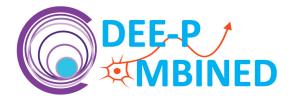


Developing the Roadmap to Validated Biomarkers and Outcome Measures for Severe DEE's



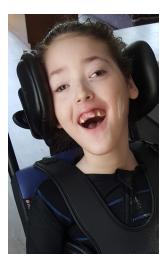














AGENDA



- 11:00 11:10 Welcome Gabi Conecker
- 11:10 11:15 Overview of Phase I Efforts and Agenda Terry Jo Bichell
- 11:15 11:25 Draft Disease Concept Map for Severely Affected DEE's and Literature Review Kyle Horning
- 11:25 11:40 Rare Diseases Rare Outcomes Measuring "Better" for DEE Patients with Severe Impairments Anne Berg
- 11:40 11:55 Extending and Validating Health Quality of Life Measure Jenny Downs
- 11:55 12:10 Extending Application of Rehabilitation Measures to DEEs Natasha Ludwig
- 12:10 12:25 Beyond Patient Journals: Using Goal Attainment Scaling (GAS) to Capture the Patient Voice Chere Chapman
- 12:25 12:30 Other Promising Initiatives Terry Jo Bichell
- 12:40 12:45 Breakout groups
 - Exploration of next steps and opportunities for accelerated progress in the 5 proposed areas
- 12:45 1:00 Wrap Up and Preparing for 11/11 Workshop Gabi Conecker and Terry Jo Bichell



Model Consortium led by patient advocacy foundations, working with the clinicians, researchers and pharmaceutical firms that are developing treatments for the disorders they represent.



COMBINEDBrain Initiatives 2021

Organize

- Collaborate with AGENDA and REN, DEE-P.
- Create searchable public catalog of resources across all member disorders.
- Launch industry advisory board Dec 2021.
- Expand Rent-a-Science-Officer program.

Strategic Plan Reassessment

• Meeting with Clinical, Scientific, and Industry Advisory Boards Dec 2021 to re-prioritize

Projected New Projects

- Patient-Reported Outcome Measure Development
 - ORCA, CVI with Duke team, anxiety/behavior measure built on ORBSID/BIAPAS
- Basket Trial for sleep
- FIND-OUT project (Fast Infant Neurodevelopmental Diagnosis Outpatient Testing)
- FDA listening sessions
- Study to compare traditional Disease Concepts with TREND reports
- DEE-P COMBINED Project for Severely Affected DEE's
- Biorepository linkages, high-throughput assays, and CSF biomarkers



OVERVIEW OF PHASE I EFFORTS



Definition of Severe DEE's

Needs 100% assistance with all activities of daily living: eating, hygiene (dressing, self-care, toileting), mobility (includes hand-use), and communication.

Many people who are severely affected by developmental or epileptic encephalopathies (DEE's) will experience cortical visual impairment, require feeding tubes, and have intractable epilepsy, with a developmental age 4 or more standard deviations below the mean.

The Problem

- Validated biomarkers and outcome measures (BOMs) are insufficient for neurodevelopmental disorders in general
- The most severely affected are a unique sub-population of DEEs
- BOMs are entirely lacking for the most severe developmental and epileptic encephalopathies

The Solution

- Cross-disorder consortia with other neurodevelopmental and epileptic disorders
- Dialogue between advocates, experts and industry
- Development of strategies for advancing validated BOMs for severe DEEs





- Conceptual Model of Severely Affected DEE's
- Goal Attainment Scaling for Severely Affected DEE's
- Expansion of Rehabilitation Measures for Severely Affected DEE's
- Reevaluation of the Vineland Scale for Severely Affected DEE's
- Expansion of Health Related Quality of Life for Severely Affected DEE's





Methods to Identify What is Important to Patients

Select, Develop or Modify
Fit-for-Purpose Clinical Outcomes
Assessments

Workshop Date: October 15-16, 2018



2017 21st Century Cures Act - Patient Involvement2018 FDA Guidance on the Science of Patient Input

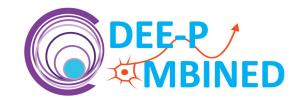
2020 FDA CDER Guidance on PFDD

FDA Patient-Focused Drug Development
Guidance Series for Enhancing the Incorporation
of the Patient's Voice in Medical Product
Development and Regulatory Decision Making





COMBINEDBrain Disease Concept DRAFTS



COMBINEDBrain Defining Con	cepts					
Communication	Neurological	Behavior	Cognition	Motor	Sleep	Musculoskeletal
8p, BBSOAS-NR2F1, 20 Expressive CHAMPI, FDVG1, communication decreased HNRNPH2, KAND, Malra, MPSII, PEX10, SATB2, SCN2A, SETBP1, SSG (profound lack), SHANKS, SLC6A1, STXBP1, SYNGAP1, USP7,	8p, BBSOAS-NR2F1, 19 Hypotonia CHAMP1, FOXG1, GLUT1, GRIN2B, HNRNPH2, KAND, Malan, PEX10, SATB2, SCN2A, SETBP1, SGS, SHANK3, SLCSA1, STXBP1, SYNGAP1, USP7,	8p, BBSOAS-NRZF1, CHAMP1, FOXG1, GRINZB, HNRNPH2, Malan, MPSII, SATB2, SCN2A, SGS, SHANK3, SLC6A1, STXBP1, SYNGAP1, USP7.	8p. BBSOAS-NRZF1, 20 Cognitive disability CHAMP1, FOXG1, GLUT1, GRIN2B, HNRNPH2, KAND, Malan, MPSII, PEX10, SATB2, SCN2A, SETBP1, SGS, SHANK3, SLCSA1, STXBP1, SYNGAP1, USP7,	8p, BBSOAS-NRZF1. 20 Fine motor skills CHAMP1, FOXG61, delayed/impaired GLUT1, GRIN2B, HNRNPH2, KAND, Malan, MPSII, PEX10, SATB2, SCN2A, SETBP1, SGS, SHANK3, SLC8A1, STXBP1, SYNGAP1, USP7,	8p, BBSOAS-NIZ2F1, 14 Initiation and maintenance CHAMP1, FOXO51, GRINZB, HNRNPH2, KAND, Malan, MPSII, SATB2, SCNZA, SOS, SHANK3, SYNGAP1,	Rp. BBSOAS- MRZF1, CHAMP1, FOXG1, GRIN2B, HNRNPH2, Malian (over time), MPSII, PEX10, SATB2, SETBP1, SGS, SHANK3, SLC6A1, SYNGAP1, 15 Craniofacial abnormalities (Includes: long chin, cieft prominent mandible, jaw abnormalities, wide mouth, flat back of head, wide-set short paiprebal fissures, short slicker, micrognathia, full synGAP1,
8p. BBSOAS-NR2F1, [8 Non-verbal communication GRINZB, HNRNPH2, GAINZB, SCN2A, SETBP1, SGS, SHANKS, SLC6A1, STXBP1, SYNGAP1, USP7, Communication through the use of facial expression, body postures and gestures [1] of the property of the pr	HNRNPH2, KAND,	8p, BBSOAS-NRZE1, 16 Impulsivity CHAMP1, FOXG1, GRINZB, HNRNPH2, KAND, Melan, MPSII, SATIB2, SOXPA, SETIB41, SYNGAP1, USP7, USP7,	8p. BBSOAS-NRZFI, 17 Attention deficit CHAMPI, FOXG1, GLUTI, GRINZB, HNRNPHZ, KAND, Malan, MPSI, SATB2, SCNZA, SETBP1, SCS, SHANK3, SLC6A1, USP7,	8p, BBSOAS-NRZF1, 20 Gross motor skills delayed/impaired GLUT1, GRINZB, HNRNPHZ, KAND, Malan, MPSII, PEX10, SATBZ, SCNZA, SETBP1, SGS, SHANRA, SLCSA1, STXBP1, SYNGAP1,	Bp, BBSOAS-NIZ2F1, 14 Snoring and/or teath grinding (Includes SETBP1, SGS, SHANKS, SYNGAP1, STXBP1 (awake bruxism),	CHAMP1, 13 Ankle abnormalities FOXG1, GLUT1, GRINZB, KAND, Malan, PEX10, SATB2, SCN2A, SETBP1, SGS, SYNGAP1 (intoeing),
8p, BBSOAS-NRZF1, CHAMP1, FOXG1, GLUT1, GRIN2B, HNRNPH2, KAND, Malan, MPSII, SATB2, SCNZA, SETBP1, SGS	Bp. BBSOAS-NR2F1, 18 Seizures (all types) CHAMP1, FOXG1, GLUT1, GRIN2B, HNRNPH2, KAND, Malan, SATB2, SCN2A, SETBP1, COCCALABATE.	8p. BBSOAS-NR2F1, 14 Temper Tantrums CHAMP1 FOXG1, GRIN2B, KAND, Malan, MPSII, SCN2A, SETBP1, SGS, SHANK3, SLCSA1,	8p, FOXG1, GLUT1, 14 Memory GRINZB, KAND, Malan, challenges SATB2, SCN2A, SETBP1, SGS, SHANK3, SLC6A1, STXBP1, USP7,	8p, BBSOAS-NRZET. 19 Balance - unsteady CHAMP1, FOXGO1, GLUT1, GRIN2B, HNRNPH2, KAND, Malan, PEXID, SATE2, SETEP1, SCNZA, SGS, SILLANZ, GOS.	GLUTI, GRINZB, 13 Disturbance FOXG1, Malan, SATB2, 5CN2A, SETBP1, SGS, SHANK3, SLC6A1, STXPP1, SYNGAP1, USP7,	8p, FOXG1, 3 Soolosis (Increased curve in GRIN2B, HNRNPH2, curve, includes kyphosis and lordosis) Hordosis (Society Society

Proximal Impact Concepts	Distal Impact C	oncente				
		•				
Self Care and Daily Living	Community/ Sc	hool	Socialization an	d Family Life		
Jg., CHAMP1, BBSOAS- IŞ ADL. Lack NZEZ1, FOXG, independence is activities of daily NBRNP12, KAND, independence is activities of daily SATB2, SGS, SCNZA, levels of assista SETBP1, SHANK3, LLCBA1, STXBP1, SYNGAP1, USP7,	FOXG1, GLUT1,	20 Academic challenges (require supportive educational needs and adaptive school placements, diet assistance)	8p, CHAMP1, BBSOAS-NR2F1, FOXG1, GLUT1, GRIN2B, KAND, Malan, SATB2, SGS, SCN2A, SETBP1, SHANK3, SLC6A1, STXBP1, SYNGAP1, USP7,	17 Behaviors are challenging in social situations, such as yelling, stubbomnes demanding, hitting, aggression or withdrawn		
Sp. CHAMP1, BBSOAS- IRZF1, FOXG1, needed INRNPH2, KAND, Malan, MPSII, PEX10, SATB2, SGS, SCN2A, SETBP1, SHANK3, SLGGA1, STXBP1, SYNGAP1, USP7,		17 Danger - decreased recognition of danger	8p, CHAMP1, BBSOAS-NR2F1, FOXG1, GRIN2B, HNRNPH2, MPSII, SATB2, SGS, SCN2A, SETBP1, SHANK3, SLCBA1, STXBP1, SYNGAP1, USP7,	16 Impulsive or Inappropriate social behavior, may greet people with grabbing		
3p, CHAMP1, BBSOAS- NR2F1, FOXG1, needed (include HNRNPH2, Malan, hygiene) MPSII, PEX10, SATB2,		16 Communication (difficult to be understood outside the family, difficulty	8p, CHAMP1, BBSOAS-NR2F1, GLUT1, GRIN2B, HNRRNPH2, Malan,	13 Engaged socially (Capable of social engagement and establishing		

Methodology

Literature review

Qualitative interviews of two caregivers for each disorder Merge the conceptual models to make a COMBINED draft Identify relevant and measurable endpoints Identify gaps in measurement assays

Severely A	ffect	ed DEEs Disease Co	r
		Neurological	
CACNA1A, CDKL5, GRINS, SCN2A, SCN8A, SGS,	6	Hypotonia (axial - includes life-threatening features related to hyptonia such as swallowing, cough reflex, not moving, pneumonia)	
CACNA1A, CDKL5, GRINS, SCN2A, SCN8A, SGS,	6	Seizures - (includes: intractable, refractory; infantile spasms, clusters, WEST syndrome, focal or generalized, tonic, myoclonic, absence, gelastic, febrile)	
CDKL5,	5	EEG abnormal (in	

CDINA





COMBINEDBrain Disease Concept DRAFTS

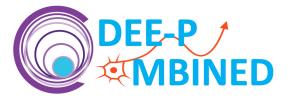


The disease concept map for severely affected DEEs are different from other neurodevelopmental disorders

Domains are different

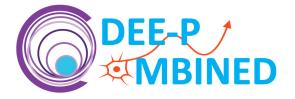
Biomarkers and Outcome Measures will be different

Draft Conceptual Model of Severely Affected DEE's



			dament and a second								And the second s
	Cognition	Communication	Property and the second	Visual	Sleep	Gastrointestinal		Skin	Behavior	Emotional	Other Physical
Hypotonia (axial - includes life-threatening features related to hyptonia such as swallowing, cough reflex, not moving, pneumonia)	Cognitive Disability	Alternative and/or augmentative communication devices used by a few (includes single switches, tobii dynavox, kids use talkers, stepbystep, big mac)	Fine motor skills delayed/impaired (includes hand use abnormalities)	Cortical visual impairment (includes cortical blindness, visual field deficits)	Initiation and maintenance difficulties of sleep (includes requent awakenings, sleep-wake transition)	Constipation	Scoliosis (includes surgical corrections)	Temperture instability (includes in extremeties)	Autism Spectrum Disorder	Irritability	Respiratory issues (includes recurrent pneumonia, ainway infections, supplemental O2, ventilation vests, respiratory failure
Seizures - (includes: intractable, refractory; infantile spasms, clusters, WEST syndrome, focal or generalized, tonic, myoclonic, absence, gelastic, febrile)	Giobal developmental delay	Expressive communication decreased profoundly	Gross motor skills delayed/impaired (includes non-ambuatory)	Strabismus (abnormal eye movements, tracking difficulties)	Seizures in sleep	Reflux	Craniofacial abnormalities (dysmorphic features)	Autonomic dysfunction (frequent fevers, extremeties cold)	Autistic traits, includes abnormal eye contact	Anxiety	Pain, high tolerance
EEG abnormal (in about 50%, miss some types of seizures from deep structures)	Memory deficits	use of facial expresion (smiles, cries, turn away,	Oral motor impairment (includes sucking and swallowing disorders, frequent drooling, and feeding difficulties, tongue thrusting, excessive chewing, mouthing behaviors, teeth grinding, dysphagia)	Nystagmus (includes interictal)	Cycle abnormalities (sleep wake cycle in 24 hours)	Vomiting	Hands and feet abnormalities, includes talipes and small feet	Hemianesthesia (Sensory deficit atternating in limb side)	Repetitive behaviors - hand-wringing	Happy demeanor (Even-keeled go with the flow, not so much behaviors and emotional reactions)	
MRI-abnormal	Attention deficit	Receptive communication decreased profound, very subtle response	Hand use impaired, loss of purposeful hand movements	Visual impairment, glasses	Excessive daytime sleepiness (includes catatonia)	Drooling (Sialorrhea)	Ankle abnormalities (pronation, inward rolling of ankle and foot)	Hirsute as infants	Sensory defensive (includes (hair brushing, around the mouth, and hands being touched)	Affection- not affectionate	Breathing disorders (respiratory distress, apnea, tachypnoea)
Ataxia	Cognitive regression	Vocalizes but does not have full speech, verbal approximations	Regression in motor skills (includes due to seizures)	Light sensitivity increased	Snoring and teeth grinding (bruxism)	Incontinence	Dental issues - Abnormal dentition	Mottled skin, rosie red skin	Sensory seeking (includes Massaging scalp breaks seizures, likes touch, snuggle, will swipe at people, love touch and stretch)	Frustration	Cardiac, long QT syndrome
Microcephaly		Regression in communication skills (includes when seizures onset)	Athetosis (includes choreoathetosis)	Exfoliation syndrome	Terrors, night terrors (unable to describe)	Tube fed (includes PEG or nasogastric tubes)	Orthopedic issues (includes hip replacements, osteotomies, dislocated hips, hip dysplasia)	Numbness of extremities	Stereotypic hand movements	Mood swings	Coughing
Tremors			Balance - unsteady	Glaucoma	Sleep apnea (includes central and obstructive	Infant feeding issues	Osteoporosis	Pallor	Hand flapping or waving movements	Pyschosis	Fetal movements delayed or reduc
Hypertonia			Dyspraxia - impaired ability to complete coordinated movements	Myokymia (eyelid twitching)	Disorientation when aroused	Aerophagia	Arophy of muscles	Vasomotor disturbance	Stereotypic behaviors (includes rocking)		Hearing impairment (central)
Myoclonus			Tremulous movements of limbs	Oculogyric crisis	REM sleep minimal	Diarrhea	Torticollis of infancy (BPTI)		Self-Stim (hand-flapping, vocal stim)		Lethargy, overwhelming
Neuro-epithelial tumors, acute myeloid leukemia, some patients born with them, AML, MML			Abnormal movements (includes jittery)	oculomotor apraxia	SUDEP (seizure in sleep causing death)	Dysphagia	Scissors legs or cross legs		Impulsive		Pre-Natal testing abnormal
Reflexes abnromal (infantile reflexes persistent)			Bradykinesia	Paroxysmal tonic upgaze		Gagging/Choking	Short stature		Maladaptive behaviors: biting, hair-pulling, pinching slapping		Pulmonary infections recurrent
Stroke, ischemic			Central motor conduction delays	saccadic eye movements		GI motility slow (obstruction)	Ribs, widenening		Self-harming, biting self, hair-pulling, scratching		Tonsils/adenoids enlarged
Cerebellar hypoplasia (includes atrophy) Does this also include cortical atrophy?			Dyskinesia	Visual developmental regression, loss of tracking		Intussusception/volvulus	Tone abnormal (@kyle horning, does this mean hypertonia, or hypotonia?)		Temper Tantrums		Urinary system abnormalities (includes bladder atonia - need catheritization, abnormal ureters, hydronephrosis, urine flow obstruction)
			Dystonia	Visuoconstructive ability impaired		Ketogenic diet -related issues (includes beneficial and adverse reactions)			ADHD		Uro-genitalia underdeveloped, hypospadius
			Fatigue						Fascination with certain sensory items, especially lights, vibration, music.		Urogenitial- kidney and bladder infections
			Hand stereotypies (mouthing and clapping)						No difficult behaviors		
			Incoordination								
			Involuntary movements								
			Repetitive movements								
			Spastic quadriparesis								

Draft Conceptual Model of Severely Affected DEE's

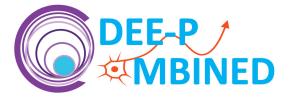


Neurological	Cognition	Communication	Motor	Visual	Sleep	Gastrointestinal	Musculoskeletal	Skin	Behavior	Emotional	Other Physical
Hypotonia (axial - includes life-threatening features related to hyptonia such as swallowing, cough reflex, not moving, pneumonia)	Cognitive Disability	Alternative and/or augmentative communication devices used by a few (includes single switches, tobii dynavox, kids use talkers, stepbystep, big mac)	Fine motor skills delayed/impaired (includes hand use abnormalities)	Cortical visual impairment (includes cortical blindness, visual field deficits)	Initiation and maintenance difficulties of sleep (includes requent awakenings, sleep-wake transition)	Constipation	Scoliosis (includes surgical corrections)	Temperture instability (includes in extremeties)	Autism Spectrum Disorder	Irritability	Respiratory issues (includes recurrent pneumonia, airway infections, supplemental O2, ventilation vests, respiratory fai
Seizures - (includes: intractable, refractory; infantile spasms, clusters WEST syndrome, focal or generalized, tonic, myoclonic, absence, gelastic, febrile)		Expressive communication decreased profoundly	Gross motor skills delayed/impaired (includes non-ambuatory)	Strabismus (abnormal eye movements, tracking difficulties)	Seizures in sleep	Reflux	Craniofacial abnormalities (dysmorphic features)	Autonomic dysfunction (frequent fevers, extremeties cold)	Autistic traits, includes abnormal eye contact	Anxiety	Pain, high tolerance
EEG abnormal (in about 50%, miss some types of seizures from deep structures)	Memory deficits	Non-verbal, but communication through the use of facial expresion (smiles, cries, turn away, laughs), body postures and gestures.	Oral motor impairment (includes sucking and swallowing disorders, frequent drooling, and feeding difficulties, tongue thrusting, excessive chewing, mouthing behaviors, teeth grinding,	Nystagmus (includes interictal)	Cycle abnormalities (sleep wake cycle in 24 hours)	Vomiting	Hands and feet abnormalities, includes talipes and small feet	Hemianesthesia (Sensory deficit atternating in limb side)	Repetitive behaviors - hand-wringing	Happy demeanor (Even-keeled, go with the flow, not so much behaviors and emotional reactions)	Birth abnormalities (Face presentation)

The severely affected sub-population of 6 disorders included:

- CACNA1A mutation
- CDKL5 mutation
- GRIN-related disorders
- SCN2A mutation
- SCN8A mutation
- Schinzel-Giedion syndrome
 - FOXG1 mutation to be added

Draft Conceptual Model of Severely Affected DEE's



Neurological	Cognition	Communication	Motor	Visual	Sleep	Gastrointestinal	Musculoskeletal	Skin	Behavior	Emotional	Other Physical
Hypotonia (axial - includes life-threatening features related to hyptonia such as swallowing, cough reflex, not moving, pneumonia)	Cognitive Disability	Alternative and/or augmentative communication devices used by a few (includes single switches, tobii dynavox, kids use talkers, stepbystep, big mac)	Fine motor skills delayed/impaired (includes hand use abnormalities)	Cortical visual	Initiation and maintenance difficulties of sleep (includes requent awakenings, sleep-wake transition)	Constipation	Scoliosis (includes surgical corrections)		Autism Spectrum Disorder	Irritability	Respiratory issues (includes recurrent pneumonia, airway infections, supplemental O2, ventilation vests, respiratory failure
Seizures - (includes: intractable, refractory; infantile spasms, clusters, WEST syndrome, focal or generalized, tonic, myoclonic, absence, gelastic, febrile)	Global developmental delay ,	Expressive communication decreased profoundly	Gross motor skills delayed/impaired (includes non-ambuatory)	Strabismus (abnormal eye movements, tracking difficulties)	Seizures in sleep	Reflux	Craniofacial abnormalities (dysmorphic features)	Autonomic dysfunction (frequent fevers, extremeties cold)	Autistic traits, includes abnormal eye contact	Anxiety	Pain, high tolerance
EEG abnormal (in about 50%, miss some types of seizures from deep structures)	Memory deficits	Non-verbal, but communication through the use of facial expresion (smiles, cries, turn away, laughs), body postures and gestures.	Oral motor impairment (includes sucking and swallowing disorders, frequent drooling, and feeding difficulties, tongue thrusting, excessive chewing, mouthing behaviors, teeth grinding,	Nystagmus (includes interictal)	Cycle abnormalities (sleep wake cycle in 24 hours)	Vomiting	Hands and feet abnormalities, includes talipes and small feet	Hemianesthesia (Sensory deficit alternating in limb side)	Repetitive behaviors - hand-wringing	Happy demeanor (Even-keeled, go with the flow, not so much behaviors and emotional reactions)	Birth abnormalities (Face presentation)

Domains shared by all disorders

Neurological: Hypotonia, Seizures

• Cognitive: Cognitive Disability, Global Developmental Delay

Communication: Expressive and Receptive disabilities, Non-Verbal, AAC Devices Used

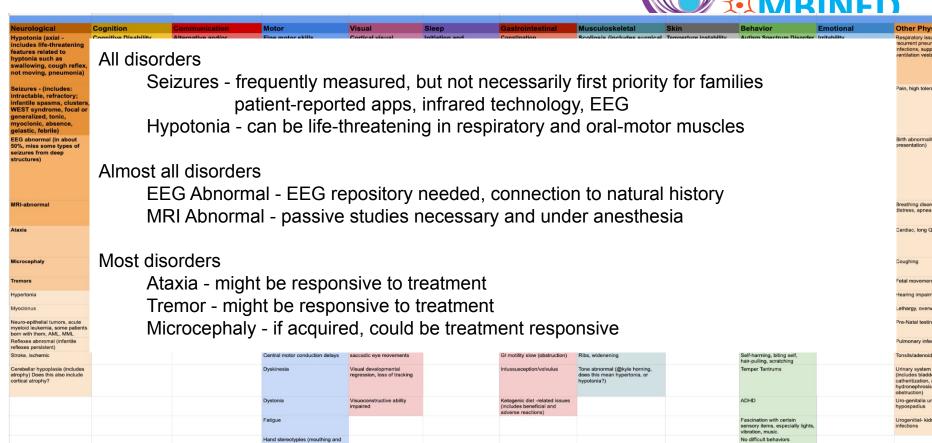
Motor: Non-ambulatory, Reduced Hand Use, Oral-Motor disabilities

Visual Cortical Visual Impairment

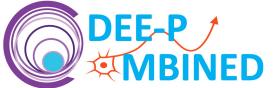
Sleep Initiation and Maintenance of Sleep

Neurological Category





Cognition Category



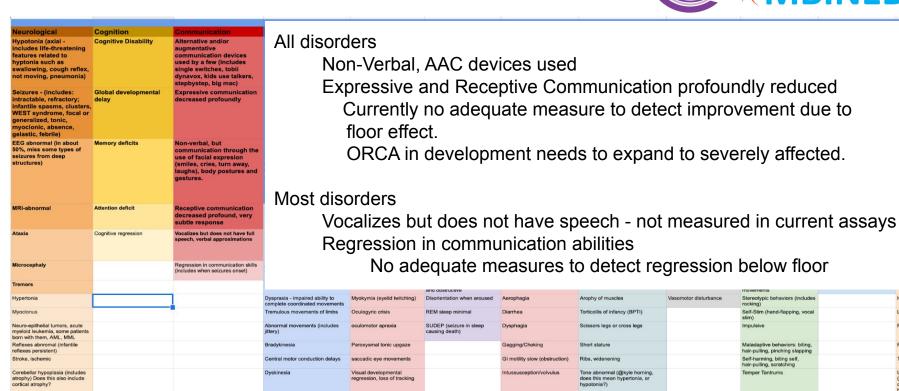
leurological	Cognition	Communication	Motor	Visual	Sleep	Gastrointestinal	Musculoskeletal	Skin	Behavior	Emotional	Other Phy			
lypotonia (axial - ncludes life-threatening eatures related to pytonia such as wallowing, cough reflex, tot moving, pneumonia)	Cognitive Disability		All disorders Cognitive disability and Global developmental delay - Bayley, Vineland, needs reanalysis, strong floor effect, not sensitive enough											
	Global developmental delay													
:EG abnormal (in about 0%, miss some types of eizures from deep tructures)	Memory deficits	Almost all Men	disorders nory deficit	t - Event-	related po	otentials r	neasure pa	assive rea	action	ppy demeanor (Even-keelec with the flow, not so much laviors and emotional ctions)	f, Birth abnormali presentation)			
IRI-abnormal	Attention deficit	Most diso	rders							action- not affectionate	Breathing disor distress, apnea			
staxia	Cognitive regression	Atte	ntion defic	it - No ad	equate m	easure fo	or DEE pati	ents		stration	Cardiac, long C			
licrocephaly		Regression in communication skills (includes when seizures onset)	Athetosis (includes choreoathetosis)	Extoliation syndrome	Terrors, night terrors (unable to describe)	Tube fed (includes PEG or nasogastric tubes)	Orthopedic issues (includes hip replacements, osteotomies, dislocated hips, hip dysplasia)	Numbness of extremities	Stereotypic hand movements	Mood swings	Coughing			
remors			Balance - unsteady	Glaucoma	Sleep apnea (includes central and obstructive	Infant feeding issues	Osteoporosis	Pallor	Hand flapping or waving movements	Pyschosis	Fetal movemen			
lypertonia			Dyspraxia - impaired ability to complete coordinated movements	Myokymia (eyelid twitching)	Disorientation when aroused	Aerophagia	Arophy of muscles	Vasomotor disturbance	Stereotypic behaviors (includes rocking)		Hearing impairs			
tyoclonus		=	Tremulous movements of limbs	Oculogyric crisis	REM sleep minimal	Diarrhea	Torticollis of infancy (BPTI)		Self-Stim (hand-flapping, vocal stim)		Lethargy, overv			
leuro-epithelial tumors, acute hyeloid leukemia, some patients orn with them, AML, MML			Abnormal movements (includes jittery)	oculomotor apraxia	SUDEP (seizure in sleep causing death)	Dysphagia	Scissors legs or cross legs		Impulsive		Pre-Natal testin			
teflexes abnromal (infantile eflexes persistent)			Bradykinesia	Paroxysmal tonic upgaze		Gagging/Choking	Short stature		Maladaptive behaviors: biting, hair-pulling, pinching slapping		Pulmonary infe			
troke, ischemic			Central motor conduction delays	saccadic eye movements		GI motility slow (obstruction)	Ribs, widenening		Self-harming, biting self, hair-pulling, scratching		Tonsils/adenoid			
erebellar hypoplasia (includes trophy) Does this also include ortical atrophy?			Dyskinesia	Visual developmental regression, loss of tracking		Intussusception/volvulus	Tone abnormal (@kyle horning, does this mean hypertonia, or hypotonia?)		Temper Tantrums		Urinary system (includes bladd catheritization, hydronephrosis obstruction)			
			Dystonia	Visuoconstructive ability impaired		Ketogenic diet -related issues (includes beneficial and adverse reactions)			ADHD		Uro-genitalia u hypospadius			
			Fatigue			***			Fascination with certain sensory items, especially lights		Urogenitial- ki			

Communication Category



Fascination with certain

sensory items, especially lights



Visuoconstructive ability

impaired

Ketogenic diet -related issues

(includes beneficial and

adverse reactions)

Dystonia

Fatigue

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ements

Pulmonary infection

Lethargy, overwh

Pre-Natal testing

(includes bladder catheritization, ab hydronephrosis, u obstruction) Uro-genitalia und hypospadius Urogenitial- kidne

Motor Category



									LIVIR		
Neurological	Cognition	Communication	Motor	Visual	Sleep	Gastrointestinal	Musculoskeletal	Skin	Behavior	Emotional	Other Ph
	Cognitive Disability	Alternative and/or augmentative communication devices used by a few (includes single switches, tobii dynavox, kids use talkers, stepbystep, big mac)	Fine motor skills delayed/impaired (includes hand use abnormalities)	All diso G		or Skills ir	npaired - r	ion-ambu	ulatory	tability	Respiratory in recurrent pre- infections, su ventilation ve
	Global developmental delay	Expressive communication decreased profoundly	Gross motor skills delayed/impaired (includes non-ambuatory)	Fi	ine Motor ral Motor	Skills implimpairme	oaired - ha ent - crucia	nd use is I for surv	critical ival and	ciety	Pain, high to
EEG abnormal (in about 50%, miss some types of leizures from deep structures)	Memory deficits	use of facial expresion (smiles, cries, turn away,	Oral motor impairment (includes sucking and swallowing disorders, frequent drooling, and feeding difficulties, tongue thrusting, excessive chewing, mouthing behaviors, teeth grinding, dysphagia)	Many d	appropri isorders	ate to me	asure in th	iis popula	ation	ppy demeanor (Even-keeler with the flow, not so much saviors and emotional ctions)	
MRI-abnormal	Attention deficit	Receptive communication decreased profound, very subtle response	Hand use impaired, loss of purposeful hand movements	Lo	oss of pu	rposeful h	and use			ection- not affectionate	Breathing disc distress, apne
Ataxia	Cognitive regression	Vocalizes but does not have full speech, verbal approximations	Regression in motor skills (includes due to seizures)	R	egressior	n in motor	abilities			stration	Cardiac, long
dicrocephaly		Regression in communication skills (includes when seizures onset)	Athetosis (includes choreoathetosis)	Exfoliation syndrome	Terrors, night terrors (unable to describe)	Tube fed (includes PEG or nasogastric tubes)	Orthopedic issues (includes hip replacements, osteotomies, dislocated hips, hip dysplasia)	Numbness of extremities	Stereotypic hand movements	Mood swings	Coughing
remors			Balance - unsteady	Glaucoma	Sleep apnea (includes central and obstructive	Infant feeding issues	Osteoporosis	Pallor	Hand flapping or waving movements	Pyschosis	Fetal moveme
Hypertonia		1	Dyspraxia - impaired ability to complete coordinated movements	Myokymia (eyelid twitching)	Disorientation when aroused	Aerophagia	Arophy of muscles	Vasomotor disturbance	Stereotypic behaviors (includes rocking)		Hearing impai
Nyocionus			Tremulous movements of limbs	Oculogyric crisis	REM sleep minimal	Diarrhea	Torticollis of infancy (BPTI)		Self-Stim (hand-flapping, vocal stim)		Lethargy, ove
Neuro-epithelial tumors, acute nyeloid leukemia, some patients forn with them, AML, MML			Abnormal movements (includes jittery)	oculomotor apraxia	SUDEP (seizure in sleep causing death)	Dysphagia	Scissors legs or cross legs		Impulsive		Pre-Natal test
Reflexes abnromal (infantile eflexes persistent)			Bradykinesia	Paroxysmal tonic upgaze		Gagging/Choking	Short stature		Maladaptive behaviors: biting, hair-pulling, pinching slapping		Pulmonary in
Stroke, ischemic			Central motor conduction delays	saccadic eye movements		GI motility slow (obstruction)	Ribs, widenening		Self-harming, biting self, hair-pulling, scratching		Tonsils/adend
Cerebellar hypoplasia (includes strophy) Does this also include cortical atrophy?			Dyskinesia	Visual developmental regression, loss of tracking		Intussusception/volvulus	Tone abnormal (@kyle horning, does this mean hypertonia, or hypotonia?)		Temper Tantrums		Urinary syste (includes blac catheritization hydronephrosobstruction)
			Dystonia	Visuoconstructive ability impaired		Ketogenic diet -related issues (includes beneficial and adverse reactions)			ADHD		Uro-genitalia hypospadius
			Fatigue						Fascination with certain sensory items, especially lights vibration, music.		Urogenitial- k infections
			Hand stereotypies (mouthing and						No difficult behaviors		

Vision Category



									AIVIB			
leurological	Cognition Cognitive Disability	Communication Alternative and/or	Motor Fine motor skills	Visual Cortical visual	Sleep	Gastrointestinal	Musculoskeletal	Skin	Behavior	Emotional	Other Pl	
protolia (axial - ciludes life-threatening eatures related to yptonia such as wallowing, cough reflex,	Cognitive Disability	augmentative communication devices used by a few (includes single switches, tobii	delayed/impaired (includes hand use abnormalities)		All diso	rders					urrent pr ections, s itilation v	
ot moving, pneumonia)		dynavox, kids use talkers, stepbystep, big mac)			C	ortical vis	sual impairr	nent - EF	RG is diffic	ult	n, high t	
eizures - (includes: ntractable, refractory; nfantile spasms, clusters, VEST syndrome, focal or eneralized, tonic, nyoclonic, absence, elastic, febrile)	Global developmental delay	Expressive communication decreased profoundly	Gross motor skills delayed/impaired (includes non-ambuatory)	Strabismus (abnormal eye movements, tracking difficulties)	and patient-reported outcome necessary							
EG abnormal (in about %, miss some types of sizures from deep	Memory deficits	Non-verbal, but communication through the	Oral motor impairment (includes sucking and	Nystagmus (includes interictal)	Most disorders							
tructures)		use of facial expresion (smiles, cries, turn away, laughs), body postures and gestures.	swallowing disorders, frequent drooling, and feeding difficulties, tongue thrusting, excessive chewing, mouthing behaviors, teeth grinding, dysphagia)		Strabismus - may not be appropriate endpoint Nystagmus - may be measurable endpoint							
IRI-abnormal	Attention deficit	Receptive communication decreased profound, very	Hand use impaired, loss of purposeful hand movements	Visual impairment, glasses	E (1,				gran aradinig, aradia ara		athing dis	
		subtle response							mouth, and hands being touched)			
taxia	Cognitive regression	Vocalizes but does not have full speech, verbal approximations	Regression in motor skills (includes due to seizures)	Light sensitivity increased	Snoring and teeth grinding (bruxism)	Incontinence	Dental issues - Abnormal dentition	Mottled skin, rosie red skin	Sensory seeking (includes Massaging scalp breaks seizures, likes touch, snuggle, will swipe at people, love touch and stretch)	Frustration	Cardiac, long	
licrocephaly		Regression in communication skills (includes when seizures onset)	Athetosis (includes choreoathetosis)	Exfoliation syndrome	Terrors, night terrors (unable to describe)	Tube fed (includes PEG or nasogastric tubes)	Orthopedic issues (includes hip replacements, osteotomies, dislocated hips, hip dysplasia)	Numbness of extremities	Stereotypic hand movements	Mood swings	Coughing	
remors			Balance - unsteady	Glaucoma	Sleep apnea (includes central and obstructive	Infant feeding issues	Osteoporosis	Pallor	Hand flapping or waving movements	Pyschosis	Fetal moven	
pertonia			Dyspraxia - impaired ability to complete coordinated movements	Myokymia (eyelid twitching)	Disorientation when aroused	Aerophagia	Arophy of muscles	Vasomotor disturbance	Stereotypic behaviors (includes rocking)		Hearing impa	
yoclonus		2	Tremulous movements of limbs	Oculogyric crisis	REM sleep minimal	Diarrhea	Torticollis of infancy (BPTI)		Self-Stim (hand-flapping, vocal stim)		Lethargy, over	
euro-epithelial tumors, acute yeloid leukemia, some patients rn with them, AML, MML			Abnormal movements (includes jittery)	oculomotor apraxia	SUDEP (seizure in sleep causing death)	Dysphagia	Scissors legs or cross legs		Impulsive		Pre-Natal tes	
eflexes abnromal (infantile flexes persistent)			Bradykinesia	Paroxysmal tonic upgaze		Gagging/Choking	Short stature		Maladaptive behaviors: biting, hair-pulling, pinching slapping		Pulmonary is	
roke, ischemic			Central motor conduction delays	saccadic eye movements		GI motility slow (obstruction)	Ribs, widenening		Self-harming, biting self, hair-pulling, scratching		Tonsils/aden	
erebellar hypoplasia (includes rophy) Does this also include rtical atrophy?			Dyskinesia	Visual developmental regression, loss of tracking		Intussusception/volvulus	Tone abnormal (@kyle horning, does this mean hypertonia, or hypotonia?)		Temper Tantrums		Urinary syste (includes bla catheritization hydronephro obstruction)	
			Dystonia	Visuoconstructive ability impaired		Ketogenic diet -related issues (includes beneficial and adverse reactions)			ADHD		Uro-genitalia hypospadius	
			Fatigue						Fascination with certain sensory items, especially lights, vibration, music.		Urogenitial- k infections	
			Hand stereotypies (mouthing and						No difficult behaviors			

Sleep Category



	Cognition	Communication	Motor	Visual	Sleep	Gastrointestinal	Musculoskeletal	Skin	Behavior	Emotional	Other Phy					
Hypotonia (axial - ncludes life-threatening features related to hyptonia such as swallowing, cough reflex, not moving, pneumonia)	Cognitive Disability	Alternative and/or augmentative communication devices used by a few (includes single switches, tobii dynavox, kids use talkers, stepbystep, big mac)	Fine motor skills delayed/impaired (includes hand use abnormalities)	Cortical visual impairment (includes cortical blindness, visual field deficits)	Initiation and maintenance difficulties of sleep (includes requent awakenings, sleep-wake transition)	All disor	G. G. G	finelules in extremeties	Autism Spectrum Disorder	•	Respiratory iss recurrent oneu sup vest					
	3lobal developmental delay	Expressive communication decreased profoundly	Gross motor skills delayed/impaired (includes non-ambuatory)	Strabismus (abnormal eye movements, tracking difficulties)	Seizures in sleep	Initiation and maintenance of sleep - potentially measurable endpoint										
EEG abnormal (in about Money Medical M	Memory deficits	Non-verbal, but communication through the use of facial expresion (smiles, cries, turn away, laughs), body postures and gestures.	Oral motor impairment (includes sucking and swallowing disorders, frequent drooling, and feeding difficulties, tongue thrusting, excessive chewing, mouthing behaviors, teeth grinding, dysphagia)	Nystagmus (includes interictal)	Cycle abnormalities (sleep wake cycle in 24 hours)	Most disorders Seizures in sleep - urgent and life-altering needs home-based measures						Most disorders Seizures in sleep - urgent and life-a				ig
MRI-abnormal A	Attention deficit	Receptive communication decreased profound, very subtle response	Hand use impaired, loss of purposeful hand movements	Visual impairment, glasses	Excessive daytime sleepiness (includes catatonia)											
Ataxia C	Cognitive regression	Vocalizes but does not have full speech, verbal approximations	Regression in motor skills (includes due to seizures)	Light sensitivity increased	Snoring and teeth grinding (bruxism)	Many di	sorders				ing (
Microcephaly		Regression in communication skills (includes when seizures onset)	Athetosis (includes choreoathetosis)	Exfoliation syndrome	Terrors, night terrors (unable to describe)	Cy	cle abnorr	nalities -	circadian	measure	S					
Fremors			Balance - unsteady	Glaucoma	Sleep apnea (includes central and obstructive		ould be eff	ective.			eme					
Hypertonia			Dyspraxia - impaired ability to complete coordinated movements	Myokymia (eyelid twitching)	Disorientation when aroused		ould be ell	CCIIVE			pair					
Myoclonus		2	Tremulous movements of limbs	Oculogyric crisis	REM sleep minimal	Ex	cessive da	avtime sle	eepiness -		oven					
Neuro-epithelial tumors, acute myeloid leukemia, some patients porn with them, AML, MML			Abnormal movements (includes jittery)	oculomotor apraxia	SUDEP (seizure in sleep causing death)		atatonia/na	•	•		ed					
Reflexes abnromal (infantile reflexes persistent)			Bradykinesia	Paroxysmal tonic upgaze		•	atatomam	a. 00.0p0)	, 110000 10	bo otaa.	infe					
Stroke, ischemic			Central motor conduction delays	saccadic eye movements					hair-pulling, scratching		enoie					
Cerebellar hypoplasia (includes atrophy) Does this also include cortical atrophy?			Dyskinesia	Visual developmental regression, loss of tracking		Intussusception/volvulus	Tone abnormal (@kyle horning, does this mean hypertonia, or hypotonia?)		Temper Tantrums		Urinary system (includes blade catheritization, hydronephrosis obstruction)					
			Dystonia	Visuoconstructive ability impaired		Ketogenic diet -related issues (includes beneficial and adverse reactions)			ADHD		Uro-genitalia u hypospadius					
			Fatigue						Fascination with certain sensory items, especially lights, vibration, music.		Urogenitial- kid infections					
			Hand stereotypies (mouthing and clapping)						No difficult behaviors							

Other categories



								T I	<u> </u>		
Neurological	Cognition	Communication	Motor	Visual	Sleep	Gastrointestinal	Musculoskeletal	Skin	Behavior	Emotional	Other Ph
Hypotonia (axial - ncludes life-threatening features related to nyptonia such as	Cognitive Disability	Alternative and/or augmentative communication devices used by a few (includes	Fine motor skills delayed/impaired (includes hand use abnormalities)	Cortical visual impairment (includes cortical blindness, visual field deficits)	Initiation and maintenance difficulties of sleep (includes requent awakenings.	Constipation	Scoliosis (includes surgical corrections)	Temperture instability (includes in extremeties)	Autism Spectrum Disorde	r Irritability	Respiratory is recurrent pne infections, su ventilation ve
Nost disord	ders						Craniofacial abnormalities	Autonomic dysfunction	Autistic traits, includes	Anxiety	Pain, high tol
Gastı	rointestina	al: Constip	ation, Refl	ux, Vomit	ting (QoL	issue)	(dysmorphic features)	(frequent fevers, extremeties cold)	abnormal eye contact		
Musc	culoskelet	al: Scoliosi	s (measura	able traje	ectory)		Hands and feet abnormalities, includes talipes and small feet	Hemianesthesia (Sensory deficit alternating in limb side)	Repetitive behaviors - hand-wringing	Happy demeanor (Even-keele go with the flow, not so much behaviors and emotional reactions)	
Skin:		Tempera	ature insta	bility (me	easurable))					
Beha	vior:	Autism t	traits (eye	contact,	ssues)	Ankle abnormalities (pronation, inward rolling of ankle and foot)	Hirsute as infants	Sensory defensive (includes (hair brushing, around the mouth, and hands being touched)	Affection- not affectionate	Breathing dis distress, apne	
Emot	ional:	Irritabilit	y (measur	able)	-	•	Dental issues - Abnormal dentition	Mottled skin, rosie red skin	Sensory seeking (includes Massaging scalp breaks seizures, likes touch, snuggle, will swipe at people, love touch and stretch)	Frustration	Cardiac, long
_				,			Orthopedic issues (includes hip replacements, osteotomies, dislocated hips, hip dysplasia)	Numbness of extremities	Stereotypic hand movements	Mood swings	Coughing
Othe	r:	Pulmon	ary Issues	(life-end	angering)		Osteoporosis	Pallor	Hand flapping or waving movements	Pyschosis	Fetal movem
			•	`	0 0,		Arophy of muscles	Vasomotor disturbance	Stereotypic behaviors (include rocking)		Hearing impa
Neuro-epithelial tumors, acute			Tremulous movements of limbs	Oculogyric crisis	SUDEP (seizure in sleep	Diarrhea	Torticollis of infancy (BPTI)		Self-Stim (hand-flapping, voca stim)		Lethargy, ove
nyeloid leukemia, some patients orn with them, AML, MML			Abnormal movements (includes jittery)	oculomotor apraxia	causing death)	Dysphagia	Scissors legs or cross legs		Impulsive		Pre-Natal tes
Reflexes abnromal (infantile eflexes persistent)			Bradykinesia	Paroxysmal tonic upgaze		Gagging/Choking	Short stature		Maladaptive behaviors: biting, hair-pulling, pinching slapping		Pulmonary in
Stroke, ischemic			Central motor conduction delays	saccadic eye movements		GI motility slow (obstruction)	Ribs, widenening		Self-harming, biting self, hair-pulling, scratching		Tonsils/adend
Cerebellar hypoplasia (includes strophy) Does this also include cortical atrophy?			Dyskinesia	Visual developmental regression, loss of tracking		Intussusception/volvulus	Tone abnormal (@kyle horning, does this mean hypertonia, or hypotonia?)		Temper Tantrums		Urinary syste (includes blac catheritization hydronephrosobstruction)
			Dystonia	Visuoconstructive ability impaired		Ketogenic diet -related issues (includes beneficial and adverse reactions)			ADHD		Uro-genitalia hypospadius
			Fatigue						Fascination with certain sensory items, especially lights vibration, music.	5,	Urogenitial- k infections
			Hand stereotypies (mouthing and clapping)						No difficult behaviors		



Summary:

- Pre-workshop document: Reviews of existing outcome measures by category, domain
- Floor effect for many outcome measures
- Need to expand validated measures to be more sensitive
- Need to study new or expanded measures across severely affected DEE's
- Need for individualized measures- i.e. Goal Attainment Scaling
- These Disease Concept Maps are <u>drafts</u> and need to be finalized



Proposed Project: Finalize the Conceptual Model of Severely Affected DEEs

- Qualitative interview-based studies of at least five DEE's with severely affected populations
- Scoping Ability Surveys of the same disorders (led by Dr. Anne Berg)
- Community Voice Reports for at least 2 disorders (via TREND Community)
- Merged conceptual map of severely affected DEE's
- Overview of relevant biomarkers and outcome measures (BOMs) corresponding to the domains in the merged map.
- Description of measures to be developed to fill gaps in BOMs.