Manuscript Details

Manuscript number	PNU_2018_746_R1
Title	Severity Assessment in CDKL5 Deficiency Disorder
Article type	Research Paper

Abstract

Background: Pathological mutations in cyclin-dependent kinase-like 5 cause CDKL5 deficiency disorder (CDD), a genetic syndrome associated with severe epilepsy, cognitive, motor, visual and autonomic disturbances. CDD is a relatively common genetic cause of early-life epilepsy. A specific severity assessment is lacking, required to monitor clinical course, define the natural history and for clinical trial readiness. Methods: A severity assessment was developed based on clinical and research experience from the International Foundation for CDKL5 Research Centers of Excellence consortium and the NIH Rett and Rett-related disorders Natural History Study consortium. An initial draft severity assessment was presented and reviewed at the annual CDKL5 Forum meeting (Boston, 2017). Subsequently it was iterated through four cycles of a modified Delphi process by a group of clinicians, researchers, industry, patient advisory groups and parents familiar with this disorder until consensus was achieved. The revised version of the severity assessment was presented for review, comment and piloting to families at the International Foundation for CDKL5 Research sponsored family meeting (Colorado, 2018). Final revisions were based on this additional input. Results: The final severity assessment comprised 51 items that comprehensively describe domains of epilepsy, motor, cognition, behavior, vision, speech and autonomic function. Parental ratings of therapy effectiveness, child and family functioning are also included. Conclusions: A severity assessment was rapidly developed with input from multiple stake-holders. Refinement through ongoing validation is required for future clinical trials. The consensus methods employed for the development of the severity assessment may be applicable to similar rare disorders.

Keywords	CDKL5; rare disorder; severity assessment; epilepsy; cortical visual impairment; intellectual disability
Manuscript region of origin	North America

Corresponding Author	Timothy Benke
Order of Authors	Scott Demarest, Elia Pestana Knight, Heather Olson, Jenny Downs, Eric Marsh, Walter Kaufmann, Carol-Anne Partridge, Helen Leonard, Femida Gwadry-Sridhar, Katheryn Frame, Helen Cross, Richard Chin, Sumit Parikh, Axel Panzer, Karen Utley, Amanda Jaksha, Sam Amin, Omar Khwaja, Orrin Devinsky, Jeffrey Neul, Alan Percy, Timothy Benke

Submission Files Included in this PDF

File Name [File Type]

PedsNeuroCover3_2019.pdf [Cover Letter]

Response to Reviewers.docx [Response to Reviewers]

Severity Assessment in CDKL5 Deficiency Disorder 2.2x.docx [Manuscript File]

Figure 1 Methods flow diagram for SA.pdf [Figure]

Figure 2 cdkl5 SA.pdf [Figure]

To view all the submission files, including those not included in the PDF, click on the manuscript title on your EVISE Homepage, then click 'Download zip file'.

Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
No data was used for the research described in the article

University of Colorado Denver
School of Medicine

Tim Benke, MD, PhD
Associate Professor
Departments of Pediatrics,
Neurology, Otolaryngology
and Pharmacology
Mail Stop 8102
12800 E. 19th Ave,
Aurora, CO 80045
303-724-3568
tim.benke@ucdenver.edu

March 18, 2019

Dear Dr. Roach,

Please find a copy of our revised manuscript titled “Severity Assessment in CDKL5 Deficiency Disorder" by Demarest et al. attached to this upload. We also provide details of how we have addressed the critiques by you and the reviewers.

We appreciate the time and effort of you and the reviewers to provide us with feedback. We have made adjustments that I hope address all concerns and improve the manuscript. I would be happy to add supplemental file/information to the Delphi process at your direction if you feel the modifications I made to the text are not sufficient. I was hoping to strike a balance.

Thank you for your consideration and we look forward to hearing from you.

Sincerely yours,

BENKE

We appreciate the constructive criticisms of the reviewers and have modified the text appropriately.

Reviewing Editor

I appreciate reviewers' request for more information about your modified Delphi process, but I am not certain that I fully agree with it. It strikes me that all of this added detail might detract from the article's readability and clarity. What I might suggest would be to segregate this information into a supplementary file which would be available to anyone trying to drill deeply into your methods yet not muddy the water for everyone else.

We have been able to address Reviewer 1's concerns in a succinct fashion by minor modifications of text in the methods and discussion.

Reviewer 1

Demarest et al present the development of an assessment tool for CDKL5 epileptic encephalopathy. The strengths of this study are the involvement of multiple stakeholders, including families, in the development of the assessment tool. This is an emerging, vital, component for research of rare diseases that often require disease individualized assessments, with the challenge of developing an instrument in a small population. There are a number of weaknesses of this study that include lack of detail on the evidence based review that guided the initial formation of the assessment tool, a significant lack of detail in the Delphi process itself, and no attempt to test the assessment to understand if it is useful or valid. This will be vital, if the investigators indeed wish to use this instrument in clinical trials. At present, it is an interesting questionnaire that could help standardize a history and physical, but does not comprise a valid instrument.

Please provide the literature that was used to form the basis of the initial items of the instrument. More detail is required on the Delphi process. What percent of responses were needed to reach consensus? What items never reached consensus? How many items were contained in the second and subsequent rounds of the Delphi? What evidence based material was provided to participants to help guide their decision, and what strength of evidence were each item? A detailed description is needed of the discussion in reaching consensus.

We have added additional details to the text. As noted in the methods, this was not conducted as a survey. Participants were provided with the prior scales for other disorders, literature used and their own experience to guide the survey. The instrument began with 24 items and converged by the 3rd and 4th rounds to ~50 items.

No attempt was made to test the utility of the instrument. Only 2 families trialed the instrument, it seems just for the amount of time needed to administer. What investigations were performed to look at consistency and validity of the measure? A detailed investigation of intraobserver validity, validity over time (i.e. administration separated by 30 days to assess differences), item dependency (where two items are so correlated that they measure the same) and where possible, comparison to other gold standard instruments.

As noted in the discussion, this scale has not yet been validated. We have noted the importance of this next step. We have outlined the necessary approach detailed by the reviewer to address these issues.

Reviewer 2

The authors of this submission report the results of a multiple institution effort to devise a severity assessment tool for management and therapeutic intervention in the CDKL5 Deficiency disorder, utilizing a modified Delphi process. The tool was then presented at an International Foundation for CDKL5 family meeting for review and piloting and finally revision. The group stayed true to the Delphi process with the exception of not using an initial survey, but elicited feedback and created a consensus among a constant group of clinicians , researchers, industry representatives and patient advisory groups/parents involved in the disease.

The tool was developed with the concept that it must be utilized across a broad range of ages, and that the examination component would be possible in the average single visit appointment time of a pediatric neurologist. The tool is an important start for CDKL5 disease management for all the above parties.

The manuscript contains a number of grammatical errors , and abbreviations that are not intuitive across all cultures of the people likely to be reading this paper. Some are common to European readers and others to US readers, but certainly all should be referenced appropriately.

We have proofed again for grammatical errors and utilized tools available for this within Word. We have removed infrequent abbreviations to improve readability.

The authors need to point out the availability of this instrument on-line and free of charge in the future if it is to be accepted in practice.

The CDD-SA is freely available for general use. We have added this statement to the Discussion.

Severity Assessment in CDKL5 Deficiency Disorder

Scott Demarest[1,2], Elia M. Pestana-Knight[3,4], Heather E. Olson[5], Jenny Downs[6,7], Eric D. Marsh[8], Walter E. Kaufmann[9], Carol-Anne Partridge[10], Helen Leonard[7], Femida Gwadry-Sridhar[11], Katheryn Elibri Frame[12], J. Helen Cross[13], Richard F. M. Chin[14], Sumit Parikh[4], Axel Panzer[15], Judith Weisenberg[16], Karen Utley[17], Amanda Jaksha[17], Sam Amin[18], Omar Khwaja[19], Orrin Devinsky[20], Jeffery L. Neul[21], Alan K. Percy[22], and *Tim A. Benke[1,2,3,23,24]

Author Affiliations:

[1]Children's Hospital Colorado and University of Colorado School of Medicine Departments of Pediatrics[2], Pharmacology[3], Neurology[23] and Otolaryngology[24], Aurora, CO, USA

[3]Cleveland Clinic, Neurological Institute and Epilepsy Center[4], Cleveland, OH, USA

[5]Department of Neurology, Division of Epilepsy and Clinical Neurophysiology, Boston Children's Hospital Boston, MA USA

[6]Telethon Kids Institute, The University of Western Australia, Perth, Western Australia, Australia

[7]School of Physiotherapy and Exercise Science, Curtin University, Perth, Western Australia, Australia

[8]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA USA and Departments of Neurology and Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA USA

[9]M.I.N.D. Institute, Department of Neurology, University of California Davis Health System, Sacramento, CA, USA and Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA

[10]CDKL5 UK, Somerset, UK

[11]Department of Computer Science, University of Western Ontario, and Pulse Infoframe, London, Ontario, Canada.

[12]CDKL5 Research Collaborative, Dexter, MI, USA

[13]UCL Great Ormond Street Institute of Child Health & NIHR GOSH BRC, London, UK

[14]University of Edinburgh and Royal Hospital for Sick Children, Edinburgh, UK

[15]DRK Westend Clinic Berlin, Berlin, Germany

[16]Neurology, Division of Pediatric Neurology, Epilepsy Section, Washington University School of Medicine, St. Louis Children's Hospital, St Louis, MO, USA

[17]International Foundation for CDKL5 Research, Wadwsorth, OH, USA

[18]University of Bristol, UK

[19]Roche Innovation Center Basel, Roche Pharmaceutical Research and Early Development NORD, Basel, Switzerland

[20]Department of Neurology, New York University, New York, NY, USA.

[21]Vanderbilt Kennedy Center, Vanderbilt University Medical Center, TN, USA

[22]University of Alabama at Birmingham, Pediatrics, Neurology, Neurobiology, Genetics, and Psychology, Birmingham, AL, USA

*Corresponding author. Email: tim.benke@ucdenver.edu

Abstract

Background: Pathological mutations in cyclin-dependent kinase-like 5 cause CDKL5 deficiency disorder (CDD), a genetic syndrome associated with severe epilepsy, cognitive, motor, visual and autonomic disturbances. CDD is a relatively common genetic cause of early-life epilepsy. A specific severity assessment is lacking, required to monitor clinical course, define the natural history and for clinical trial readiness.

Methods: A severity assessment was developed based on clinical and research experience from the International Foundation for CDKL5 Research Centers of Excellence consortium and the NIH Rett and Rett-related disorders Natural History Study consortium. An initial draft severity assessment was presented and reviewed at the annual CDKL5 Forum meeting (Boston, 2017). Subsequently it was iterated through four cycles of a modified Delphi process by a group of clinicians, researchers, industry, patient advisory groups and parents familiar with this disorder until consensus was achieved. The revised version of the severity assessment was presented for review, comment and piloting to families at the International Foundation for CDKL5 Research sponsored family meeting (Colorado, 2018). Final revisions were based on this additional input.

Results: The final severity assessment comprised 51 items that comprehensively describe domains of epilepsy, motor, cognition, behavior, vision, speech and autonomic function. Parental ratings of therapy effectiveness, child and family functioning are also included.

Conclusions: A severity assessment was rapidly developed with input from multiple stake-holders. Refinement through ongoing validation is required for future clinical trials. The consensus methods employed for the development of the severity assessment may be applicable to similar rare disorders.

Key words: CDKL5; rare disorder; severity assessment; epilepsy; cortical visual impairment; intellectual disability.

Introduction

Pathological mutations in cyclin-dependent kinase-like 5 (*CDKL5*)[1-5] result in CDKL5 Deficiency Disorder Disorder (CDD, OMIM 300203, 300672, also referred to as CDKL5 Disorder, CDKL5 Syndrome and CDKL5). Previously considered a "Rett variant", this unique disorder [6, 7], has overlapping features with many of the developmental encephalopathies, disorders defined by genetic or presumed genetic etiology, severe seizures and intellectual/cognitive disability[8]. Incidence varies from ~1:40,000 -60,000[9-11]; approximately one-half to one-third as common as Dravet syndrome (1:20,000-50,000)[12, 13] or Rett syndrome (1:10,000 female births)[14]. Thus, CDD is a diagnostic consideration in young children with severe, early-onset epilepsy.

CDD is associated with high rates of severe epilepsy as well as cognitive, motor, visual and autonomic disturbances [4, 15-22]. Although surveys have reported the characteristics and frequency of CDD features[6], no clinical severity assessment has integrated CDD's clinical manifestations. Assessments for Rett Syndrome[23-26], FOXG1[27], tuberous sclerosis[28], and other developmental epileptic encephalopathies[29, 30] incorporate many CDD features, but none provide a focused nor comprehensive assessment of CDD patients. A specific severity CDD assessment targeting all clinical features is lacking and needed for clinicians to evaluate care, define natural history, inform specialist and therapeutic referrals, and with appropriate validation, to assess the outcomes of interventions in clinical trials. Given the recent initiation of human therapeutic trials (CBD[31], Ataluren **ClinicalTrials.gov: NCT02758626**, ganaxalone **ClinicalTrials.gov: NCT03572933**, TAK-935 **ClinicalTrials.gov: NCT03694275**) and the reversibility of symptoms in CDD animal models[32], a validated assessment is urgently needed for CDD clinical trials.

We established a uniform clinical approach to patients as part of the International Foundation for CDKL5 research (IFCR) Centers of Excellence (COE) at three sites (Children's Hospital Colorado/University of Colorado School of Medicine, Boston Children's Hospital and Cleveland Clinic) and sites associated with

the NIH-funded Rett and Rett-related disorders Natural History Study (NHS) (U54 HD061222; **ClinicalTrials.gov: NCT00299312/NCT02738281**). Each site collects clinical or research data on CDD patients. Application of scales and assessments developed for Rett syndrome were not adequate to capture unique features of CDD. The CDD Severity Assessment (CDD-SA) intends to capture unique features of CDD, such as epilepsy severity, cognitive, motor and visual impairment and specific aspects of movement disorder. This assessment needs to be comprehensive but efficient to administer. It must capture the distribution of abilities of CDD patients without saturating. Given the multiple stakeholders with overlapping goals for this type of assessment, we supplemented our clinical research infrastructure by recruiting into our group an international and multi-disciplinary panel of clinicians, researchers and industry professionals outside of the COE and NHS along with parents of patients directly involved in CDD patient advocacy groups. This collaboration provided input to develop and refine the CDD-SA as described here.

Methods

Clinically obtained or research-subject data available under IRB approvals (COMIRB 13-2020, 15-2332, Cleveland Clinic IRB 14-478, need Boston COE IRB P00016602 and UAB NHS parent IRB F150518001) of 111 unique patients with CDD were reviewed. Based on these data, review of available scales and literature noted above, an initial CDD-SA was developed by the principal investigator (PI: TAB) and presented at the annual CDKL5 Forum meeting (Boston, November 2017). This was followed by an open forum allowing input from stakeholders for feedback and queries. Revisions were made based on this input. We questioned whether the CDD-SA should be for clinical or research purposes, the potential domains to assess, the optimal type(s) of response scale to use, and the time-frame of evaluation that is assessed (e.g., birth to present, prior 6 months to present, last month to present and last week to present). Domains considered to be relevant included: overall severity of disorder, epilepsy, cognition, motor

function, vision, autonomic disturbances and movement disorders. Response scale that were considered included: 5-point scales (evaluating frequency or severity of a feature), Likert scales (evaluating the appropriateness of a statement) and global impressions of severity or change (caregiver- and clinician global impression scales). We agreed that a clinical component provided by an examination was needed to complement and inform caregiver reported observations, leading to parent and clinician sections of the CDD-SA.

The CDD-SA was then iteratively evaluated through four cycles of anonymous modified Delphi[33] comment and consensus by an international panel of clinicians, researchers, industry, patient advisory groups and parents familiar with CDD (Figure 1). The group grew in numbers from those initially present at the Boston LouLou Foundation CDKL5 Forum to the full CDD-SA advisory group (SAAG, Table 1). Each CDD-SA version was emailed to the group and returned to the PI with comments and suggested changes. The number of questions in each domain, the specific items in each domain and the wording of items were debated and modified to accurately reflect experiences of each group of contributors. The number of items began at 24 and converged by the 3rd round to approximately 50 items, similar to the final. The feasibility of applying the CDD-SA in a clinical setting led to a reduction of items in each domain. The PI reviewed all comments, developed an independently ascertained best consensus from suggested changes, revised the CDD-SA and returned this to the review group with prior anonymous comments to provide historical background from the previous CDD-SA version. This allowed the group to understand the rationale for emerging consensus and provide commentary as to whether the emerging consensus was tracking with the intended changes to the CDD-SA. While this was not a survey-based approach like a traditional Delphi process the overall method of eliciting feedback and creating consensus was similar. The number of participants remained consistent throughout the review period, with no drop outs, providing a representative stakeholder input. The penultimate CDD-SA version was presented by the PI at the IFCR annual meeting to parents of over 100 CDD patients (Denver, June 2018) for review, comment

and trial. All families present were provided access to the CDD-SA and comments were solicited and received for a duration of four weeks after the conference. Two families (whose children were not managed by the PI) agreed to trial the CDD-SA at the meeting; the time to administer the CDD-SA was measured and collected. The final revision of the CDD-SA was based on this additional input to result in the current CDD-SA (Figure 2). There was full consensus by SAAG members on the final CDD-SA.

Results

After multiple revisions by the SAAG, the domains selected were epilepsy, cognition and motor, vision and autonomic function. Movement disorders were included within the motor domain. Clinical examination components were separated from the parent-report section within the cognition, motor, vision, and autonomic domains. This allowed a combination of parent or caregiver-report and a clinician completed portion based on physical exam findings. Parental components would be completed prior to the clinical examination; the time to complete this component has not yet been captured. In a pilot clinical examination, the parent portion was reviewed and the clinical portion was completed in 30 minutes by each of the two volunteer families.

Use of a global impression of severity[24] was rejected by the SAAG because these impression scales may rate self (caregiver)-described and patient-specific features that limit comparisons between patients. Thus the clinical value of a global impression of severity may not translate to research settings and could be a limitation in that context. The 5-point scale (0=normal, 5=most severe), similar to that used in the Rett syndrome Motor-Behavioral Assessment (MBA) [25] was selected, with higher scores more severe. Likert scales were added, as a compromise to deletion of the global impressions scale, for ratings of overall child improvement and parent/caregiver resilience and adaptability (-5=worse, 0 = no change, 5=best possible) and evaluation of therapies (-5=worse, 0 = no change, 5=best possible).

The SAAG determined that the CDD-SA evaluation time-frame should reflect developmental and longitudinal changes[20]. Use of the birth-to-present questions were limited since they could reflect ceiling effects or static assessments that would be insensitive to change. Month-to-present time-frames were considered most likely to reflect accurate changes, though week-to-present time-frames could be substituted if a clinical trial required frequent assessments. Since clinical assessments not part of a clinical trial may occur at 6-monthly intervals, 6-month to present time-frames were also included.

The wording of the items was simplified during the iterations substantially, especially in the epilepsy domain given the complexities of classifying seizures. CDD is associated with multiple seizure types, including prolonged and atypical aura, epileptic spasms, tonic, tonic-clonic, myoclonic and atypical absence [18, 19, 22, 34-36]. Further, a single seizure may involve multiple types that evolve, while other seizures can be challenging to characterize even by experts using video EEG [37]. This feature of epilepsy associated with CDD makes traditional seizure counting difficult for parents and caregivers [38, 39]. Rather, estimates of frequency and impact on function were agreed upon instead. While this approach substitutes one subjective assessment for another, it becomes more patient-centered.

The clinical portion was based on features typically evaluated during an exam by a pediatric neurologist. However, certain CDD-SA components would likely add time to the routine visit, especially if that clinical visit includes a discussion of clinical decision making. Regardless of the country and practice considerations, the CDD-SA had to provide relevant data that could be assimilated and utilized at a clinical visit. The final domains and details of the exam were considered recommendations: clinicians would tailor their approach such that not every item within their usual assessment would necessarily be included for all visits or all patients, although the items seek to limit clinician-to-clinician variability. It can be challenging to assess the breadth of features and the functional impact of movement disorders within a clinical visit. Also, any clinical examination is a snap-shot in time, and may not assess some areas captured for which extended observation by a parent or caregiver may be more informative. There are similar

challenges when assessing cognition and vision in CDD patients who are often non-verbal and have some degree of visual impairment. Cognition assessment is limited by both exam time and CDD features to assessing choice and visual attention in the CDD-SA.

In summary (Table 2 and Figure 2), the final CDD-SA comprised 4 domains: 1) Epilepsy, 2) Motor, 3) Cognition, Behavior and Vision and 4) Autonomic, that are nearly equally weighted with similar maximum scores (69, 65, 65 and 44, respectively) on items that mostly were scored on a 0 to 5 range. Impressions of overall improvement, parent/caregiver resiliency and therapy utility were each given a -5 to 5 Likert scale. An optional part of the CDD-SA was medical decision making. While no points were assigned to each intervention, the goal was to provide a formulaic framework to track the impact of these when the CDD-SA is used in a primarily clinical setting. Secondary scoring of data to reflect impact could be developed based on features such as patient discomfort and invasiveness, financial impact, impact to parent/caregivers, etc.

Discussion and Conclusions

Using a modified Delphi process, we developed a new clinically relevant and easily administered severity assessment (SA) for CDD (CDD-SA). With on-going natural history studies such as the NIH-funded NHS and current and planned drug trials specifically for patients with CDD, our CDD-SA offers the ability capture aspects of this disorder that may change with time or in response to interventions. In the first instance, we have provided some evidence for its content validity, basing the CDD-SA on available literature, the clinical and research experience of an international panel of experts and the lived experience of our parent participants. We achieved a consensus across a broad spectrum of international clinicians from multiple specialties and subspecialties, parents, lay organizations and industry professionals to develop this CDD-SA .

A limitation of the process was the lack of a framework with an objective 'gold-standard' to validate our CDD-SA. Further, both the stakeholders and the PI could not reliably determine the relative value of specific recommendations, nor the validity of the scale to measure the feature of interest. Bias by the PI in adjudicating disagreements and alternative views could be an inherent limit of this process but was countered by extensive expertise of the investigators and the lived experiences of families in the consultation process. The SAAG input helped ensure the comprehensive and disease appropriate nature of the CDD-SA and it is unlikely that the primary domains will need major alterations in the future. The SAAG-approved SA is being applied in CDD Centers of Excellence and can be applied in other clinical and research settings. This will provide the basis for future validation that will include some refinement of necessary items and language. In addition, qualitative data is needed to validate parental interpretations of questions and refine future versions in order to determine the sensitivity of the CDD-SA. A quantitative dataset with a large sample size will be necessary to determine change with interventions, evaluate interrater reliability, factor analyses, stability and responsiveness over time.

We propose that our clinical assessment will have immediate utility with clinicians who see children with CDD. The CDD-SA is freely available for general use. This methodology could be applied to the development of clinical assessments for other rare genetic disorders and the framework could potentially serve as an early foundation to other constituent organizations. Key aspects that allowed this to happen included an initial framework (COE and NHS) that standardized the identification of clinical features relevant to CDD. Next, those that were outside of the COE and NHS were included in the process. The support of patient advocacy groups and associated parents/caregivers provided mission-critical context. Finally, a willingness to collaborate by the SAAG despite many other commitments and time constraints allowed the process to move forward.

Acknowledgements:

We sincerely thank all of the patients and families that have participated in this research.

Scott Demarest: NIH/NINDS NSADA K12 (1K12NS089417-01), Children's Hospital Colorado Research Institute and the International Foundation for CDKL5 Research

Elia M. Pestana Knight: nothing to declare.

Jenny Downs: International Foundation for CDKL5 Research, NHMRC #1103745

Heather Olson: International Foundation for CDKL5 Research, NIH/NINDS K23 NS107646-01

Eric D. Marsh: NIH U54 HD061222

Walter E. Kaufmann: International Foundation for CDKL5 Research

Carol-Anne Partridge: nothing to declare

Helen Leonard: NHMRC Senior Research Fellowship #1103741, International Foundation for CDKL5 Research

Femida Gwadry-Sridhar: nothing to declare

Katheryn Elibri Frame: nothing to declare

J. Helen Cross: nothing to declare

Richard F. M. Chin: nothing to declare

Sumit Parikh: International Foundation for CDKL5 Research

Axel Panzer: nothing to declare

Judith Weisenberg: International Foundation for CDKL5 Research

Karen Utley: nothing to declare

Amanda Jaksha: nothing to declare

Sam Amin: nothing to declare.

Omar Khwaja: nothing to declare

Orin Devinsky: nothing to declare

Jeffery L. Neul: NIH U54 HD061222

Alan K. Percy: NIH U54 HD061222; Rett Syndrome Research Trust

Tim A. Benke: International Foundation for CDKL5 Research, Loulou Foundation, NIH U54 HD061222, Children's Hospital Colorado Foundation Ponzio Family Chair in Neurology Research

Declaration of interest:

Scott Demarest: Consulting for Upsher-Smith and BioMarin. All remuneration has been made to his department.

Elia M. Pestana Knight: None

Jenny Downs: Consultancy for Avexis, Anavex, GW and Marinus. Any remuneration has been made to her department.

Heather Olson: None

Eric D. Marsh: Funding from the NIH, Rettsyndrome.org, and Rett Syndrome Research Trust, Site PI on studies from GW pharma, Zogenix Pharma, Marinus pharma, consultant to Stoke therapeutics.

Walter E. Kaufmann: None

Carol-Anne Partridge: None

Helen Leonard: None

Femida Gwadry-Sridhar: None

Katheryn Elibri Frame: None

J. Helen Cross: J Helen Cross has participated as a clinical investigator for Zogenix, GW Pharma, Marinius Pharmaceuticals and Vitaflo. She has been a member of advisory boards and speaker for Eisai, GW Pharma, Nutricia and Zogenix. All remuneration has been made to her department.

Richard F. M. Chin: None

Sumit Parikh: None

Axel Panzer: None

Judith Weisenberg: None

Karen Utley: None

Amanda Jaksha: None

Sam Amin: None.

Omar Khwaja: None

Orin Devinsky: Consultancy/advisory: Privateer Holdings/Tilray, Egg Rock/Papa & Barkley, Receptor Life Sciences, Empatica, Tevard, Engage, Rettco, Pairnomix/Q-state, Zogenix and GW Pharmaceuticals.

Jeffery L. Neul: Funding from the NIH, Consultancy with Acadia, AveXis, Biohaven, GW Pharmaceuticals, Neuren, Newron, Takeda, Teva

Alan K. Percy: Consultancy for Anavex, AveXIs, and GW Pharmaceuticals; Clinical Trial with Newron Pharmaceuticals

Tim A. Benke: Consultancy for AveXis, Ovid, Takeda and Marinus. All remuneration has been made to his department.

Table 1: CDD Severity Assessment Advisory Group (SAAG). Affiliations for non-authors noted.

Sam Amin	Helen Leonard
Richard Chin	Eric Marsh
J Helen Cross	Lorraine Masuoka (Marinus)
Scott Demarest	Jeff Neul
Orrin Devinsky	Heather Olson
Jenny Downs	Axel Panzer
Katheryn Frame	Sumit Parikh
Jayne Gershkowitz (Amicus)	Carol-Anne Partridge
Femida Gwadry-Sridhar	Alan Percy
Joe Horrigan (Amo)	Elia M. Pestana-Knight
Amanda Jaksha	Sunny Philp (University of Birmingham, UK)
Walter Kaufmann	Robin Ryther (Washington University, USA)
Michael Johnson (Imperial College, UK)	Meghan Thorne-Miller (Roche)
Omar Khwaja	Karen Utley
Denise Lasbury (CDKL5-UK)	Judy Weisenberg
Dan Lavery (LouLou Foundation)	Ashley Winslow (LouLou Foundation)

Table 2. Composition of the CDD-SA by domain and source of data

Domain	By Caregiver	# questions	By Clinicians	# questions	Total # questions
1. Epilepsy	Yes	15	No	0	15
2. Motor	No	0	Yes	13	13
3. Cognition and Vision	Yes	1	Yes	12	13
4. Autonomic	Yes	9	Yes	1	10
5. Overall	Yes	2	No	0	2
6. Therapies	Yes	1	No	0	1
7. Scale Scoring	No	-	Yes		
8. Visit notes	No	-	Yes		

Figure 1: Modified Delphi process for CDD-SA development.

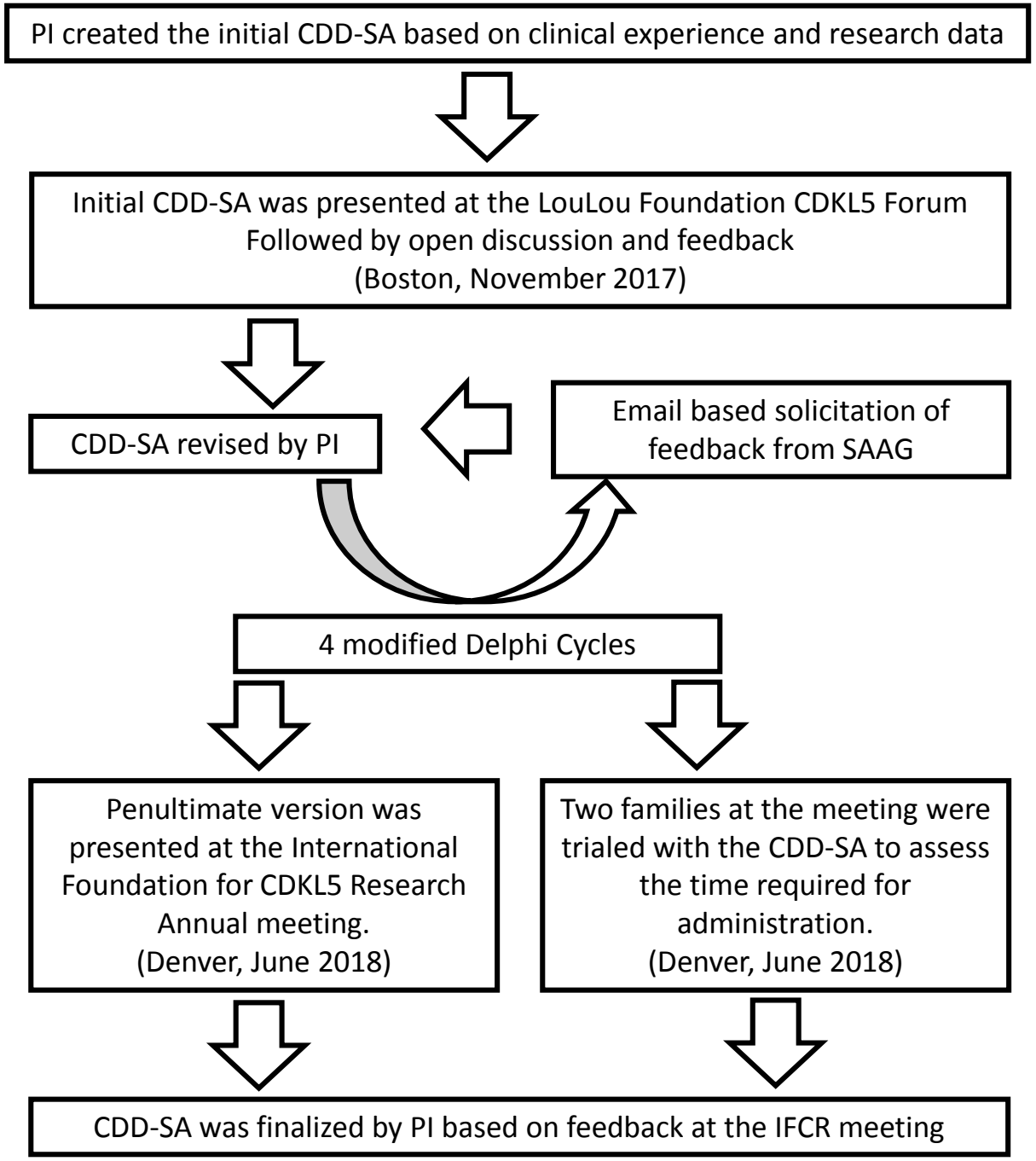
Figure 2: CDD-SA. The Final CDD-SA with brief instructions on completion.

References

1. Tao J, Van Esch H, Hagedorn-Greiwe M, Hoffmann K, Moser B, Raynaud M, Sperner J, Fryns JP, Schwinger E, Gecz J *et al*: **Mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5/STK9) gene are associated with severe neurodevelopmental retardation**. *Am J Hum Genet* 2004, **75**(6):1149-1154.
2. Weaving LS, Christodoulou J, Williamson SL, Friend KL, McKenzie OL, Archer H, Evans J, Clarke A, Pelka GJ, Tam PP *et al*: **Mutations of CDKL5 cause a severe neurodevelopmental disorder with infantile spasms and mental retardation**. *AmJ HumGenet* 2004, **75**(6):1079-1093.
3. Archer HL, Evans J, Edwards S, Colley J, Newbury-Ecob R, O'Callaghan F, Huyton M, O'Regan M, Tolmie J, Sampson J *et al*: **CDKL5 mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients**. *J Med Genet* 2006, **43**(9):729-734.
4. Bahi-Buisson N, Villeneuve N, Caietta E, Jacquette A, Maurey H, Matthijs G, Van EH, Delahaye A, Moncla A, Milh M *et al*: **Recurrent mutations in the CDKL5 gene: genotype-phenotype relationships**. *AmJ MedGenetA* 2012, **158A**(7):1612-1619.
5. Hector RD, Kalscheuer VM, Hennig F, Leonard H, Downs J, Clarke A, Benke TA, Armstrong J, Pineda M, Bailey MES *et al*: **CDKL5 variants: Improving our understanding of a rare neurologic disorder**. *Neurol Genet* 2017, **3**(6):e200.
6. Fehr S, Wilson M, Downs J, Williams S, Murgia A, Sartori S, Vecchi M, Ho G, Polli R, Psoni S *et al*: **The CDKL5 disorder is an independent clinical entity associated with early-onset encephalopathy**. *EurJ HumGenet* 2013, **21**(3):266-273.
7. Mangatt M, Wong K, Anderson B, Epstein A, Hodgetts S, Leonard H, Downs J: **Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome**. *Orphanet J Rare Dis* 2016, **11**:39.
8. Paciorkowski AR, Seltzer LE, Neul JL: **Developmental Encephalopathies**. In: *Swaiman's Pediatric Neurology*. Edited by Swaiman KF, Ashwal S, Ferriero DM, Schor NF, Finkel RS, Gropman AL, Pearl PL, Shevell MI, 6 edn. Philadelphia: Mosby; 2018: 242-248.
9. Lindy AS, Stosser MB, Butler E, Downtain-Pickersgill C, Shanmugham A, Retterer K, Brandt T, Richard G, McKnight DA: **Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with epilepsy and neurodevelopmental disorders**. *Epilepsia* 2018, **59**(5):1062-1071.
10. Kothur K, Holman K, Farnsworth E, Ho G, Lorentzos M, Troedson C, Gupta S, Webster R, Procopis PG, Menezes MP *et al*: **Diagnostic yield of targeted massively parallel sequencing in children with epileptic encephalopathy**. *Seizure* 2018, **59**:132-140.
11. Symonds JD, Zuberi SM, Vincent A, Lang B, Dorris L, Brunklaus A, Ellis R, Jollands A, Joss S, Kirkpatrick M *et al*: **The Genetic and Autoimmune Childhood Epilepsy (GACE) Study**. In: *American Epilpesy Society: 2017; Washington, D.C.* 2017.
12. Rosander C, Hallbook T: **Dravet syndrome in Sweden: a population-based study**. *Dev Med Child Neurol* 2015, **57**(7):628-633.
13. Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX, Kuzniewicz MW: **Incidence of Dravet Syndrome in a US Population**. *Pediatrics* 2015, **136**(5):e1310-1315.
14. Laurvick CL, de Klerk N, Bower C, Christodoulou J, Ravine D, Ellaway C, Williamson S, Leonard H: **Rett syndrome in Australia: a review of the epidemiology**. *J Pediatr* 2006, **148**(3):347-352.
15. Buoni S, Zannolli R, Colamaria V, Macucci F, di Bartolo RM, Corbini L, Orsi A, Zappella M, Hayek J: **Myoclonic encephalopathy in the CDKL5 gene mutation**. *Clin Neurophysiol* 2006, **117**(1):223-227.
16. Bahi-Buisson N, Nectoux J, Rosas-Vargas H, Milh M, Boddaert N, Girard B, Cances C, Ville D, Afenjar A, Rio M *et al*: **Key clinical features to identify girls with CDKL5 mutations**. *Brain* 2008, **131**(Pt 10):2647-2661.

17. Nemos C, Lambert L, Giuliano F, Doray B, Roubertie A, Goldenberg A, Delobel B, Layet V, N'Guyen MA, Saunier A *et al*: **Mutational spectrum of CDKL5 in early-onset encephalopathies: a study of a large collection of French patients and review of the literature**. *ClinGenet* 2009, **76**(4):357-371.
18. Castren M, Gaily E, Tengstrom C, Lahdetie J, Archer H, Ala-Mello S: **Epilepsy caused by CDKL5 mutations**. *Eur J Paediatr Neurol* 2011, **15**(1):65-69.
19. Melani F, Mei D, Pisano T, Savasta S, Franzoni E, Ferrari AR, Marini C, Guerrini R: **CDKL5 gene-related epileptic encephalopathy: electroclinical findings in the first year of life**. *Developmental Medicine and Child Neurology* 2011, **53**(4):354-360.
20. Fehr S, Leonard H, Ho G, Williams S, de Klerk N, Forbes D, Christodoulou J, Downs J: **There is variability in the attainment of developmental milestones in the CDKL5 disorder**. *J Neurodev Disord* 2015, **7**(1):2.
21. Fehr S, Downs J, Ho G, de Klerk N, Forbes D, Christodoulou J, Williams S, Leonard H: **Functional abilities in children and adults with the CDKL5 disorder**. *Am J Med Genet A* 2016, **170**(11):2860-2869.
22. Fehr S, Wong K, Chin R, Williams S, de Klerk N, Forbes D, Krishnaraj R, Christodoulou J, Downs J, Leonard H: **Seizure variables and their relationship to genotype and functional abilities in the CDKL5 disorder**. *Neurology* 2016, **87**(21):2206-2213.
23. Downs J, Stahlhut M, Wong K, Syhler B, Bisgaard AM, Jacoby P, Leonard H: **Validating the Rett Syndrome Gross Motor Scale**. *PLoS One* 2016, **11**(1):e0147555.
24. Neul JL, Glaze DG, Percy AK, Feyma T, Beisang A, Dinh T, Suter B, Anagnostou E, Snape M, Horrigan J *et al*: **Improving Treatment Trial Outcomes for Rett Syndrome: The Development of Rett-specific Anchors for the Clinical Global Impression Scale**. *J Child Neurol* 2015, **30**(13):1743-1748.
25. Neul JL, Fang P, Barrish J, Lane J, Caeg EB, Smith EO, Zoghbi H, Percy A, Glaze DG: **Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome**. *Neurology* 2008, **70**(16):1313-1321.
26. Colvin L, Fyfe S, Leonard S, Schiavello T, Ellaway C, de KN, Christodoulou J, Msall M, Leonard H: **Describing the phenotype in Rett syndrome using a population database**. *ArchDisChild* 2003, **88**(1):38-43.
27. Ma M, Adams HR, Seltzer LE, Dobyns WB, Paciorkowski AR: **Phenotype Differentiation of FOXG1 and MECP2 Disorders: A New Method for Characterization of Developmental Encephalopathies**. *J Pediatr* 2016, **178**:233-240 e210.
28. Humphrey A, Ploubidis GB, Yates JR, Steinberg T, Bolton PF: **The Early Childhood Epilepsy Severity Scale (E-Chess)**. *Epilepsy Res* 2008, **79**(2-3):139-145.
29. Purusothaman V, Ryther RC, Bertrand M, Harker LA, Jeffe DB, Wallendorf M, Smyth MD, Limbrick DD: **Developing the Pediatric Refractory Epilepsy Questionnaire: a pilot study**. *Epilepsy Behav* 2014, **37**:26-31.
30. Carpay HA, Arts WF: **Outcome assessment in epilepsy: available rating scales for adults and methodological issues pertaining to the development of scales for childhood epilepsy**. *Epilepsy Res* 1996, **24**(3):127-136.
31. Devinsky O, Verducci C, Thiele EA, Laux LC, Patel AD, Filloux F, Szaflarski JP, Wilfong A, Clark GD, Park YD *et al*: **Open-label use of highly purified CBD (Epidiolex(R)) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes**. *Epilepsy Behav* 2018, **86**:131-137.
32. Trazzi S, De Franceschi M, Fuchs C, Bastianini S, Viggiano R, Lupori L, Mazziotti R, Medici G, Lo Martire V, Ren E *et al*: **CDKL5 protein substitution therapy rescues neurological phenotypes of a mouse model of CDKL5 disorder**. *Hum Mol Genet* 2018, **27**(9):1572-1592.

33. Jorm AF: **Using the Delphi expert consensus method in mental health research**. *Aust N Z J Psychiatry* 2015, **49**(10):887-897.
34. Moseley BD, Dhamija R, Wirrell EC, Nickels KC: **Historic, clinical, and prognostic features of epileptic encephalopathies caused by CDKL5 mutations**. *PediatrNeurol* 2012, **46**(2):101-105.
35. Bahi-Buisson N, Kaminska A, Boddaert N, Rio M, Afenjar A, Gerard M, Giuliano F, Motte J, Heron D, Morel MA *et al*: **The three stages of epilepsy in patients with CDKL5 mutations**. *Epilepsia* 2008, **49**(6):1027-1037.
36. Guerrini R, Parrini E: **Epilepsy in Rett syndrome, and CDKL5- and FOXG1-gene-related encephalopathies**. *Epilepsia* 2012, **53**(12):2067-2078.
37. Klein KM, Yendle SC, Harvey AS, Antony JH, Wallace G, Bienvenu T, Scheffer IE: **A distinctive seizure type in patients with CDKL5 mutations: Hypermotor-tonic-spasms sequence**. *Neurology* 2011, **76**(16):1436-1438.
38. Goldenholz DM, Rakesh K, Kapur K, Gainza-Lein M, Hodgeman R, Moss R, Theodore WH, Loddenkemper T: **Different as night and day: Patterns of isolated seizures, clusters, and status epilepticus**. *Epilepsia* 2018, **59**(5):e73-e77.
39. Tharayil JJ, Chiang S, Moss R, Stern JM, Theodore WH, Goldenholz DM: **A big data approach to the development of mixed-effects models for seizure count data**. *Epilepsia* 2017, **58**(5):835-844.


PI created the initial CDD-SA based on clinical experience and research data
Initial CDD-SA was presented at the LouLou Foundation CDKL5 Forum
Followed by open discussion and feedback
(Boston, November 2017)
CDD-SA revised by PI
Email based solicitation of feedback from SAAG
4 modified Delphi Cycles
Penultimate version was presented at the International Foundation for CDKL5 Research Annual meeting.
(Denver, June 2018)
Two families at the meeting were trialed with the CDD-SA to assess the time required for administration.
(Denver, June 2018)
CDD-SA was finalized by PI based on feedback at the IFCR meeting

CDKL5 Severity Assessment (SA)

Instructions to Parents/Caregivers and Clinicians:
1) Focus on last 30 days. Some questions also require review of last 6 months.

2) Circle most appropriate number or response. Keep in mind that larger numbers mean more severe.

3) Parents/caregivers: Fill out the BLUE and GREEN Sections PRIOR to your clinic visit to review DURING your clinic visit with your Clinician. At FIRST visit, allow more time for Clinician to review terminology with Parents/caregivers to ensure that scoring is similar in future visits. If an item is not answered, strike through the question.

4) Clinician: Review BLUE and GREEN Sections with Parents/caregivers. Utilize examination findings to fill out ORANGE (examination) section. Confirm YELLOW highlighted findings with parents/caregivers. If an item is not answered, strike through the question.

5) Clinician: Utilize section totals to consider clinical decision-making.

6) Clinician: Utilize grey section as a template for clinical decision-making.

Part 1: Epilepsy (Parental completion)

(1) Frequency of NON-CONVULSIVE seizures, focusing on last 30 days:

Include ONLY for NON-CONVULSIVE:

Absences (unresponsiveness not interrupted by touch)

Auras (pre-seizure activity) that do not lead to a convulsion

Never had any non-convulsive seizure = 0
None > 6 months = 1
Monthly (on average no more than 1 per month) = 2
Weekly (on average, 2-4 per month) = 3
Daily (on average, 5-30ish per month) = 4
More than daily (more than 30ish per month) = 5

(2) Frequency of CONVULSIVE seizures focusing on last 30 days:

(Convulsive: Tonic, tonic-clonic or drops that are disruptive and bothersome to patient or family. If the convulsive seizure changes during the event to spasms or jerks (or vice versa) DO NOT count the associated spasms or jerks separately below. For example, a hypermotor-tonic-spasms sequence is counted as 1 seizure in this question.)

Never had any convulsive seizure = 0
None > 6 months = 1
Monthly (on average no more than 1 per month) = 2
Weekly (on average, 2-4 per month) = 3
Daily (on average, 5-30ish per month) = 4
More than daily (more than 30ish per month) = 5

(3) ISOLATED Epileptic spasms and myoclonic jerks that cluster and are disruptive to patient or family (See note above, do not double count) focusing on last 30 days:

Never had spasms or jerks= 0
None > 6 months = 1
Monthly (on average no more than 1 per month) = 2
Weekly (on average, 2-4 per month) = 3
Daily (on average, 5-30ish per month) = 4

More than daily (more than 30ish per month) = 5

(4) Epileptic spasms and myoclonic jerks that don't cluster and are not disruptive to patient or family focusing on last 30 days

Never had spasms or jerks= 0
None > 6 months = 1
Monthly (on average no more than 1 per month) = 2
Weekly (on average, 2-4 per month) = 3
Daily (on average, 5-30ish per month) = 4
More than daily (more than 30ish per month) = 5

(5) Number of seizure types in last 30 days:

Never had a seizure = 0
One seizure type = 1
Two seizure types = 2
Three seizure types = 3.
Four seizure types = 4
Five or more seizure types = 5

(6) Prolonged seizure, occurrence and duration of episode in last 30 days:
(Prolonged seizures: continuous convulsive seizure lasting more than 5 minutes multiple convulsive seizures lasting more than 5 minutes without resolution of consciousness between seizures)

None ever = 0
None in last 6 months = 1
Once or twice in last 6 months = 2
Once or twice in last 30 days = 3
More than twice in last 30 days = 4 (on average, 2-4 per month)
More than 5 times in last 30 days = 5 (on average, 5 or more per month)

(7) Severity of prolonged seizures in last 30 days requiring use of rescue medications (use max score)

No use of rescue medication in last 30 days = 0
Used once in last 30 days = 1
Used twice in last 30 days = 2
Used 3x in last 30 days = 3
Used 4x in last 30 days = 4
Used 5 or more times in last 30 days = 5

(8) Severity of prolonged seizures in last 30 days causing hospital use (use max score)

No emergency department visits in last 30 days = 0
One emergency department visit in last 30 days = 1
Two emergency department visits in last 30 days = 2
Three or more emergency department visits in last 30 days = 3
Admitted once to hospital more than 24 hours in last 30 days = 4
Admitted to hospital and required ICU in last 30 days = 5

(9) Number of anticonvulsants used during LIFETIME, not including rescue, VNS or Diet:

None = 0
One anticonvulsants = 1
Two anticonvulsants = 2
Three anticonvulsants = 3
Four = 4
Five or more = 5

(10) Current anticonvulsants used during LAST 30 DAYS, not including rescue, VNS or ketogenic diet:
- None = 0
- One anticonvulsants = 1
- Two anticonvulsants = 2
- Three anticonvulsants = 3
- Four = 4
- Five or more = 5

(11)Current use of ketogenic diet in last 30 days (0 = never, 1 = past, 2= current):

(12)Current use of VNS in last 30 days (0 = never, 1 = past and shut off, 2= current):

(13) Subjective parental impression of seizures in last 30 days:
- Complete cessation (no evidence) of seizures = 0
- Partial improvement (at least 50% better) of seizures = 1
- Some but < 50% improvement in seizures = 2
- No improvement in seizures = 3
- Worsening of seizures = 4
- Most severe ever = 5

(14) Subjective parental impression of seizures in last 30 days: On average over the last 30 days, how many good days per week does patient have? A "good" day may be defined as: minimally disrupted by seizures or engaged, interactive, able to finish therapies throughout the day.
- Hardly ever, it has been a really good month = 0
- Only a few days this past month = 1
- More than half of the days per week are good = 2
- Always at least 2 or 3 days per week = 3
- Maybe 1 or 2 good days per week = 4
- Never has any good days per week = 5

(15) Longest seizure free period with focus on last 30 days
- No seizures ever = 0
- Greater than 6 months = 1
- Greater than 1 month = 2
- Greater than 1 week = 3
- Greater than 1 day = 4
- Always with daily seizures = 5

Part 3: Cognition, Behavior, Vision and Speech (Parental completion)

1) Spells of irritability that are disruptive to child, family or caregivers in last 30 days
- No irritability = 0
- Once or twice, not disruptive, consolable = 1
- Once or twice, at least once inconsolable = 2
- 3-4 times, consolable = 3
- 3-4 times, at least once inconsolable = 4
- More than 4 times, and/or more than twice inconsolable = 5

Part 4: Autonomic (Parental completion)

1) Swallowing abilities in last 30 days
- Normal swallow = 0
- Occasional choke/gag = 1
- More than 30 minutes to eat meal = 2
- Feeding tube present, some oral = 3
- Feeding tube only = 4

Parenteral (intravenous) required OR diagnosed with aspiration pneumonia = 5

2) Reflux
- No issues = 0
- Controlled, no medications (just diet, etc) = 1
- Controlled, on medications as needed= 2
- Controlled, on daily medications = 3
- Impactful (uncontrolled or associated with patient distress) = 4

3) Constipation
- No issues = 0
- Controlled, no medications (just diet, etc) = 1
- Controlled, on medications as needed= 2
- Controlled, on daily medications = 3
- Impactful (uncontrolled or associated with patient distress) = 4

4) Abnormal breathing (not associated with seizures) in last 30 days
- No issues = 0
- Occasional breath-holding or hyperventilating = 1
- Daily breath-holding or hyperventilating = 2
- Add 1 for cyanosis (blueness around mouth or face)
- Add 1 for concern about this by parents or care-givers

5) Toileting in last 30 days
- Normal = 0
- Timed for both = 1
- Timed for 1 = 2
- Diaper only = 3

6) Pain responsiveness in last 30 days
- Normal = 0
- Delayed to minor = 1
- Absent to minor = 2
- Delay to major = 3

7) Sleep in last 30 days (Please note: Arousals occur in all children. Count arousals that the parents notice due to crying or other disruptions enough to awaken the parents.)
- Normal, no issues = 0
- Arouses less than once per week = 1
- Arouses more than once per week = 2
- Arousals require parental attention: add 1
- Choose one of the following:
  - Most Arousals lasting 1-2 hours: add 1
  - Most Arousals/awake lasting > 2h: add 2

8) Daytime sleepiness in last 30 days
- Normal, no issues = 0
- Rare but not disruptive (impactful to patient, teachers, family) = 1
- 1 day per week, disruptive (impactful to patient, teachers, family) = 2
- 2-6 days per week, disruptive = 3
- 7 days per week, disruptive = 4
- Constant, throughout every day, disruptive = 5

9) Infections in last 30 days (include aspiration pneumonia also scored in question 4.1)

None, no issues = 0

Common, only 1-2 events, such as others in house also ill =1

One or more uncommon events (like aspiration pneumonia or urinary tract infection) or more than 2 common events = 2

Choose one of the following:

Needing emergency department visit (not captured by that related to seizure): Add 1

Needing hospitalization (not captured by that related to seizure): Add 2

Part 5: Overall impressions from caregivers (Parental completion):

1) In the last month, OVERALL ISSUES with my child are better, worse or the same?

-5	-4	-3	-2	-1	0	1	2	3	4	5
Really worse					Same					Really better

2) In the last month, the ADAPTABILITY OR RESILIENCE of caregivers at home is better, worse or the same?

-5	-4	-3	-2	-1	0	1	2	3	4	5
Really worse					Same					Really better

Part 6: Therapies in last 30 days (Parental completion)

Circle Therapy and fill in frequency

PT: ____ times per month; Increased, decreased or same (circle) in last 6 months

ST: ____ times per month; Increased, decreased or same (circle) in last 6 months

AT: ____ times per month; Increased, decreased or same (circle) in last 6 months

VT: ____ times per month; Increased, decreased or same (circle) in last 6 months

OT: ____ times per month; Increased, decreased or same (circle) in last 6 months

Feeding therapy (if separate from ST) : ____ times per month; Increased, decreased or same (circle) in last 6 months

Other_____: ____ times per month; Increased, decreased or same (circle) in last 6 months

Other_____: ____ times per month; Increased, decreased or same (circle) in last 6 months

Definitions: PT = physical therapy, ST = speech therapy, AT = augmentative communication therapy (add here, even if part of ST), VT = vision therapy, OT = occupational therapy

Rate the overall effectiveness of ALL therapies in last 30 days:

-5	-4	-3	-2	-1	0	1	2	3	4	5
Unhelpful (Losing skills)					Same (maintaining skills)					Really helpful (new skills learned)

Part 2: Motor (Completed by Clinician, with input from caregivers where noted)

1) Walk

Walks normally = 0

Walks independent, reduced ability, able to walk > 25 ft= 1

Walks independent, reduced ability, able to walk < 25 ft= 2

Walks with assistance (not independent) > 25 ft = 3

Walks with assistance (not independent) < 25 ft = 4

Not walking = 5

Demarest et al, Figure 2

2) Stands

Stands normally (including: goes from sit to stand) = 0
Stands, but some trouble, > 20s= 1
Stands 10-20s only = 2
Stands < 3s (no assistance) = 3
Stands only with assistance >3s = 4
Not standing (less than 3s with assistance)= 5

3) Sits

Sits > 30s = 0
Sits < 30s = 1
Sits only with assistance (holding hips) = 3
Head control only, no trunk control = 4
No head control = 5

4) Hypotonia

Normal = 0
Add for each:
Axial (+1)
Upper limb (+2)
Lower limb (+2)

5) Weakness

Normal = 0
Add for each:
Axial (+1)
Upper limb (any: +1; severe: +2)
Lower limb (any: +1; severe: +2)

6) Fine Motor

Normal hand use = 0
single pincer = 1
bilateral rake = 2
single rake = 3
Grabs only if object placed in hands or bats at objects = 4
No hand use = 5

7) Dystonia (abnormal fixed position) and Rigidity (if in doubt, score higher)

Normal = 0
Add for each:
Upper extremities (+1)
Lower extremities (+1)
Constant (more than 50% of the visit and not intermittent or distractible) (+1)
Axial (+1)
Oro-facial (for example, grimace)(+1)

8) Chorea and/or athetosis (if in doubt, score higher)

Normal = 0
Add for each:
Upper extremities (+1)
Lower extremities (+1)
Constant (more than 50% of the visit and not intermittent or distractible) (+1)
Axial (+1)

Demarest et al, Figure 2

Oro-facial (for example, oro-facial dyskinesia)(+1)

9) Stereotypies: (abnormal movements of arms, hands or legs not better described by chorea or athetosis; count time when not distracted by no-no, other device or verbal distraction)

Not observed, not reported = 0
By report but not on exam = 1
Rare during exam = 2
Almost half of the exam = 3
More than half of the exam = 4
All, nearly all of the exam = 5
Describe (circle): wringing hands, tapping/touching with hands, mouthing hands, flicking fingers, leg crossing, other:_____

10) Impact of Dystonia/Rigidity, Chorea/Athetosis and Stereotypies

Not observed, not reported = 0
By report but not on exam = 1
Distractible and do not limit function = 2
Minor limit on function = 3
Impactful and interfering but some function present = 4
Major impact (example: fully prevents hand use or sitting or walking) = 5

11) Contractures-Arms

Fully flexible = 0
Loss of range, no effect on function = 1
Loss of range, somewhat tight, hard to dress, etc = 2
Loss of range, very tight, very impactful = 3
No range, fixed in 1 arm = 4
No range, fixed in both arms = 5

12) Contractures-legs

Fully flexible = 0
Loss of range, no effect on function = 1
Loss of range, somewhat tight, hard to dress, etc = 2
Loss of range, very tight, very impactful = 3
No range, fixed in 1 leg = 4
No range, fixed in both legs = 5

13) Curvature and Scoliosis (degrees noted on exam or Cobb angle measured on X-ray)

None = 0
Less than 10 = 1
10-20 = 2
20-40 = 3
> 40 = 4
Repaired = 5

Part 3: Cognition, Behavior, Vision and Speech (Completed by Clinician, with input from caregivers where noted)

2) Alertness and interaction during visit (minimum 20 minutes)

100 %, all of visit = 0;
Not all of visit but more than half = 1
Half of visit = 2
Less than half of visit= 3,
Not interactive (awake but “shut down”)
or sleepy for nearly all of the visit but not entirely =4

Not interactive (awake but “shut down”) or asleep during all of the visit = 5
Per the parent, was this typical (yes/no):

3) Irritability or crying during visit (minimum 20 minutes)
None of visit = 0;
Rare but not more than half, consoles on own = 1
Half of visit = 2
More than half of visit, occasionally consolable= 3,
Nearly all of the visit but not entirely, rarely consolable =4
All of the visit, inconsolable = 5
Per the parent, was this typical (yes/no):

4) Self-injury during visit (minimum 20 minutes)
None of visit = 0;
Rare but not more than half = 1
Half of visit = 2
More than half of visit = 3,
Nearly all of the visit but not entirely =4
All of the visit = 5
Per the parent, was this typical (yes/no):
Describe (biting self, hitting self, head banging, other):

5) Aggressive behavior during visit (minimum 20 minutes)
None of visit = 0;
Rare but not more than half = 1
Half of visit = 2
More than half of visit = 3,
Nearly all of the visit but not entirely =4
All of the visit = 5
Per the parent, was this typical (yes/no):
Describe (biting others, hitting others, intentional spitting, other):

6) Hyperactivity during visit (minimum 20 minutes)
None of visit = 0;
Rare but not more than half = 1
Half of visit = 2
More than half of visit, = 3,
Nearly all of the visit but not entirely =4
All of the visit = 5
Per the parent, was this typical (yes/no):

7) Bruxism (during 20 minute exam)
Not observed, not reported = 0
By report but not on exam = 1
Rare during visit = 2
Up to and almost half of visit = 3
More than half of visit = 4
Nearly all or the entire visit = 5
Per the parent, was this typical (yes/no):

8) Vision (acuity, function, attention, etc.)

OKN: Suggested use of typical clinical tool and have been "calibrated" as normal by the clinician. Suggested use of OptOK app on ipad at full intensity in darkened room at 5-10 cm from eyes.

Normal vision, normal OKN = 0
Fixes and follows faces, reduced or ignored OKN = 1
Fixes, occasionally follows faces or objects= 2
Fixes only, no follow faces or objects = 3
Fixes only to bright light = 4
No visual attention = 5

9) Eye movements: indicate all that are present

Normal (no points)
Add for each:
Dysconjugate, intermittent (add 1 point)
Dysconjugate, constant (add 2 points)
Horizontal or vertical nystagmus (add 1 point)
Roving (add 1 point)
Rotatory nystagmus (add 1 point)

10) Speech

Full sentences, normal = 0
Phrases = 1
Words = 2
Single words or signs = 3
No words, only vocalizations = 4
No vocalizations = 5

11) Non-verbal communication observed during minimum 20 minute visit (Parents must bring device to visit. Note or skip if left at home).

Points, propositive, normal; 4+ signs = 0
3+ Signs = 1, or multiple choices with eye gaze or similar device = 1
1-3 Signs = 1, or simple choices with eye gaze or similar device = 2
Plays games with toy or object = 3
Intermittent play or interest with toy or object = 4
None observed = 5

12) Two object choice during minimum 30s (2 toys or 2 foods or combo, verbal introduction) (Parents or clinician need to have on hand for visit.)

Verbal or instant reach and grab= 0
Choice, reach and grab with < 5s delay = 1
Choice, reach and grab with > 5s delay = 2
Choice with reach only = 3
Choice with eyes only (looks at what they want) = 4
Unable to perform or No choices = 5

13) Receptive language (allow 30s minimum of direct conversation)

Normal, follows 2 step commands, normal eye contact = 0
Follows 1 step command or abnormal eye contact = 1
Responds to voice with eye contact or similar (smiles, alerts, etc) for 5-20s =2
Responds to voice with eye contact or similar < 5s = 3
Inconsistent response to voice with eye contact or similar < 5s = 4
Unable to perform or No eye contact or similar to voice = 5

Part 4: Autonomic (Completed by Clinician)
Instructions: Circle items if present (Strike through if not performed)

10) Distension on exam: add 1
Apnea seen on exam (prolonged auscultation): Add 1
Oral cyanosis seen on exam: Add 1
Peripheral circulation (pull off socks or gloves, leave for 5 minutes before assessment)
Hands and feet warm and pink = 0
Cold hands: add 1
Cold feet: add 1
Purple or cyanotic hands: add 1
Purple or cyanotic feet: add 1
Abnormal skin (thin, atrophic, etc) associated with any above: add 1

Part 7: Scoring (Compare to last visit)

Part 1-Epilepsy total (max = 69):
Part 2 Motor total (max = 65):
Part 3 Cognition and Vision total (max = 65):
Part 4 Autonomic/Other total (max = 44):
Part 5 Overall/Resiliency total (range -10 to 10):
Part 6 Therapy utility total (range -5 to 5):

Part 8: Clinical Decision Making:

Seen today by (circle): pediatrician, neurologist, developmental pediatrician, geneticist, epileptologist
Circle aspects of plan
Anticonvulsant adjustment
New therapy referral: OT, PT, ST, VT, AT, Feeding (if separate from ST) other:_____
Ophthalmology or vision referral
Referral to: epilepsy, movement, GI, pulmonary, orthopedics, physical medicine, developmental pediatrician, psychologist, sleep specialist, endocrine, gynecologist, immunologist, social work, other:_____
Anticonvulsant monitoring (eg. CBC, liver panel, vitamin D)
Other:

EEG-routine EEG-overnight EEG- 2 days or more ECG
Holter Echo Sleep study Swallow study Xray of back Xray of limb