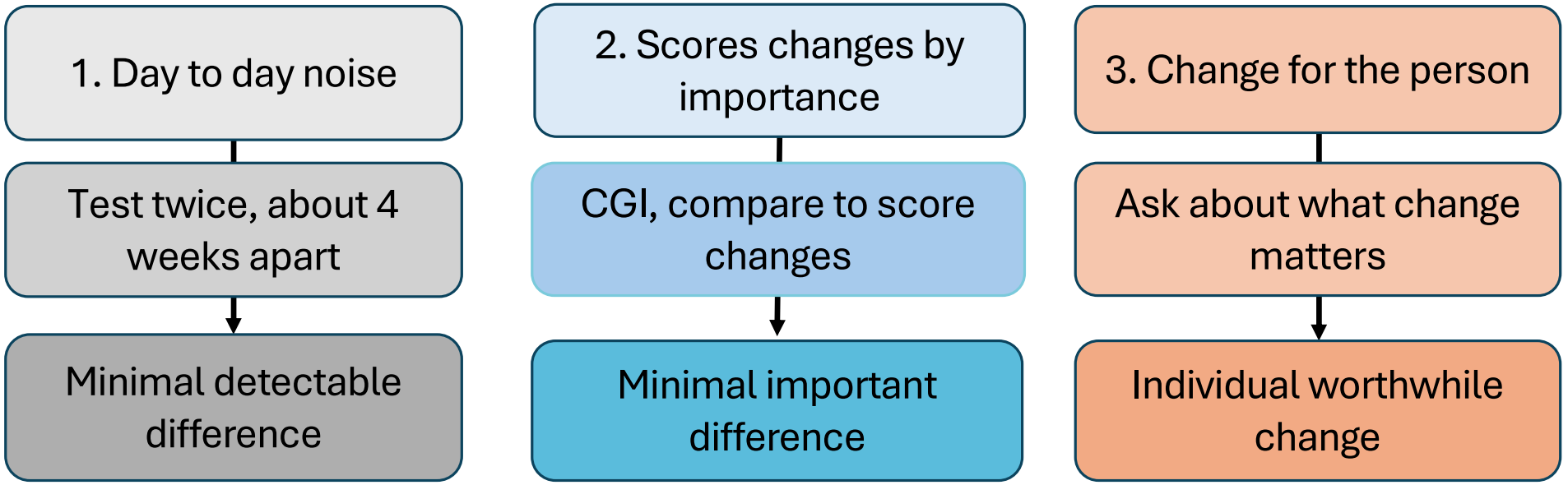
Ongoing projects

- Longitudinal stability and meaningful change
  - *See PMID: 40924387, others under construction!*
- Seizure diaries (Scott Demarest)
- Movement disorders (Bernhard Suter, Heather Olson, Tim Benke)
- Mortality in U01 and other time-limited studies (Dana Price)
- Social Determinants of Health (Lauren Mitchell, Judy Weisenberg, Raj Rajaraman, Jacinta Saldaris, Helen Leonard, Olga Novak, Sydney Panagos, Jenny Downs, Tim Benke)
- Specific anti-seizure medications (Raj Rajamaran)
- Aerodigestive (Raj Rajamaran)

Discussion points: *Measuring meaningful change, CGI, and the Global Severity Measure*

Jenny Downs

Measuring change in the Clinical Trial Readiness study

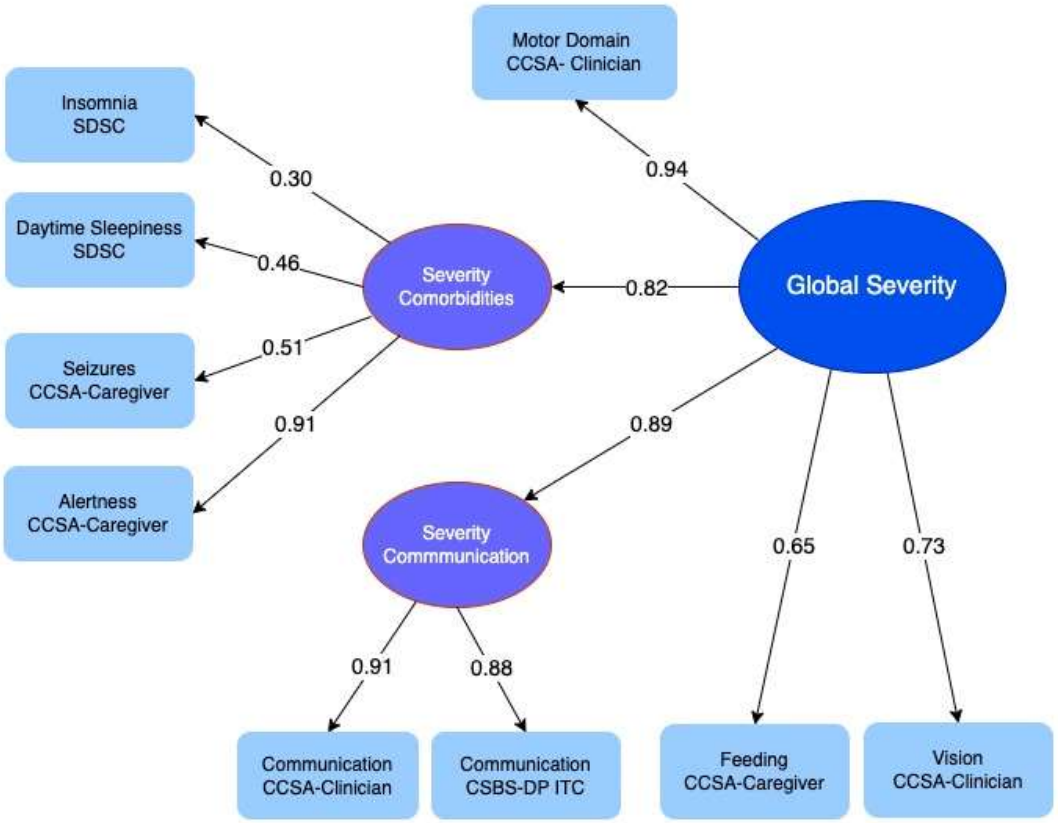


- Test-retest reliability ✓
- MDD
  - 15-20% for CCSA/sleep
  - ~10% for communication

- Clinician CGI for severity, parent CGI for domains
- Need correlation with change in score of >=0.3
  - Preliminary but not achieved

- Parent workshop and survey
- Codes for meaningful change – differences by impairment
- NEXT – map vignettes to score changes, accounting for different levels at baseline

Global severity measure

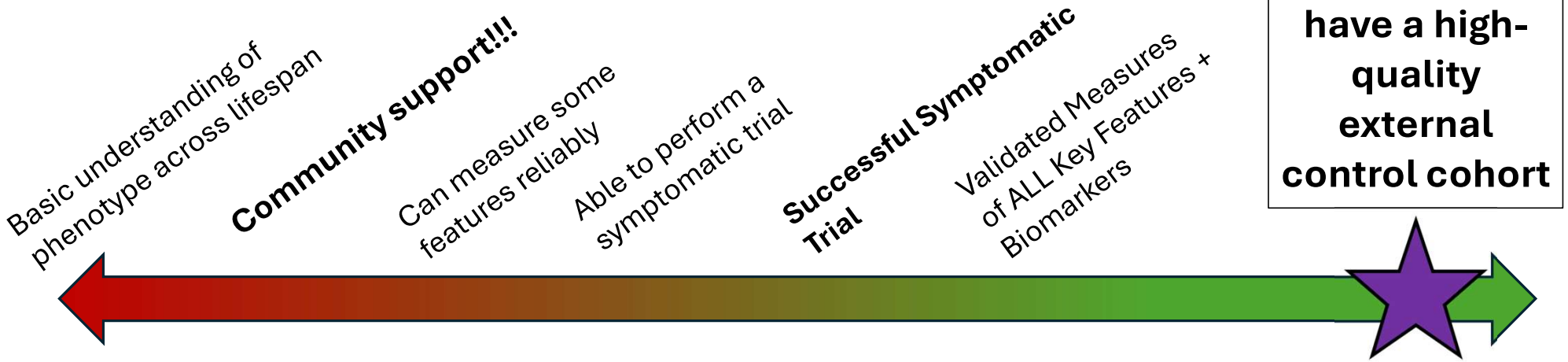


- Component domains map to complexity of CDD and priorities
- Combines multiple validated measures, each weighted to give a total score out of 100
- Good reliability and validity
- Change with time
  - Stable across 6-month periods
  - MDD - 9%
- Potential as a secondary endpoint in a clinical trial
- FDA: views favorably compared to CGI-S

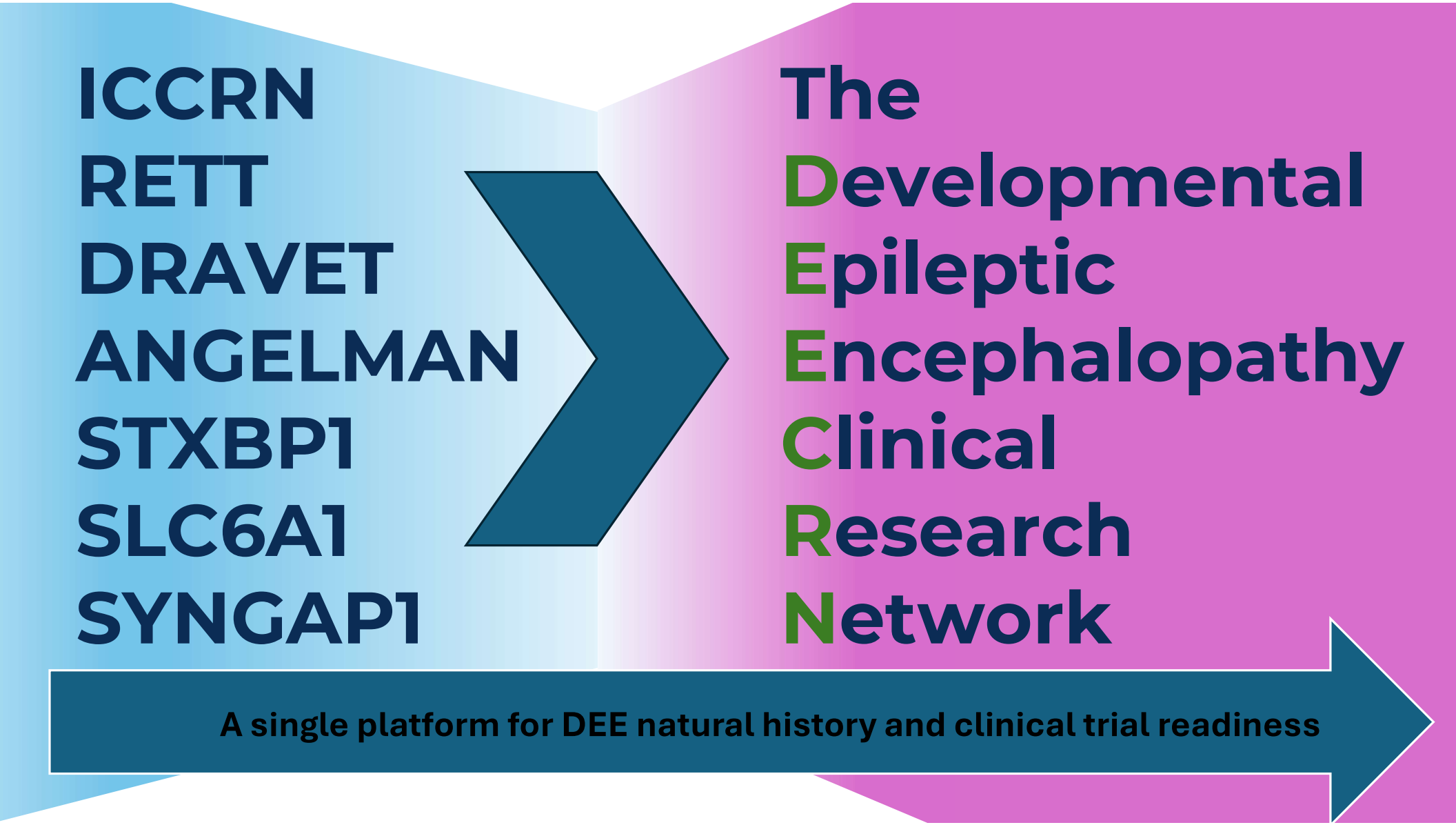
CDD is Clinical Trial Ready

- Validated Outcome Measures ☑
- Validated Biomarkers ☑
- Longitudinal Trajectory and Phenotype ☑

Understand longitudinal trajectory and have a high-quality external control cohort



The Spectrum of Trial Readiness


ICCRN
RETT
DRAVET
ANGELMAN
STXBP1
SLC6A1
SYNGAP1
The
Developmental
Epileptic
Encephalopathy
Clinical
Research
Network
A single platform for DEE natural history and clinical trial readiness

DEECRN Guiding Principles:

1: Continually delineate the natural history of all genetic DEEs including the etiologies, phenotypes, and burden of disease

2: Validate and iteratively improve a Suite of Clinical Outcome Assessments to best capture all DEE manifestations

3: Develop and maintain a clinical trial network capable of iteratively testing new therapies for DEEs as a basket, or for specific etiologies, to enable better, faster, and cheaper clinical trials

4: Ensure regulatory grade data capture and sophisticated interrogation of data to support multifaceted stakeholder goals

Want to know more about DEECRN?

Email: Vanessa Vogel-Farley
DEECRN Operations Director
vanessa@rareepilepsynetwork.org

AGAIN: Huge Thanks!

All participating families

Financial support/funding

NIH/NINDS U01NS114312

IFCR Karen Utley!!!

International Foundation for CDKL5 Research

loulou FOUNDATION
Tackling CDKL5 Deficiency

National Institute of Neurological Disorders and Stroke

ICCRN International CDKL5 Clinical Research Network

Baylor College of Medicine
Boston Children's Hospital
Children's Hospital Colorado
Children's Hospital of Philadelphia
Cleveland Clinic
NYU Langone Health
TELETHON KIDS INSTITUTE Discover. Prevent. Cure.
UCLA
Washington University in St. Louis School of Medicine

www.cdkl5researchnetwork.org

Thank you!

Lauren Mitchell: Project manager and Data Manager (Past: Sharon Pincus, Gina Vanderveen, Andi Fidell) & Jacinta Saldaris (The Kids)

Site coordinators and Staff:

- CHCO: Flor Abila, Kaitlyn Kennedy, Megan Abbott, Jen Sargent, Megan Stringfellow
- CHOP: Holly Dubbs, Erin Prange, Caroline Kessler, Dennis Flysch, Jenny Minnick
- BCH: Nancy Aly, Kathryn Mansour, Isabel Haviland, Jenna Lucash, Lindsay Swanson, William Hong, Meagan Tsou, Sophie Hurewitz
- BCM: Sorsha Dunn and Elif Dundar
- WASHU: Sydney Panagos, Olga Novak, Ali Vonderheid
- Cleveland: Xiaoming Zhang
- UCLA: Angela Martinez
- NYU: Audrey Brown, Julianna Laze, Sarah Bacher
- The Kids: Jacinta Saldaris