

Towards a Composite Clinical Endpoint: Identifying a Core Set of Patient and Caregiver Relevant Outcome Measures Through Qualitative Research on the Global Impact of Dravet Syndrome

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BACKGROUND

- ▶ Dravet syndrome (DS) is a rare epileptic encephalopathy with onset during the first year of life in an otherwise healthy infant [1]. The clinical picture is characterized by frequent convulsive febrile seizures, followed later by nonfebrile seizures, mainly clonic and unilateral, of long duration and frequent status epilepticus [1].
- ▶ Children with DS have significant developmental disabilities, including cognitive, social and behavioural impairments, which can impact their health-related quality of life (HRQoL).
- ▶ Available treatments are non-curative and prognosis is generally poor [2]. As such, children and young persons with DS require intensive care and supervision, which also impacts the HRQoL of their caregivers.

PURPOSE

- ▶ Although seizures are the most commonly measured endpoint in clinical trials, there are important impacts of DS which are often overlooked and not measured.
- ▶ The main objective of the study was to identify a core set of concepts, relevant to the patient and caregiver experience of DS, which could be assessed as outcomes in clinical trials.
- ▶ This research forms part of a longer term project with the ambition of using a core set of outcomes measures to define a single measure of improvement/composite endpoint in DS trials.

RESULTS

Concepts Elicited from Interviews: Symptoms

- ▶ The most commonly reported symptom was seizures, which was elicited by all participants (n=11). Types of seizures reported included generalised (n=10), convulsive (n=8), absence (n=7), tonic clonic (n=6), myoclonic and focal/partial (n=5, respectively).
- Seizures were reported to last between five seconds and several hours, which varied by age, treatment and type of seizure. Frequency of seizures was reported to be variable and occur in a series with seizure-free intervals in between.

"He has generalised tonic-clonic seizures, all the limbs jerk, the eyes are rolled upwards." (01-F-37-CG)

"She had partial seizures, her vision was lost, her head was turning on one side, her eyes on one side, she was awake, but she was no longer with us." (08-M-37-CG)

Concepts Elicited from Interviews: Triggers

- ▶ Numerous triggers of seizures were reported by participants, the most common of which included fever (n=11), changes in external temperature (n=9), submersion in water (n=7), excitement (n=5) and illness/infection (n=5).

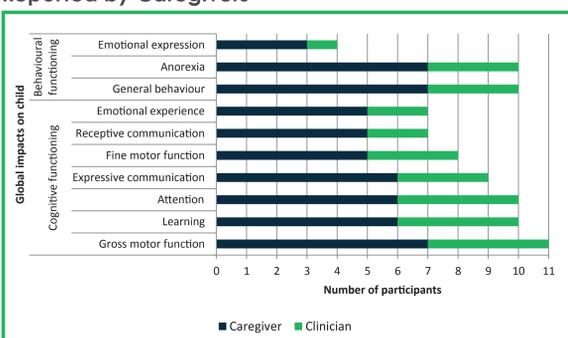
"These kids, the minute they have a fever, when their temperature rises, they have a seizure." (05-F-42-CG)

"We noticed that our child had seizures when he was too excited. We went out, we went to a party, we saw Father Christmas or that sort of thing, or when there were too many people, too much noise... he had a seizure." (05-F-42-CG)

Concepts Elicited from Interviews: Impacts

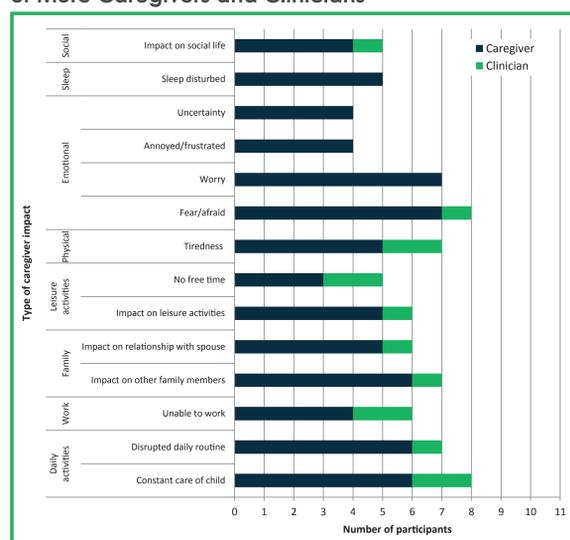
- ▶ A range of impacts on children with DS were identified, most commonly cognitive functioning (e.g. gross motor function [n=11], learning and attention [n=10, respectively], expressive communication [n=9], fine motor function [n=8], receptive communication and emotional experience [n=7, respectively]) and behavioural functioning (e.g. general behaviour, anorexia [n=10, respectively] and emotional expression [n=4]; **Figure 2**).

Figure 2. Impact Concepts of Children with DS Reported by Caregivers



- ▶ Participants reported a range of impacts on caregivers, which were grouped into the broad domains of: daily activities, work, family, leisure activities (n=9, respectively), emotional (n=8), sleep (n=7), financial (n=6), social and physical (n=5, respectively); **Figure 3**).

Figure 3. Caregiver Impact Concepts Reported by Four or More Caregivers and Clinicians



- ▶ Sub-concepts that were less frequently reported related to work (e.g. time off work [n=3]; form of refuge [n=2]), physical (e.g. impact of carrying child [n=3]), financial (e.g. reduced income, receive financial assistance [n=3], respectively; buy specialist equipment [n=2]), emotional (e.g. angry, sad/ depressed [n=3 respectively]; stressed, anxiety [n=2, respectively]) and daily activities (e.g. assistance with daily activities [n=2]).

Concepts Elicited from Interviews: Coping Strategies

- ▶ Participants mentioned a range of coping strategies to help patients and their caregivers to manage DS. The most frequently reported concepts were: home adjustments (n=7), use of assistive aid/devices (n=6), coping strategies related to daily activities (n=5), preventative behaviours (n=3) and communication (n=1).

Development of Conceptual Model

- ▶ A conceptual model was developed based on the concepts elicited in the interviews, representing all the symptom, trigger, impact and coping strategy concepts (**Figure 4**). Notably, a wide range of concepts were elicited only by caregivers and not reported by clinicians, highlighting the value of the caregiver perspective in DS.
- ▶ In particular, the following coping strategies were only mentioned by caregivers: management of seizures, coping relating to daily activities, use of assistive aids, preventative behaviours and home adjustments, suggesting that these are not aspects of DS upon which clinicians focus.
- ▶ Additionally, a wider range of concepts were elicited by caregivers than clinicians for the following domains: cognitive functioning (e.g. expressive communication), behavioural functioning (e.g. behaviour and anorexia) and secondary impacts on the child (e.g. social functioning and somnolence).

METHODS

Figure 1. Overview of Methodology

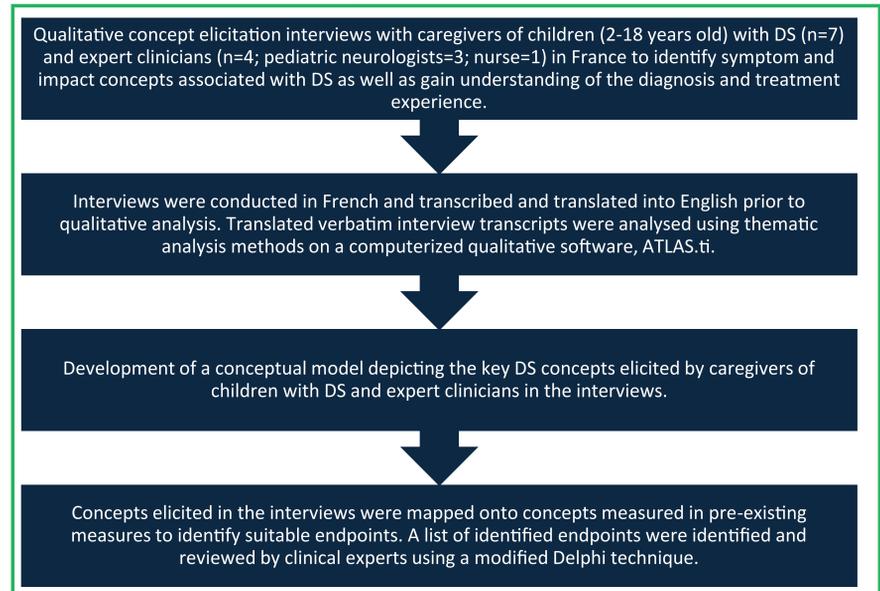
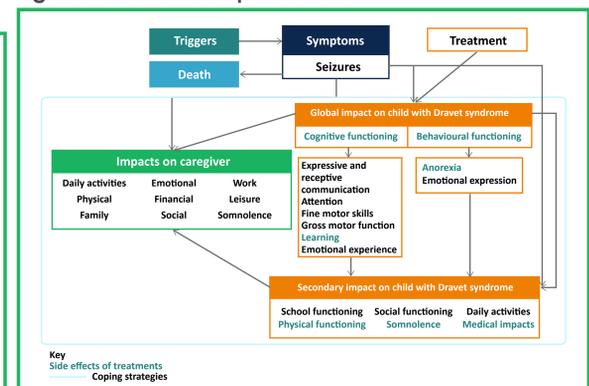


Figure 4. Draft Conceptual Model



Mapping Concepts to Outcome Measures

- ▶ This exercise involved identifying concepts within the conceptual model for which a treatment effect could reasonably be expected and mapping them on to existing outcome measures to determine the conceptual coverage of these measures.
- ▶ The result of this exercise was a comprehensive list of potential outcome measures that could be included in a clinical trial of DS.

Modified Delphi Panel

- ▶ Eight expert clinicians participated in a Delphi panel [3] to identify from the comprehensive list, the five key concepts/outcomes that best characterize the patient and caregiver experience of DS.
- ▶ The process was implemented in two rounds. Clinicians were asked to assign 17 concepts with a score from 0-100 (0, not at all important; 100, very important).
- In the first round, seizures were rated as the most important for patients, and for caregivers it was impact on the family. Concepts with a total perceived importance score of 629 or lower were removed, reducing the number of concepts to ten.
- In round two, the clinicians were asked to assign a 0-100 score, and rank in order of importance (1, most important; 10, least important) the remaining ten concepts. The top five ranked concepts are presented in **Table 1**.

Table 1. Highest Ranked Concepts in Second Round of Modified Delphi Technique

Concept	Type of concept
Seizures	Patient
Cognitive functioning – expressive communication	Patient
Cognitive functioning – receptive communication	Patient
Daily activities	Caregiver
Social functioning	Caregiver

CONCLUSIONS

- ▶ The impact of DS as experienced by patients and caregivers extends beyond the direct impact of seizures. Notably, a wide range of impacts on children with DS and their caregivers have been identified.
- ▶ If the benefit of therapeutic interventions is to be fully understood, it is important that a range of patient- and caregiver-relevant outcome measures are captured.
- ▶ From this qualitative research the authors identified a core set of caregiver- and patient-relevant outcome measures that could be used in clinical trials in DS.
- ▶ Further work is underway to understand the cross-cultural validity of these concepts/outcome measures.
- ▶ These outcome measures, if appropriate, will be included in a randomized controlled trial for a new pharmacotherapy for DS.

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