Developmental & Epileptic Encephalopathies (DEE)

Patient-Led Listening Session (PLS) with FDA CBER Summary

November 22, 2024







This listening session was organized by the Developmental and Epileptic Encephalopathies Project (DEE-P Connections), in partnership with the Rare Epilepsy Network (REN).

With hosts Gabi Conecker, Executive Director and Co-Founder of Decoding Developmental Epilepsies (home of DEE-P Connections) and SCN8A Parent, and Christina Saninocencio, Chair of the Rare Epilepsy Network, Co-Founder - LGS Foundation, and LGS Sibling.

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Introduction to Developmental and Epileptic Encephalopathies (DEE) and Neurodevelopmental Disorders (NDDs)

Developmental and Epileptic Encephalopathies (DEEs) and Neurodevelopmental Disorders (NDDs) encompass a diverse group of severe conditions that significantly impact cognitive, motor, and communication skills. DEEs often have an identified genetic cause but the cause may be presumed to be genetic if a specific genetic variant cannot be identified. The majority but not all children with a DEE have seizures and underlying neurobiological abnormalities that impair development. Irrespective, these conditions manifest in infancy or early childhood and profoundly affect quality of life.

Importantly, there is variation in phenotype including the presence of seizures. However, many with DEEs or NDDs may face similarly profound impairments due to other neurological or developmental challenges. Despite differences in clinical presentation, shared difficulties—such as communication barriers, motor dysfunction, feeding issues, and co-occurring medical conditions—unite these groups in their need for innovative treatments and comprehensive support.

This report highlights the voices of families and caregivers, whose experiences provide critical insights into the needs, challenges and priorities of this diverse and severely affected community.

1. EXECUTIVE SUMMARY

The Developmental and Epileptic Encephalopathies (DEE) Patient Listening Session, organized by DEE-P Connections (DEE-P) and the Rare Epilepsy Network (REN), held on November 22, 2024, brought together parents, patient advocates and researchers to discuss the challenges and priorities of the DEE community. FDA representatives were present as listeners to the sessions.

Key Themes Highlighted:

- **Shared Challenges Across Diagnoses:**
  Families emphasized the devastating impact of uncontrolled seizures and non-seizure symptoms, such as communication barriers, hypotonia, gastrointestinal issues, sleep disruptions, and developmental delays, irrespective of the diagnosis. These challenges profoundly affect the quality of life for both children and their families.

- **Barriers to Clinical Trial Participation:**
  Parents identified logistical challenges, financial burdens, and restrictive trial protocols as significant barriers. Decentralized trials, local data collection, and flexible trial designs were proposed to improve accessibility and participation.

- **Limitations of Current Outcome Measures:**
  Existing clinical outcome assessments fail to capture small but meaningful improvements in profoundly impaired children. Caregivers stressed the need for tools that measure real-world progress on issues that are most important to them. Caregivers

highly value tools that allow more creative measures such as home-based monitoring, caregiver observations, and indicators to compare “good days” and “bad days.”

- **Risk Tolerance for New Treatments:**
  Families expressed a high tolerance for risk, given the relentless progression of DEEs. They are willing to endure substantial burdens and side effects if treatments promise improvements in quality of life, comfort, and functional abilities.

- **Community-wide data on Needs and Priorities across the DEE/NDD Communities**

  Professor Jenny Downs presented insights from *The Inchstone Project* (www.inchstoneproject.org), a global consortium evaluating the unmet needs of DEE/NDD caregivers and the limitations of clinical outcome assessments (COAs) in capturing small but meaningful improvements ("inchstones"). Using data from a survey of 267 families, she highlighted commonalities across DEE conditions, emphasizing expressive and receptive communication as top priorities for improvement regardless of etiology, age, or severity. Her presentation underscored the profound impacts of these conditions on children, families, and communities, aligning with caregiver experiences shared during the session. Professor Downs emphasized the need for tailored tools, transdiagnostic approaches, and robust trial designs to advance clinical trial readiness and develop impactful therapies in this underserved population.

This report amplifies the voices of the DEE community, whose testimonies provide critical guidance for the development of treatments that reflect the realities and priorities of those living with these conditions.

The session underscored the urgency for disease-modifying therapies that address shared challenges across the DEEs.

2. INTRODUCTION

A Patient Listening Session (PLS) provides an opportunity for the FDA to gain insights into what matters most to patients, caregivers, and advocates during the development of medical products. These sessions enable FDA review staff to better understand the health-related experiences, perspectives, and needs of those directly impacted by specific conditions, ensuring that patient voices are incorporated into regulatory decision-making.

With these goals in mind, a PLS on Developmental and Epileptic Encephalopathies (DEE) and Neurodevelopmental DIsorders (NDD) was held on November 22, 2024. The session highlighted the challenges faced by patients and families impacted by DEE/NDDs, as well as community priorities for treatment and care. The audience included representatives from FDA Centers/Divisions, as listed *in Appendix A*.

The PLS was organized in collaboration with representatives from DEE-P Connections, Rare Epilepsy Network (REN), and other patient advocacy organizations working within the DEE community. The session featured testimonies from caregivers who shared personal stories, challenges, hopes for the future, as well as an overview of The Inchstone Project survey results on priorities of over 250 caregivers representing more than 21 DEE etiologies. *List of speakers in Appendix B*.

FDA Patient Listening Session Goals and Topics:

During the session, families from across the DEE/NDDs community highlighted the shared challenges faced by children with these conditions. These included refractory seizures and a wide array of non-seizure issues that significantly impact family quality of life. Key areas of unmet need voiced by caregivers included difficulties with communication, fine and gross motor skills, intellectual disabilities, sleep disruptions, hypotonia, movement disorders, cortical visual impairment (CVI), pulmonary complications, gastrointestinal issues, and behavioral challenges.

The conversation also centered on what matters most to families in the context of clinical trials, including barriers to participation, the need for more inclusive and accurate clinical outcome assessments (COAs), and families' willingness to tolerate substantial risk for treatments that offer meaningful improvements in their children's quality of life.

As Christina SanInocencio noted, the urgency for more effective treatment options cannot be overstated. Patients and families need disease-modifying therapies that address underlying conditions, better control seizures, alleviate co-morbidities, and improve quality of life. Advancing treatment options for rare disorders is essential, offering hope and meaningful change for those who face these challenges daily—both current patients and those in the future.

3. CAREGIVER PRESENTATIONS

Gabi : Parent of 12-year-old with SCN8A-DEE

E.C is a 12-year-old boy living with SCN8A-DEE, a rare and severe genetic disorder. Within days of E.C.'s birth, he exhibited irregular movements and failure to thrive. For months, E.C. remained undiagnosed while experiencing dangerous infantile spasms. His seizures worsened over the next year, and developmental milestones were never met. Eventually, Elliott was diagnosed with SCN8A.

Despite taking a combination of four daily anti-seizure medications, E.C.'s seizures are still unpredictable and intractable. E.C. takes a total of 16 medications each day to control a multitude of symptoms. None of these medications address the root cause of E.C.'s symptoms or truly improve his quality of life.

Beyond seizures, E.C. faces several other significant challenges. He has cortical visual impairment (CVI), which means he struggles to see the world clearly, limiting his engagement with his surroundings. Severe hypotonia impacts his motor function, making it impossible for him to sit up, hold toys, or perform other basic movements. He also lacks the strength to cough, making common illnesses life-threatening and often requiring ICU stays.

E.C.'s communication is limited due to his condition**.** His mother has never heard him say "I love you" or express his emotions verbally, making caregiving particularly challenging.

The family's hopes for treatment are centered on improving E.C.'s communication, muscle tone, and quality of life. Even small gains, like increased head control, the ability to sit comfortably, or the strength to effectively swallow saliva from his mouth, thereby avoiding aspiration, would dramatically improve his quality of life.

Patricia : Parent to 9 year old with FOXG1 syndrome

K.G. was born the day after Christmas in 2013, the youngest of five children. At two months of age, she experienced a medical crisis when she turned blue in her mother's arms. This led to numerous hospital visits and her first surgery. Over the next nine years, K.G. would undergo more than 60 surgeries and procedures.

In 2022, K.G. was diagnosed with FOXG1 syndrome, a rare genetic disorder that explains her severe seizures, GI dysfunction, chorea movements, and inability to sit or walk unassisted. She is largely non-verbal, speaking only the word "Mom." Despite this, K.G. and her mother have developed a unique and deeply personal form of communication. This bond has become the cornerstone of their relationship.

K.G's condition has dramatically impacted the family's quality of life. Her mother is forced to balance Kinsley's care with the needs of her other children, leading to significant emotional and financial strain, including the loss of her husband's business. The family faces isolation, often spending time in hospitals instead of participating in regular family activities like vacations or outings.

A meaningful treatment for K.G. would address her movement challenges, reduce hospitalizations, and improve her quality of life, allowing her family more quality time together at home. K.G.'s mother hopes that such treatments will not only help her daughter but also other families facing similar struggles with complex medical conditions.

Shannon : Parent to 6 year old (deceased), with CRELD1-related epilepsy

Though Z.G. was born healthy, things quickly changed when she began experiencing seizures. After years of uncertainty and numerous tests, Z.G.'s family learned that she had a rare, genetic condition called Creld1.

As Z.G.'s symptoms progressed, her seizures became more frequent and difficult to manage, despite being on multiple anti-seizure medications. Over time, she was diagnosed with Lennox-Gastaut syndrome, a severe epilepsy syndrome secondary to her CRELD1 condition, marking a significant progression of her disease. She also began to display other symptoms such as global developmental delay, failure to thrive, difficulty swallowing, hypotonia, and a range of comorbidities, including nephrocalcinosis and diabetes insipidus.

Z.G.'s family faced tremendous challenges balancing caregiving with everyday life. Her mother gave up her full-time job to become Z.G.'s primary caregiver, and her father had to close his business. The financial burden, compounded by frequent hospitalizations, made it even more difficult to maintain a semblance of normalcy.

Z.G.'s family was unable to control her seizures despite trying numerous medications and therapies. They had hoped for better treatment options that could improve muscle tone, reduce seizures, and alleviate other symptoms. The family believes that improved disease management and better treatments could have led to a better quality of life for Z.G and the family, with fewer hospitalizations and more time spent together.

Shawn : Parent to 7 year old with SCN2A

H.R.E. was born healthy and met early developmental milestones with joy. However, at 11 months of age, her life changed dramatically when she developed infantile spasms. This catastrophic seizure disorder altered the trajectory of her life and her family's.

H.R.E.'s seizures are relentless, occurring frequently and often in clusters. She can no longer sit, stand, or speak, and is completely dependent on her family for all daily activities. Her condition also causes significant issues with communication, as she cannot express pain, needs, or emotions.

For H.R.E.'s family, there are numerous challenges. The constant worry about seizures coupled with frequent alarms from the seizure monitor leads to sleep disturbances that further contribute to the family's exhaustion. The emotional toll of not being able to alleviate H.R.E.'s pain weighs heavily on them, and her father describes the overwhelming feeling of being unable to truly understand what his daughter is trying to communicate.

The family's life is marked by constant medical appointments and hospitalizations, leaving little room for typical family activities. Though they wish for better seizure control, H.R.E.'s father made it clear that even small improvements would allow them more quality time as a family,

with fewer trips to the hospital and improved communication. For families like theirs, the burden of doing nothing is devastating, as harm is already pervasive and guaranteed. While the risk/benefit calculus is complex, there could be a tremendous appetite for risk if there is even the possibility of relief.

Karen : Parent to 18 year old with CDKL5 deficiency disorder

When S.U. was born, she was the picture of health. Her mother described how she smiled early, rolled over early, and was a little chunk. At 10 weeks, S.U. experienced her first seizure. Her family spent years navigating the healthcare system, seeking answers to her unexplained symptoms. After numerous tests and accumulating multiple diagnoses along the way, they finally received an answer: S.U. had a mutation on the CDKL5 gene.

S.U.'s condition has caused severe developmental delays, intractable epilepsy, GI issues, and sensory sensitivities. She is non-verbal and entirely dependent on her mother for care. Her mother described the challenge of balancing caregiving with family life, as Samantha requires 15 medications and visits 14 medical specialists.

The sleep disturbances that come with S.U.'s condition have caused extreme sleep deprivation for her as well as her mother, making it hard to function during the day. S.U.'s family is isolated, with their lives revolving around hospital visits and therapy sessions.

For S.U.'s family, a meaningful treatment would address her GI dysfunction, sleep disturbances, and seizures. These improvements would significantly enhance their quality of life, allowing them more time together as a family and less time spent managing S.U.'s complex medical needs.

Megan : Parent to 6 year old with KCNT1-related Epileptic Encephalopathy

L.W. was born healthy, meeting typical milestones until the onset of seizures at 10 months old. Since then, her life has been defined by relentless, uncontrolled seizures that have caused rapid developmental regression. L.W. now requires full-time care, as she has lost most functional abilities.

Despite being on a variety of medications, L.W.'s seizures continue to persist, and her family struggles to manage her medical needs. Her condition has led to severe fatigue, as she sleeps 16-20 hours a day due to constant subclinical seizure activity. Her family has faced tremendous emotional, financial, and physical strain as they balance caregiving with everyday life.

L.W.'s parents hope for a treatment that would reduce seizure activity and allow L.W. more "awake time" to experience the world and interact with her family. Megan noted that "no improvement would be too small" to motivate them to pursue improved treatments as they know their time with L.W. is limited and want their other children to be able to enjoy more wakeful moments with their sister.

The family is actively involved in clinical research and hopes for treatments that will improve L.W.'s quality of life and reduce the burdens on her caregivers.

Mino : Parent to 2 year old with SCN8A mutation

A.S., now nearly 3 years old, began life with subtle developmental delays that worsened over time. His first signs of illness came when he failed to latch, track objects, and interact with his parents. At six months old, A.S. was diagnosed with infantile spasms, which led to multiple treatments and therapies, though none were truly effective.

A.S.'s life is impacted by daily seizures and multiple comorbidities, including hypotonia, constipation, and urinary retention. Despite participating in a clinical trial that initially showed promise, his seizures continued and he eventually required more invasive treatments. Minoo had to leave her job and the family is socially isolated as A.S.'s medical needs make it difficult to leave the house or travel.

The family's wish for A.S. is effective symptom management that would improve his ability to communicate, perform daily tasks independently, and provide more substantive seizure control. If this were feasible, A.S.'s family would experience improved quality of life and reduced caregiver burden.

Key Takeaways

The experiences shared during these testimonies illuminated not only the similarities in symptoms across the DEEs, but also the shared priorities of the DEE community. Parent priorities were not only reducing seizure burden but also addressing comorbidities and improving functional abilities for better quality of life and easing the burden of caregiving. These testimonies emphasize the importance of patient-centered approaches in drug development, clinical trial design, and regulatory decision-making. By addressing these needs, we can bring meaningful change and hope to families living with DEEs.

4. MODERATED DISCUSSION

Following the parent testimonies, speakers participated in a moderated question and answer session to further explore the perspectives of families affected by DEEs/NDDs. This part was moderated by Gabi Conecker, Co-Founder of DEE-P Connections. The questions focused on identifying key symptoms to target potential treatments and meaningful measures of improvement, understanding the barriers that limit participation in clinical trials, and exploring ways to make them more accessible. The discussion also explored the challenges with current clinical outcome assessments which are often poorly matched with unique and varied developmental progression of children with DEE/NDDs as well as the level of risk and burden families are willing to tolerate for potentially effective treatments given the uncertain benefits, side effects, and trial demands.

QUESTION 1. SYMPTOMS AND TREATMENT GOALS

The caregivers highlighted several **critical symptoms** they hoped potential treatments could address and articulated the ways in which they would measure success. Despite differences in diagnosis, there is significant overlap in the challenges faced, reflecting the similarities across the DEE community.

Communication Barriers

- Caregivers expressed the deep emotional impact of their children's communication limitations and the desire to understand their children's thoughts, needs, and discomforts in order to provide more appropriate and targeted care.
  - ➔ Even small gains, such as the ability to nod yes or no or point to a painful area, would have a profound effect on children and families.
  - ➔ Success would be measured by improvements in expressive and receptive communication, enabling better interactions and reducing frustration for both patients and families.

Tone and Movement Challenges

- Hypotonia and hypertonia (either low or high muscle tone) was frequently cited as a significant issue. It can contribute to major health issues (e.g. high aspiration risk, urinary & bowel difficulties, and respiratory issues) and also limits mobility, creates discomfort, and complicates daily caregiving tasks such as dressing, transferring, and positioning the child.
  - ➔ Success would be measured by increased tone or relaxation of muscles, greater ease in caregiving, and improved gross motor function and hand use enabling more independence.

Seizure Control

- Seizures, when present, were consistently identified as one of the most devastating symptoms, impacting every aspect of a child's health and development.

- Uncontrolled seizures lead to sleep disturbances, hospitalizations, developmental regression, and increased risks of life-threatening complications.
  - ➔ Success would be measured by fewer and less severe seizures, reduced hospitalizations, and greater opportunities for developmental progress, even in small but meaningful ways (i.e. improved head control, muscle tone for gross motor function, eye tracking, or communication).

Gastrointestinal (GI) Issues

- Though the particulars of GI challenges vary, they are pervasive in this population. Some children experience constipation requiring interventions like suppositories, while others face explosive diarrhea, malnutrition due to constant movement, or the inability to take in nutrition orally.

➔ Success would be measured by improved digestion, bowel regularity, reduced reliance on invasive interventions, and the ability to safely feed orally.

Sleep Disturbances

- Poor sleep affects the entire family, leading to increased seizures, developmental challenges, and caregiver exhaustion.
  ➔ Success would be measured by longer, more restful sleep and improvements in overall health and functioning.

Comfort and Quality of Life

- Caregivers expressed a desire for their children to experience more comfort, relaxation, and joy in their daily lives.
  ➔ Success would be indicated by fewer visible signs of discomfort, more joyful vocalizations, and increased ability to engage and participate in family activities in their own way.

QUESTION 2. CHALLENGES IMPACTING CLINICAL TRIAL PARTICIPATION

Caregivers in the DEE/NDD community identified multiple burdens and barriers that hinder participation in clinical trials and made a number of recommendations for ways to make trials more accessible. The DEE community needs innovative, family-friendly trial designs that minimize logistical, financial, and medical burdens. Reducing diverse access barriers would ultimately accelerate research, leading clinical trials to become a more viable and impactful tool for advancing treatments and improving outcomes across the ever-expanding number of DEEs.

Key Barriers to Participation:

- Trial Design

Challenges: Narrow eligibility criteria including disease-specific trials despite pre-clinical evidence that indicates benefits across DEEs exclude many families, leading to missed opportunities for broader community benefit. Additionally, rigorous clinical trial requirements, such as medication washout periods, pose risks to patients by leaving them unprotected against seizures or other life-threatening symptoms.

Solutions: Flexible, pragmatic and innovative trial designs to reduce risks, broader inclusion criteria, and accommodation for individual needs.

- Financial Burden

Challenges: Families often face financial hardships due to unpaid time off work and uncovered travel expenses. Even when trial-related costs are reimbursed, broad economic impacts remain.

Solutions: Comprehensive support for families, including financial assistance for lost income and childcare for siblings.

- Logistics and Travel Challenges

Challenges: Traveling with medically complex children is extremely difficult due to the medical fragility of many and the need for extensive medical equipment and planning. Emergencies during travel, such as equipment failure, pose significant risks and added stress.

Solutions: Decentralized trials with local data collection (e.g., bloodwork and assessments done locally) and remote participation through telehealth visits. Families stressed the need for trials to be flexible and creative.

- Delays in Research and Data Sharing

Challenges: Families expressed frustration with the slow pace of research and limited collaboration between institutions. Data from existing trials often isn't shared with families or outside of the study, delaying therapeutic advancements.

Solutions: Increase data sharing and streamline protocols to accelerate progress.

Recommendations for Accessible Clinical Trials

- Decentralized and Localized Trials
- Flexibility in Protocols
- Broader Inclusion Criteria - account for the common challenges across the ever growing number of rare genetic epilepsies when new compounds or treatments indicate broad applicability.
- Financial Assistance for indirect costs to better support families
- Faster Research and Data Collaboration for this time-sensitive community
- Share trial data, when possible, with the community
- Minimize Invasiveness

QUESTION 3. OUTCOME ASSESSMENTS IN CLINICAL TRIALS

Caregivers highlighted significant challenges with current clinical outcome assessments (COAs) for children with DEEs/NDDs, emphasizing the need for more inclusive, accurate, and family-centered tools to track their children's progress in clinical studies, clinical care, and daily life.

Key Challenges with Current COAs:

Standardized Scales Do Not Capture Patients with DEEs

Developmental tools like the Vineland and Bayley scales may fail to accommodate the abilities of many children with DEEs as their conditions prevent them from meeting even the lowest developmental benchmarks. Accordingly, there may be a floor effect due to poor granularity in the items such that the COA is unable to measure small but meaningful improvements in those with profound impairments. This leads to frustration and often discourages families from participation, as these assessments fail to recognize progress or abilities specific to their children.

Variations in abilities are evident within the DEE community itself. Caregivers emphasize the need for COAs tailored to the unique abilities and progress of DEE patients, capturing the inchstones of progress that are so important to patients and caregivers and essential for meaningful measurement of this population in clinical trials of potentially disease-altering treatments.

Narrow Focus on Seizures

Many clinical trials prioritize seizure frequency or severity, but families stress that this alone may not be their greatest priority and does not reflect overall progress or quality of life. For example, seizures on a good day may persist but the child may still show improvements in mood, comfort, or motor activity.

Focus on Developmental Milestones

Traditional milestone tracking (e.g., walking, talking) provides limited information for many patients with DEE/NDDs where more granular assessments of "inchstones" would be more useful. Families have their own measures, such as tracking bowel movements, eye contact, or sounds of happiness, to monitor well-being and progress on issues of most importance to their families but which remain largely unmeasured within most existing COAs..

Expanding Data Collection Methods

Caregiver-reported data is a valuable cornerstone of current COAs, offering unique insights into a child's condition. To complement this information and capture nuanced changes more effectively, additional tools like video or audio recordings, telehealth evaluations, and remote

monitoring can be integrated. These methods provide a more comprehensive and accurate picture of a child's condition while easing the burden on families.

Recommendations for Improving COAs

- **Better Tailored Outcomes of Interest**
    - Ensure that COAs used with individuals profoundly impaired focus on measures suitable for the multiple and severe impairment, that can identify small domain improvements such as for head control, track movement with their eyes, or vocalize happiness. Introduce ratings that compare "good days" versus "bad days" as indicators of improvement. Parents stressed the urgent need to be creative and enable measurement that is true, highlighting that time is a critical concern for many families due to the progressive nature of their children's conditions.

- **Collaborate with Caregivers**
    - Families are the experts on their children and should be included in developing COAs. They emphasize that progress in small, meaningful areas (e.g., fewer hospitalizations, improved bowel function) can have a transformative impact on quality of life.

- **Broaden Data Collection Methods**
    - Include **home monitoring** to capture changes that may not be observed in clinical settings. This includes incorporating caregiver observations through video or audio recordings and telehealth visits, allowing a fuller picture of the child's condition in their natural environment. Develop or modify tools that track specific behaviors, such as eye contact, comfort levels, and mood changes, which families already monitor informally.

- **Pair Seizure Data with Broader Outcomes**
    - Combine seizure tracking with other measures, such as communication, motor skills, mood and other family-reported indicators, to provide a fuller picture of the child's well-being.

- **Tailor COAs to the DEE Community**
    - Design assessments that resolve the floor effect in children with DEEs, ensuring the full range of abilities and challenges are captured across this population, consider

developing and adapting COAs across different conditions to enable faster and more efficient progress.

Current COAs fail to accurately capture the realities faced by families impacted by DEEs. By adopting more appropriate, flexible, comprehensive, and creative assessment methods, clinical studies can better evaluate progress and outcomes that matter most to families. These changes would help bridge the gap between clinical settings and real-life experiences, ultimately driving capacity to measure meaningful advancements in DEE research and clinical care.

QUESTION 4. RISK TOLERANCE

Caregivers shared their perspectives on the level of risk or burden they would be willing to accept in exchange for potentially effective treatments, emphasizing that decisions are influenced by their children's current condition, the potential benefits, and the severity of the trial's demands.

In the DEE community, there is a generally high tolerance for risk, as families are already living with high risk and poor outcomes daily and the prospect of disease progression.

Caregivers emphasized that risk is already an inherent and unavoidable part of life with DEE/NDDs, making them more accepting of the possibility of risks associated with experimental treatments. Families often weigh risks against the relentless progression of the disease, which guarantees worsening conditions without intervention.

The Risk/Reward Calculus

Families expressed a willingness to accept substantial risks, such as unknown side effects or uncertain outcomes, if the treatment offers transformative potential such as meaningful quality-of-life improvements or addresses multiple symptoms.

Personalized Approach to Risk Tolerance

Decisions about risk are influenced by a child's current health and stability.

- During periods of stability, families may be more cautious to avoid disruption.
- During severe health declines, families may take on higher risks to seek improvements.

Risk tolerance also varies from family to family with some being driven also by the hope of advancing treatment options for future generations.

Emotional and Situational Factors

The immediate condition of the child and the potential burden on the family, such as travel, invasive procedures, or impacts on other children in the family, shape the willingness to accept clinical trial or treatment-related risks.

Considerations: Travel and Time Commitment and Unknown Side Effects

- Logistical challenges like travel with medically fragile children remains a substantial barrier.
- Some families are willing to endure long travel and extensive clinic days if the treatment offers significant and immediate benefits.

Key Sentiments: Hope of a Better Life for Current or Future Generations

- The promise of improved outcomes—whether immediate or for future generations—motivates families to take significant risks.
- Some families are willing to endure high burdens if it means leaving a legacy of better treatment options for others.
- For families with children who may not have long life expectancies, treatments that offer immediate improvements in comfort or functionality are worth higher risks.

Overall Takeaways

Families affected by DEEs already live with substantial risks and burdens daily. They are generally willing to tolerate high levels of risk and trial burden for treatments that promise meaningful improvements in quality of life or address multiple symptoms. However, risk tolerance is highly situational, influenced by the child's health, the treatment's anticipated benefits, and the family's ability to manage logistical challenges. A personalized and flexible approach to trial design is essential to accommodating these variations.

5. ABSTRACT OF PRESENTATION BY PROFESSOR JENNY DOWNS

To provide a research perspective that complements the voices of parents, Professor Jenny Downs was invited to share insights from collaborative work of The Inchstone Project on clinical outcome assessments (COAs) and their critical role in addressing the unmet needs and priorities of the DEE/NDD community. Professor Downs has made consultancy for Marinus, Ultragenyx, Acadia, Avexis, Orion, Takeda, Neurogene and Taysha and was Associate Investigator on Clinical Trials with Anavex and Newron; All remuneration has been made to her department.

Shared Priorities and Challenges in DEE Conditions

- Urgency for Comprehensive Clinical Trial Readiness:

DEE conditions impact not only the functioning and well-being of affected children but also their families and communities. Wide and integrated research programs are necessary to address these challenges, including registries, natural history data, and trial networks. Current efforts often focus on individual DEE conditions, but with over 800 monogenic DEE disorders identified and growing potential for precision treatments, a transdiagnostic approach is essential to streamline progress across shared symptoms and challenges.

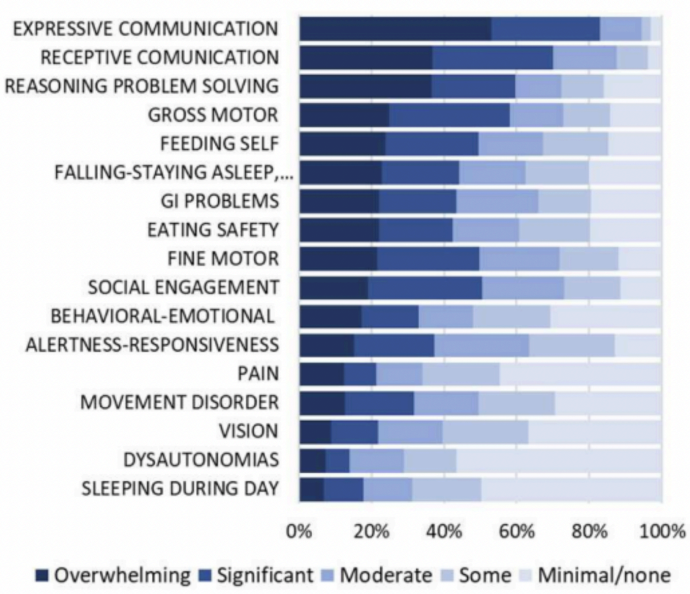
- Transdiagnostic Research Framework:

A transdiagnostic approach, which cuts across diagnostic boundaries, is particularly relevant to DEEs due to shared symptoms like communication and other function impairments, and co-occurring disorders such as autism and cortical visual impairment (CVI). Data from *The Inchstone Project* highlights the many commonalities across genetic groups, reinforcing the

need for clinical trial readiness that accounts for overlapping priorities and core symptoms across the DEE community.

- Unmet Needs in Non-Seizure Domains

A survey of 267 families identified expressive and receptive communication as having the most impact on the child and top priorities for improvement, followed by abilities to problem solve, mobility, feeding, and hand use.



In the survey, parents described meaningful change for their identified priority domains. Some meaningful changes were tailored to individual abilities, such as improved eye gaze for nonverbal children or better dexterity for operating communication devices. Other meaningful changes spanned different severities of impairment. For example, parents of children with

different levels of symbolic communication described the expression of needs, wants and pain as meaningful. Irrespective of the domain or child's impairment, achieving meaningful change was anticipated to enhance mental health, independence, social interaction, and safety for the children, while reducing caregiver stress and improving quality of life for the family.

- Implications for Better Measurement and Treatments:

Developing fit-for-purpose outcome measures is critical for accurately assessing meaningful changes, for example, resolving floor effects when assessing severely to profoundly impaired children. Measures must reflect (1) real-world meaningful progress in priority domains such as communication and (2) broader outcomes such as behavioral regulation and participation in family activities like shared meals to reflect quality of life and explain why the meaningful change is important. Additionally, adopting innovative trial designs, such as transdiagnostic approaches in basket trials where appropriate, can efficiently deliver new knowledge and treatments, leveraging similarities across conditions.

Key Takeaways:

- DEE conditions have profound impacts on children, families, and communities.
- The genomics revolution is fuelling a vibrant pre-clinical research culture, creating opportunities for precision medicine.
- Fit-for-purpose outcome measures and optimal trial designs are essential for effective treatment development.
- Transdiagnostic approaches can drive efficiencies by addressing shared challenges across DEE conditions

6. CONCLUSIONS AND KEY TAKEAWAYS

The voices shared by families of children with DEE/NDD and the evidence from the broader research literature converge on critical themes to highlight shared challenges, priorities, and opportunities for advancing clinical trial readiness and therapeutic development for the DEE/NDD community. By integrating insights from both lived experience and empirical evidence, we can more effectively identify shared priorities, refine therapeutic approaches, and ultimately improve the lives of those affected by DEEs and their families.

Evidence from the families and literature converges on the following points:

- **The Need for Comprehensive Clinical Trial Readiness**

Clinical trials require a robust foundation, including registries, natural history data, and networks for trial implementation. Current efforts often focus on individual DEE conditions, but with over 800 identified monogenic DEE disorders, a transdiagnostic approach could streamline progress across etiologies with shared symptoms and challenges.

- **Transdiagnostic Research and Commonalities Across DEEs**

A transdiagnostic framework would address overlapping symptoms like communication impairments, CVI, and co-occurring conditions such as autism. Data and experience illustrated significant similarities across different DEE groups as did parent descriptions of their child's challenges, reinforcing the potential for cross-condition measures and inclusion in trials.

- **Priorities for Treatment and Measurement**

Parent surveys revealed top priorities in non-seizure domains, including expressive and receptive communication, hand use, and feeding skills. Parents also described critical needs for management of comorbidities such as seizures, sleep, GI function and movement disorder.

- **Why Small Changes Matter**

Parents emphasized the importance of many small developmental gains, which can improve a child's physical and mental health, independence, and safety, while enhancing family well-being and day-to-day care. Standard scores often fail to reflect these meaningful changes, described by parents who were continually dismayed when meaningful changes were identified when their child was assessed. Evidence underscores the need for real-world, purpose-built outcome measures or careful adaptations of existing COAs for children with severe to profound developmental impairments.

Key Takeaway

Advancing therapeutic development for DEEs requires integrating transdiagnostic approaches, purpose-built outcome measures, and innovative trial designs, such as basket trials, to efficiently test therapies across multiple DEE conditions. Leveraging shared challenges across disorders will help more rapidly deliver meaningful changes that improve the lives of a broader

subsection of affected individuals and their families, reflecting the nuanced progress that matters most to them.

8. APPENDICES

Appendix A: List of Organizers

This listening session was organized by DEE-P Connections, in partnership with the Rare Epilepsy Network (REN).

Appendix B: List of Host and Organizers

- Gabi Conecker MPH: Executive Director and Co-Founder Decoding Developmental Epilepsies,

  SCN8A Parent

- Christina Saninocencio: Chair - Rare Epilepsy Network, Founder - LGS Foundation, LGS Sibling

- JayEtta Hecker MS: Co-Founder - Decoding Developmental Epilepsies, Session Coordinator, SCN8A Grandmother

- Ilene Penn Miller JD, LLM: Executive Director - Rare Epilepsy Network, Hypothalamic Hamartoma Parent

Appendix C: List of DEE Parent Testimonials

- Gabi C. Parent of child with SCN8A-DEE
- Karen U. Parent of child with CDKL5
- Megan W. Parent of child with KCNT1
- Minoo D. Parent of child with SCN8A
- Patricia G. Parent of a child with FOXG1
- Shannon G. Parent of child with Creld1
- Shawn E. PhD, Parent of child with SCN2A

Appendix D: Clinical Expert Presentation by Dr. Jenny Downs, PhD.
Head of Child Disability Research Program, The Kids Research Institute, Perth, Australia

https://www.dropbox.com/scl/fi/3k0br3av1hyipnpfiuwfu/DEE-Patient-Listening-Session-Downs-Nov24.pptx?rlkey=0vbll6lb5rb9mhlizar1ljpfr&st=2p6631e3&dl=0

Appendix E: List of FDA Offices and Centers/Divisions Represented

Center for Biologics Evaluation and Research (CBER)

- CBER/OCD/PS – Office of the Center Director/Policy Staff
- CBER/OTP/OCE– Office of Therapeutic Products/Office of Clinical Evaluation
- CBER/OTP/OCE/DCEGM – Office of Therapeutic Products/Office of Clinical Evaluation/ Division of Clinical Evaluation General Medicine
- CBER/OTP/OCE/DCEGM/GMB1 – Office of Therapeutic Products/Office of Clinical Evaluation/Division of Clinical Evaluation General Medicine/ General Medicine Branch 1
- CBER/OTP/OCE/DCEGM/GMB2 – Office of Therapeutic Products/Office of Clinical Evaluation/Division of Clinical Evaluation General Medicine/ General Medicine Branch 2
- CBER/OTP/PSPS – Office of Therapeutic Products/Policy and Special Projects Staff

Center for Drug Evaluation and Research (CDER)

- CDER/OND/ON – Office of New Drugs/Office of Neuroscience
- CDER/OND/ORDPURM/DRDMG – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics

Disclaimer
Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the DEE-P Connections' and Rare Epilepsy Network's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of Developmental and Epileptic Encephalopathies (DEEs) and Neurodevelopmental Disorders (NDDs) health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire DEEs and NDDs patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.