

## “Developing Comparative Effectiveness Research in Dravet Syndrome”

Patient-Centered Outcomes Research Institute (PCORI)  
Pipeline to Proposal Tier I Project Summary

In 2016, Mary Anne Meskis (Executive Director of the Dravet Syndrome Foundation) and Kelly Knupp, MD (Children’s Hospital Colorado and DSF Medical Advisory Board Member) were awarded a Pipeline to Proposal Tier I contract by PCORI. The purpose of this project, titled “Developing Comparative Effectiveness Research in Dravet Syndrome,” was to assemble a network of engaged stakeholders who could help identify the aspects of Dravet syndrome that are troubling to the patient and could be developed into a study of comparative effectiveness. Comparative Effectiveness Research (CER) is the direct comparison of different health care interventions (not necessarily medications) to determine which works best with respect to patient health, risks, and side effects. This is different from a typical research study in that two or more treatments are compared to each other rather than to a placebo or lack of treatment. (BETTER DESCRIPTION PLEASE) Participants included 6 parent caregivers, X clinicians, X researchers, and X industry representatives.

The project consisted of eight monthly teleconferences and one in-person meeting at the American Epilepsy Society Annual Meeting in Houston, TX in December 2016. Each teleconference focused on a specific aspect of Dravet syndrome that was identified through a previous DSF Caregiver Survey. Topics included Behavior; GI/Eating Concerns; Seizures; Orthopedic and Gait Issues; Sleep; and Transition to Adult Care. In light of the sensitive nature of Sudden Unexpected Death in Epilepsy (SUDEP) and mortality, that topic was addressed at the in-person meeting in December 2016. During the calls, Dr. Knupp and Ms. Meskis reviewed the topic, then spent the first half of the call soliciting the caregivers’ experiences and thoughts. After that, the clinicians, researchers, and industry representatives were invited to share their experiences and ask the caregivers questions. The last portion of the call was reserved for general discussion.

The purpose of this Tier I project was to establish communication among an engaged network of stakeholders so that this network could further discuss and refine the issues during Tier II (in 2017-2018 pending successful application), arriving at a meaningful, measurable, appropriate CER question that can be properly studied in a Tier III project (again, pending successful application in 2018.)

The following brief summary of each call serves to keep the Dravet syndrome community informed of what is taking place during these effective collaboration sessions.

### *Behavior*

Caregivers emphasized that behavior is dependent on many factors including recent seizure activity, quality of sleep, medication levels, and cognitive development. Cooperation in non-preferred activities such as getting dressed and ready to leave the house is difficult to achieve, and as the patients grow it becomes more difficult to get them to do what is required in a timely manner. Most of the participants have had little to no success using ADHD medications to reduce unwanted behaviors, but have seen some success with other medications such as Belviq and Prozac. Parents agreed that the behaviors are

much more problematic than the seizures, especially as the children grow, because the behaviors permeate every activity of the day while the seizures are short events.

The professionals inquired about medications including ADHD meds and behavioral therapy. They noted they see impulsivity, perseveration, and OCD behaviors in their office, but the behaviors the parents described in the initial part of the conversation are likely exhibited during the patient's preparation for the appointment, so they may miss them. Researchers offered their perspective, noting that mouse models try to test these things and there are inherent deficiencies with SCN1A mutations. Limitations include not recording how close recent seizures were to anxiety or behavioral testing.

### *GI and Eating Concerns*

Caregivers report several eating and GI issues including both low and elevated appetite, food aversions, constipation, and difficulty chewing. Most parents were unsure whether these difficulties were due to a physical feeling in their stomach, habit, behavioral, or med-related and were unsure how to best address them.

Clinicians felt it was multi-factorial and see these issues in other epilepsies. They noted much of this is appropriate for a 2-3 year old and when we view the patients at their developmental age, it is not entirely abnormal. Clinicians asked whether parents were concerned about the challenge of eating, the idea of eating as a family, or the actual nutritional value.

### *Seizures*

The unpredictable aspect of seizures appeared in many caregiver comments. They noted that seizures change in type, severity, length, daytime vs. nighttime, etc., and often increase with puberty. MORE HERE

Clinicians agreed that unpredictability is difficult to live with and expressed frustration in not being able to treat all kind of seizures. Some asked whether there were specific types that warranted targeting more than others (prolonged convulsive ones, NCSE, other?)

### *Mortality and Sudden Unexpected Death in Epilepsy (SUDEP)*

Many participants were able to attend this meeting in-person, including one bereaved parent. An additional bereaved parent joined via teleconference to contribute their perspective. One parent described their experience with multiple organ failure and brain death following a prolonged seizure, while the other described their experience with SUDEP, which occurred in the daytime during a very brief period of unsupervised time not associated with sleep. Both parents had been advised of SUDEP and mortality in a respectful manner by their neurologist prior to their child's death, but most of the parents present had learned of SUDEP via the internet rather than their neurologist. Several parents discussed the enormous responsibility the elevated risk of mortality places on siblings who share a bed or care for the patient alone.

Industry representatives from a pharmaceutical company noted that the expert neurologists present for this conversation may be the exception rather than the rule, and that there exists a need for education about SUDEP and how to discuss it among general neurologists. In addition, they suggested that the approach in clinic should mirror that taken in more recognized life-threatening diseases like pediatric cancer, where social workers are brought in at an early stage to discuss these types of matters.

Clinicians concurred that there is no good way to address the topic, but some ways may be better than others. Most said they bring the topic of mortality up *after* the initial visit or diagnosis visit because parents are often overwhelmed by all of the information given at the first appointment. They vary their approach based on the individual caregivers, their general levels of anxiety, etc. Some neurologists direct patients to the Danny Did Foundation, where the topic is addressed sensitively and appropriately. Concerns about the responsibility placed on siblings who sleep with the Dravet patient appeared in this group as well.

Clinicians note that the only risk factor for SUDEP that they can affect is seizure frequency, so they tend to chase seizure control despite the fact that many cases of SUDEP occur in patients who appear to be enjoying periods of relative seizure control just before the event happens. This led to discussion about interventions including some marriage of the co-sleeping deterrent and Emfit or Sami monitor's ability to detect lack of movement that could enact an arousing shake, vibration, or compression.

### *Orthopedic and Gait Issues*

The parents of older patients concurred that orthotics including AFOs and SMOs were mildly successful at stabilizing balance or improving gait in the short term, but that most reverted to their previous crouch or ataxic gait. Parents noted that gait was worse when medications were high, particularly Onfi, and when seizure control was poor. The characteristic gait and lack of endurance limits families because they must always have a (sometimes large) stroller or wheelchair and cannot access uneven terrain. Many parents saw improvement in core strength with hippotherapy but noted insurance coverage for this intervention was difficult to procure.

Clinicians expressed uncertainty about what to recommend. Most send patients to physiatry or suggest AFOs but there isn't really any research showing what works. Providers would like a consistent screening tool that is more than just a timed walk so they can track individual patients' progress and compare data reliably across centers.

### *Sleep*

According to the caregivers present, very few patients sleep by themselves unmonitored. Most sleep with the patient, several use baby monitors, pulse oximeters, and, occasionally, a night nurse. Several have had sleep studies that have not been terribly abnormal and have been difficult to obtain. Melatonin and clonidine have been used by some, but both seem to lose efficacy over time. Nocturnal seizures can be disruptive to sleep and parents often "tag team" or sleep in separate rooms, and the lack of overnight monitoring is one reason parents cite for not placing their adult patients in group

homes. Travel is difficult, expensive (due to the need for an extra room), and not a vacation when no one sleeps.

Clinicians agree that sleep studies seem relatively normal and are frustrating to obtain. Many do not feel they are properly trained to diagnose or address sleep issues.

### *Adult Care and Transition*

As more of the pediatric population ages into the adults system, caregivers express concern about the transition and would like a primer for adult neurologists that might include what the pediatric experts think would be most important for them to know as they take over care. Adults are larger in size and require adult-size IVs, braces, beds, etc., but many still function as if they were 3-4 years old, preferring the children's videos, stickers, etc. found in a pediatric hospital. In addition, the child life specialists are helpful for these patients and not found in adult care settings. Caregivers note respite is more difficult to find for older patients. The legal requirements in terms of guardianship, health directives, and trusts can be daunting. Most Medicaid waivers end between 18 and 21 years of age, and deciding which waiver would best suit the patient in adulthood can be difficult. In addition, parents worry about prescription drug coverage for both stiripentol (often approved by insurers for children but not yet established for adults) and newer treatments whose primary indication will be for the pediatric population.

Clinical practice for transition to adulthood varies by institution. Some see patients well into adulthood while others transition care between 18 and 25 years of age. This transition may or may not be well supported by the hospital and requires more physician time than is billable to insurers. Clinicians would appreciate adult neurologist education in the form of CME webinars or meetings with local neurologists and suggest the inclusion of a designated adult neurologist at any centers claiming excellence in Dravet syndrome.