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ORIGINAL ARTICLE

# Caregiver-reported meaningful change in functional domains for individuals with developmental and epileptic encephalopathy: A convergent mixed-methods design

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## Abstract

**Aim:** To investigate how caregivers of children with developmental and epileptic encephalopathy and severe developmental impairments describe meaningful change for functional domains and why it is important.

**Method:** This was a convergent mixed-methods design study. A survey was completed by 267 parents of children aged 12 months or older. For prioritized functional domains (communication, gross motor, fine motor, eating), parents reported the smallest improvement that would be important and explained why. Data were analyzed using directed content analysis and meaningful change codes were mapped to impairment levels.

**Results:** The median age of the children was 8 years 8 months (interquartile range 4 years 2 months–14 years 6 months) and 149 (55.8%) were female. Content analysis yielded 86 meaningful change codes. Common codes described capacity to communicate preferences and emotions, gain sitting and walking skills, grasp objects for play, eat foods without choking, or using utensils. Some codes were reported for each impairment level (e.g. communicating needs/wants/likes for expressive communication); others were specific to an impairment level (e.g. gaining head control if unable to walk). Meaningful change was anticipated to affect health, independence and safety, care regimens, and quality of life of affected individual and families.

**Interpretation:** The meaningful change codes indicate critical components within domains for evaluations in clinical trials.

The number of rare developmental and epileptic encephalopathy (DEE) conditions being identified has increased exponentially because of advances in genetic diagnostic technologies.[1] DEEs are frequently associated with refractory seizures but some children with a genetic variant that is associated with a DEE do not have epilepsy.[2] Irrespective, conditions that can co-occur with a DEE include global developmental delay, intellectual developmental disorder, cortical visual impairment, autism spectrum disorder, sleep and gastrointestinal disorders, and behavioural dysregulation.[3,4]

**Abbreviations:** CFCS, Communication Function Classification System; COA, clinical outcome assessment; DEE, developmental and epileptic encephalopathy; EDACS, Eating and Drinking Ability Classification System.

Other children can have phenotypes that are phenotypically similar to a DEE but no genetic cause is found and they may be presumed to have a genetic cause.[1,5]

Knowing the genetic cause of DEEs has spurred development and testing of precision therapies with potential to correct or ameliorate the pathophysiology due to deleterious genetic variants.[4] To establish the value of new therapies, clinical trials must demonstrate that they improve important outcomes for patients in a meaningful manner.[6,7] Fit-for-purpose clinical outcome assessments (COAs) capture the relevant concept of interest and provide scores that are reliable, valid, and responsive to change.[6,8] There is little information on what constitutes a meaningful or worthwhile improvement in DEEs. It is essential to know what meaningful change is when interpreting findings in clinical trials, for children with a DEE and their families, national regulatory agencies, and payers.

Qualitative methods can investigate meaningful change at the individual level.[9,10] We previously explored meaningful change by interviewing 15 parents of 10 children with SCN2A-DEE.[11] Parents described small but meaningful steps of developmental progress in communication, gross and fine motor function, and activities of daily living which varied with the severity of their child's developmental impairments and perceived risks associated with the potential therapy (symptom management vs genetic). Parents explained that changes were meaningful if they supported their child's well-being and the family's capacity to provide daily care.[11] However, existing qualitative data provide only a partial view in one condition (SCN2A-DEE[11]) and a more complete understanding could be derived from synthesizing more extensive quantitative and qualitative data sets.

The Inchstone Project is an international caregiver-led initiative that aims to ensure fit-for-purpose COAs are available to measure meaningful progress of individuals with severe impairments in response to new treatments.[12] As part of the project, we surveyed parents of children with severe neurodevelopmental impairments to identify their priorities for improvement across a wide range of functional, behavioural, and health domains. This study addressed two primary research questions: how do caregivers describe meaningful change for high priority functional ability domains (i.e. communication, gross motor, fine motor, eating), and is meaningful change similar or different for different impairment levels? A secondary research question addressed why the expressed meaningful changes were important.

**What this paper adds**

- Some meaningful change codes for communication were similar across levels of impairment.
- Most meaningful change codes were unique for specific gross motor levels of impairment.
- Meaningful change was anticipated to support health, independence, safety, care, and well-being.

# METHOD

## Study design

This was a convergent mixed-methods design study (questionnaire variant),[13] nested within a larger community survey. Quantitative and qualitative data were collected in parallel, analyzed separately, then merged. In this study, quantitative data documented child functional impairments and whether parents prioritized a functional ability domain. Qualitative data, collected as open-text responses, described meaningful change in prioritized functional ability domains and the rationale. Quantitative and qualitative data were merged to explain meaningful change for prioritized functional ability domains and compare meaningful change in these domains across levels of impairment. The analysis was fixed a priori. The aims were to (1) characterize child functional abilities, (2) describe patterns of meaningful change for high priority core functional domains, (3) explain meaningful change by level of impairment and explore similarities (divergence) and differences (convergence), and (4) explain why the meaningful change was important. See the procedural flowchart for the study in Figure S1.

The North Star Review Board (protocol NB300112) determined the protocol to be exempt and this was acknowledged by the Johns Hopkins School of Medicine and Nationwide Children's Hospital institutional review boards. The study was also approved by the Human Research Ethics Committee at The University of Western Australia (2019/RA/4/20/6198). All participants provided online informed consent to participate.

## Survey participants

Parental advocacy groups representing several DEEs within the DEE-P Connections network (https://deepconnections.net/) invited their members to participate in a survey administered online in CLIRINX[14] between June and November 2023. Primary caregivers of a child at least 12 months old identified whether their child had epilepsy, autism spectrum disorder, developmental delay, intellectual developmental disorder, or other neurodevelopmental conditions. Severely impaired communication was an essential eligibility criterion. In early recruitment stages, severe mobility impairment or severe eating difficulty (reliance on a G-tube or significant safety concerns when eating orally) was also required but these were removed in response to caregiver feedback that severe to profound impairments might be present in someone who can walk independently and eat safely.

## Procedures

The larger survey included 20 questions on demographics and diagnoses, and 58 questions on development, health, priority domains, and meaningful change, 18 of which requested open-text responses. Levels of impairment for communication and eating were derived from classification scales used for cerebral palsy[15] and adapted for use in DEEs.[16,17] These included the Communication Function Classification System (CFCS) and the Eating and Drinking Ability Classification System (EDACS). Gross motor function was classified using the Functional Mobility Scale adapted for Rett syndrome.[18] Level of hand function was classified as able to use a pincer grasp, reach and grasp hand-sized objects, grasp an object if placed in the hand, or unable to grasp objects.[19] Because the CFCS and Functional Mobility Scale are intended for children 2 years and older, parents' descriptions of severe communication or gross motor delay indicated severe impairment for these children. Parents identified the top three of 17 functional, behavioural, or health domains in which they would most like to see improvement, with the option to add additional domains. For each top domain, they described in open text the smallest improvement or step forward in that area that would be important to them or their child (i.e. a 'wish') and explained why that improvement would be important.

## Analysis

Descriptive statistics were used to summarize the characteristics of the individuals and parents' priorities for improvement. We analyzed data for the four functional ability domains (communication [expressive, receptive], gross motor, hand function, eating [safety, independence]).

Conventional content analysis (by SH) was used to identify patterns in the data.[20] Coding was inductive (i.e. derived from the data). First, all wishes were collated and sorted by functional domain categories (e.g. gross motor, fine motor). All responses were reviewed to ensure coder familiarity with the data. Non-English responses were translated into English using Google Translate. Second, each wish was read and reread, and codes were developed for each identified unit of meaning. Each wish could be associated with multiple codes. Responses were then coded for a second time by SH to ensure consistency across codes. Twenty per cent of codes were also coded by JD, resulting in 92% intercoder agreement. All inconsistencies were discussed and resolved. Third, we identified the need for more specific codes (e.g. specific descriptors of modes of communication) and a third round of coding was conducted by SH. Twenty per cent of codes were again coded by JD, yielding an intercoder reliability of 86%. Again, all differences were discussed and resolved until full agreement was reached. The remainder of the data set was reviewed by SH and relevant coding changes were applied. Codes were categorized by the level of impairment in each functional domain. The same procedures were used to categorize data on why the meaningful change would be important, led by JD, and 20% were also coded by ATB (89% intercoder agreement). Qualitative and quantitative data were integrated in tabular form to illustrate patterns.

## Trustworthiness

Strategies were taken to maintain credibility, transferability, dependability, and confirmability.[21] Review of the findings with the investigator team was conducted throughout the coding and supported analytic credibility. Extensive and frequent reflective peer debriefing limited investigator bias in coding and both coders agreed on the final coding tree. Rich descriptions of the data supported transferability of the data. Dependability and confirmability were enhanced by the transparent and logical explanation of the steps and decisions made, using notes to document coding processes as an audit trail. Coders engaged in reflexive discussions, acknowledging their perspectives (caregiver, allied health), when coding.

# RESULTS

## Participants

A total of 267 parents completed the questionnaire. Descriptive characteristics are presented in Table 1. The median age of the children was 8 years 8 months (interquartile range 4 years 2 months–14 years 6 months) and most ($n = 149$, 55.8%) were female. A genetic cause was identified in 236 (88.4%). A diagnosis of epilepsy or history of seizures was reported in 201 (75.3%), of whom nearly half (46%) were prescribed more than two antiseizure medications and 51 had Lennox–Gastaut syndrome. A description of the cohort is provided in Table 1. The most severe level of communication impairment (modified CFCS) was reported for 199 (78%) of those 2 years or older and 9 out of 11 (82%) of children younger than 2 years; the most severe level of gross motor impairment (modified Functional Mobility Scale) was for 134 (52%) of those 2 years or older and 8 out of 11 (73%) of children younger than 2 years; and the most severe level of impairment (modified EDACS) of eating for 73 (27%) with complete G-tube dependence and 27 (14%) who did not have a G-tube but for whom there were substantial safety concerns. Ninety-three (35%) needed help to grasp or could not grasp objects (Table 1).

For the functional domains, expressive communication was the most frequently identified priority (79.4%) followed by gross motor skills (38.6%) and receptive communication (27.3%). Eating independently, hand use, and eating safety were identified by 16.1%, 13.1%, and 10.5% respectively. For the parents prioritizing a functional domain, most described meaningful change ($n = 493$ out of 498, 99%) and why the meaningful change they had identified was important (493 out of 498, 99%).

**TABLE 1** Distribution of clinical features and diagnoses for study participants ($n = 267$).

| Variable | | *n* (%) |
|---|---|---|
| Age (years) | Younger than 5 | 79 (29.6%) |
| | 5–12 | 98 (36.7%) |
| | 12–18 | 47 (17.6%) |
| | 18 and older | 43 (16.1%) |
| Sex | Female | 149 (56%) |
| Primary aetiology | Genetic | 236 (88.4%) |
| | Non-genetic | 31 (11.6%) |
| Gene | *SHANK3* | 49 (18.4%) |
| | *SCN8A* | 32 (12.0%) |
| | *FOXG1* | 24 (9.0%) |
| | *SCN2A* | 21 (7.9%) |
| | *ASXL1* | 18 (6.7%) |
| | *ASXL3* | 18 (6.7%) |
| | Other (20 genes) | 193 (72.3%) |
| | Unknown or no genetic diagnosis | 31 (11.6%) |
| **Other neurological diagnoses** | | |
| Global developmental delay[a] | None | 5 (2%) |
| | Diagnosed | 231 (87%) |
| | Suspected | 31 (12%)[a] |
| Intellectual developmental disorder (age ≥5 years, $n = 206$) | None | 6 (3%) |
| | Diagnosed | 175 (85%) |
| | Suspected | 25 (12%) |
| Autism | None | 106 (40%) |
| | Diagnosed | 99 (37%) |
| | Suspected | 62 (23%) |
| Cortical visual impairment[b] | None | 142 (53%) |
| | Diagnosed | 88 (33%) |
| | Suspected | 36 (14%) |
| Diagnosis of epilepsy/seizures | None | 66 (25%) |
| | Epilepsy diagnosis | 169 (63%) |
| | Seizures, no epilepsy diagnosis | 32 (12%) |
| Number of antiseizure medications (if history of epilepsy or seizures, $n = 201$) | None | 26 (13%) |
| | 1 | 44 (22%) |
| | 2 | 38 (19%) |
| | 3 | 33 (16%) |
| | ≥4 | 60 (30%) |
| **Impairment in the four cardinal functions** | | |
| **Communication** (modified Communication Function Classification System if 2 years or older) | **<2 years ($n = 11$)** | |
| | Profound delay | 9 (82%) |
| | **≥2 years ($n = 256$)** | |
| | Effectively communicates back and forth with known and new people | 7 (2.7%) |
| | Communicates back and forth with known but less effective with new people | 50 (19.5%) |
| | Seldom or never communicates effectively even with familiar people | 199 (78%) |
| | **Total severe/profound impairment** | **208 (78%)** |

**TABLE 1** (Continued)

| Variable | | *n* (%) |
|---|---|---|
| **Gross motor** (mobility) (modified Functional Mobility Scale if 2 years or older) | **>2 years (*n* = 11)** | |
| | Profound gross motor delay | 8 (73%) |
| | **≥2 years (*n* = 256)** | |
| | Walk independently – 5 yards | 91 (36%) |
| | Walk with assistance | 31 (12%) |
| | Wheelchair dependent | 134 (52%) |
| | **Total severe/profound impairment** | **142 (53%)** |
| **Hand use** | Pincer grasp | 93 (35%) |
| | Reach and palmer grasp | 81 (30%) |
| | Grasp when placed in hand | 56 (21%) |
| | Unable to grasp object | 37 (14%) |
| | **Total severe/profound impairment** | **93 (35%)** |
| **Eating** (modified Eating and Drinking Ability Classification System) | No concerns when swallowing | 129 (48.3%) |
| | Concerns for choking when feeding | 27 (14%) |
| | G-tube dependent – partial | 38 (14%) |
| | G-tube dependent – full | 73 (27%) |
| | **Total severe/profound impairment** | **100 (37%)** |
| Number of severely/profoundly impaired cardinal domains | 0 | 42 (16%) |
| | 1 | 68 (25%) |
| | 2 | 53 (20%) |
| | 3 | 47 (18%) |
| | 4 | 57 (21%) |
| | Median (interquartile range) | 2 (1–3) |
| Country/region | North America | 227 (83.9%) |
| | Western Europe | 15 (5.6%) |
| | Australia/New Zealand | 10 (3.7%) |
| | UK | 10 (3.7%) |
| | Other[c] | 8 (3.0%) |

[a]Four overall and one with SHANK3 had an isolated delay. Classified as suspected global developmental delay.

[b]One missing value.

[c]'Other' includes countries in South America, Eastern Europe, Middle East, and Africa.

## Meaningful change in the functional domains

The 493 open-text responses yielded one or two codes each. For example, 'Pain - where, what it is, when it started, etc.' was coded as 'Express pain/hurt/discomfort' and 'Head control/being able to sit independently' was coded as 'Head control' and 'Sitting independently'. In summary, there were 86 meaningful change codes (Table 2). Integrating quantitative and qualitative data, the three most frequent meaningful change codes by level of impairment for each domain are presented in Table 3. All codes by level of impairment are presented in Table S1.

### Communication

Wishes for expressive communication resolved into 18 codes, most commonly, to demonstrate preferences and express pain, hurt, or discomfort. Codes for modes of communication ranged from being able to speak in sentences to non-verbal communication methods (Table 2). Codes for meaning and purpose (e.g. demonstrating preference, expressing emotions) were represented across all levels of communication impairment (modified CFCS[16,17]) whereas codes for the non-verbal modes of communication were more frequently described for children with greater communication impairment (Table 3 and Table S1).

Wishes for receptive communication resolved into eight codes that were general (e.g. consistent and appropriate responsiveness) or specific (e.g. understanding simple instructions) (Table 2). There were similarities in the codes for individuals who could not communicate back and forth compared with those who could only communicate back and forth with known individuals (e.g. general comprehension, understanding yes/no), although codes for the latter group included skills such as understanding basic words and images (Table 3 and Table S1).

**TABLE 2** The 86 meaningful change codes identified for communication (expressive and receptive), gross motor, eating (safely and independently), and hand function.

| Cardinal function (number of codes) | Category (number endorsed/category) | Codes | Number endorsed/code |
|---|---|---|---|
| Expressive communication ($n = 18$ codes) | Demonstrating preference ($n = 83$) | Basic communication of needs/wants/likes | 55 |
| | | Communicate yes/no | 21 |
| | | Make choices | 7 |
| | Expressing emotions ($n = 61$) | Express pain/hurt/discomfort | 37 |
| | | Express feelings/emotions | 24 |
| | Social connections ($n = 2$) | Identify parents by name | 2 |
| | Using words ($n = 35$) | Using words (not specified) | 23 |
| | | Using single words | 10 |
| | | Using phrases/sentence | 2 |
| | Using AAC or signs ($n = 47$) | Aided communication | 34 |
| | | Signs (not specified) | 8 |
| | | Indicating words/phrases/sentences | 5 |
| | Non-verbal ($n = 51$) | Using limbs | 29 |
| | | Using eyes | 10 |
| | | Using vocalizations | 7 |
| | | Using body movements | 3 |
| | | Using facial expressions | 2 |
| | Other ($n = 12$) | Consistency of communication | 12 |
| Receptive communication ($n = 8$ codes) | Specific skills ($n = 9$) | Understanding names of things | 4 |
| | | Understanding yes/no | 3 |
| | | Understanding images/pictures | 2 |
| | General skills ($n = 52$) | General comprehension | 24 |
| | | Following simple instructions | 14 |
| | | Consistent appropriate responsiveness | 10 |
| | | Understanding basic words | 3 |
| | | Understanding complex vocabulary | 1 |
| Gross motor ($n = 21$ codes) | Walking ($n = 26$) | Walking independently | 12 |
| | | Walking (not specified) | 3 |
| | | Walking independently longer distances | 2 |
| | | Walking short distances inside the house | 2 |
| | | Walking with assistance | 2 |
| | | Increased tolerance of gait trainer | 2 |
| | | Walking in all environments | 1 |
| | | Walking with less support | 1 |
| | Standing ($n = 13$) | Increase leg strength when weight bearing | 4 |
| | | Stand without assistance | 3 |
| | | Stand (not specified) | 3 |
| | Sitting ($n = 26$) | Sitting independently | 22 |
| | | Sit (not specified) | 4 |
| | Transfers ($n = 10$) | Assisting carers with movements/transfer | 10 |
| | Head and trunk control ($n = 12$) | Head control | 8 |
| | | Trunk control | 4 |
| | Other ($n = 12$) | Control/flexibility of arms/legs | 6 |
| | | Proprioception and balance | 2 |
| | | Crawling | 2 |
| | | Rolling over | 1 |
| | | Stretching legs out | 1 |

**TABLE 2** (Continued)

| Cardinal function (number of codes) | Category (number endorsed/category) | Codes | Number endorsed/code |
|---|---|---|---|
| Eating safely ($n = 11$ codes) | Swallowing ($n = 11$) | Not choking/coughing/aspirating | 6 |
| | | Swallowing solid/thickened food | 2 |
| | | Not needing to thicken food | 1 |
| | | Swallowing liquids | 1 |
| | | Swallowing (not specified) | 1 |
| | Chewing ($n = 12$) | Eat a variety of foods | 6 |
| | | Chew soft/textured/solid food | 5 |
| | | Chew for longer | 1 |
| | Eating behaviours ($n = 11$) | Taking manageable bites | 6 |
| | | Finishing chewing before taking next bite | 4 |
| | | Restrict hunger | 1 |
| Eating independently ($n = 14$ codes) | Independence ($n = 13$) | Autonomy and no supervision | 13 |
| | Use of utensils ($n = 21$) | Use cutlery (spoon, knife, fork) | 15 |
| | | Drink independently | 5 |
| | | Spoon feeds self after spoon is loaded | 1 |
| | Managing food ($n = 10$) | Finger feeds self | 6 |
| | | Better control of tongue | 2 |
| | | Not overfilling the mouth | 1 |
| | | Less mess | 1 |
| | Approach to mealtimes ($n = 7$) | Eating all food | 2 |
| | | Not over-eating | 1 |
| | | Enjoying food | 1 |
| | | Consistently eating | 1 |
| | | Concentrating on eating | 1 |
| | | Identification of different foods | 1 |
| Hand function ($n = 14$ codes) | Skill and strength ($n = 35$) | Grasp toy/object/page – assistance free (including play) | 16 |
| | | Push buttons – technology/devices – consistently | 6 |
| | | Dexterity (not specified) | 3 |
| | | Able to use fingers in isolation | 2 |
| | | Move hand to mouth | 2 |
| | | Use both hands | 2 |
| | | Hand strength and control | 1 |
| | | Writing and colouring | 1 |
| | | Initiate hand movements | 1 |
| | | Use palms when flat in crawling position | 1 |
| | Control of movement ($n = 4$) | Less involuntary hand movements | 2 |
| | | Less hand chewing | 1 |
| | | Less tremor | 1 |
| | | Relaxation of muscles | 1 |

## Gross motor

Wishes for gross motor resolved into 21 codes that mostly described walking, standing, sitting, transfers, and head and trunk control (Table 2). The codes varied for each level of gross motor impairment (modified Functional Mobility Scale[18]). Example codes described walking longer distances (distance not specified) for individuals able to walk at least 5 yards, independent walking and sitting for individuals who needed assistance to walk, and development of head and trunk control and sitting for individuals unable to walk (Table 3 and Table S1).

## Eating

There were 25 codes for eating: 11 for eating safely and 14 for eating independently. Common codes for eating safely described swallowing and chewing different textures of food and eating behaviours such as taking manageable bites and

**TABLE 3** The top three meaningful change codes (qualitative) described for communication, gross motor, eating, and hand function categorized by the level of impairment (quantitative).

| | | | | |
|---|---|---|---|---|
| **Communication (total 26 codes)** | | | | |
| | **Effectively communicates back and forth with known and new people** | **Communicates back and forth with known but less effective with new people** | **Seldom or never communicates effectively even with familiar people** | - |
| **Expressive communication (total 18 codes)** | | | | |
| 1 | Express feelings/emotions (*n* = 2) | Basic communication of needs/wants/likes (*n* = 6) | Basic communication of needs/wants/likes (*n* = 49) | - |
| 2 | Express pain/hurt/discomfort (*n* = 1) | Express pain/hurt/discomfort (*n* = 6) | Using body movements (*n* = 38) | - |
| 3 | Communicate yes/no (*n* = 1) | Aided communication (*n* = 6) | Aided communication (*n* = 31) | - |
| **Receptive communication (total 8 codes)** | | | | |
| 1 | | General comprehension (*n* = 4) | General comprehension (*n* = 20) | - |
| 2 | | Follow simple instructions (*n* = 4) | Follow simple instructions (*n* = 10) | - |
| 3 | | Understanding yes/no (*n* = 1) | Consistent appropriate responsiveness (*n* = 10) | - |
| **Gross motor (total 21 codes)** | | | | |
| | **Walk independently – 5 yards or metres** | **Walks with assistance** | **Unable to walk** | - |
| 1 | Walking independently for longer distances (*n* = 2) | Walking independently (*n* = 2) | Sit independently (*n* = 20) | - |
| 2 | Proprioception and balance (*n* = 1) | Walking in all environments (*n* = 2) | Assisting carers with movements/transfer (*n* = 8) | - |
| 3 | - | Sitting independently (*n* = 2) | Head control (*n* = 7) | - |
| **Eating (total 25 codes)** | | | | |
| | **No concerns when swallowing** | **Concerns for choking when feeding** | **G-tube dependent/unable to eat safely and may require G-tube** | |
| | **Eating safely (total 11 codes)** | | | |
| 1 | Not choking/coughing/aspirating (*n* = 3) | Taking manageable bites (*n* = 5) | Eat variety of food (*n* = 2) | - |
| 2 | Finishing chewing before taking next bite (*n* = 3) | Chew soft/textured/solid food (*n* = 3) | Not choking/coughing/aspirating (*n* = 1) | - |
| 3 | Eat a variety of foods (*n* = 2) | Not choking/coughing/aspirating (*n* = 2) | Swallowing solid/thickened foods (*n* = 1) | - |
| **Eating independently (total 14 codes)** | | | | |
| 1 | Autonomy and no supervision (*n* = 7) | Autonomy and no supervision (*n* = 6) | Drink independently (*n* = 2) | - |
| 2 | Use of cutlery (spoon, knife, fork) (*n* = 7) | Use cutlery (spoon, knife, fork) (*n* = 6) | Use cutlery (spoon, knife, fork) (*n* = 2) | - |
| 3 | Enjoying food (*n* = 1) | Finger feeds self (*n* = 4) | Finger feeds self (*n* = 1) | - |
| **Hand function (total 14 codes)** | | | | |
| | **Ability to use a pincer grasp** | **Reach and palmer grasp** | **Grasps objects when placed in the hand** | **Unable to grasp objects** |
| 1 | Grasp toy/object/page – assistance free (including play) (*n* = 5) | Grasp toy/object/page – assistance free (including play) (*n* = 6) | Grasp toy/object/page – assistance free (including play) (*n* = 3) | Grasp toy/object/page – assistance free (including play) (*n* = 2) |
| 2 | Push buttons - technology/devices – consistently (*n* = 4) | Move hand to mouth (*n* = 2) | Push buttons - technology/devices – consistently (*n* = 1) | Push buttons - technology/devices – consistently (*n* = 1) |
| 3 | Less hand chewing (*n* = 1) | Use both hands (*n* = 1) | Able to use fingers in isolation (*n* = 1) | Able to use fingers in isolation (*n* = 1) |

All codes per functional domain and wishes for each level of impairment are reported. See Table S1 for all wishes and codes.

finishing chewing before the next bite (Table 2). Notably, the codes 'not choking, coughing, and aspirating' and 'eating a variety of foods' were described across each eating impairment level (modified EDACS[16,17]). Codes described the manner of eating (e.g. manageable bites, eating slowly) for less impaired children whereas codes described swallowing thickened foods, liquids, and textured food for more impaired children (Table 3 and Table S1). Codes for eating independently described eating without supervision, use of utensils (e.g. cutlery, bottles/cups), managing food (e.g. finger feeding, not overfilling mouth, less mess), and the child's approach to mealtimes (e.g. eating all food, enjoying and concentrating on their food; Table 3) across the impairment levels (Table 3 and Table S1). There were few codes for children with severe impairments, probably because many (73%) in this category were fed by gastrotomy tube.

### Hand function

Wishes for hand function resolved into 14 codes for skills, strength, and control of movement (Table 2). Dexterity involving manipulation of toys (e.g. objects, pages) and technology (e.g. push buttons, devices) was described frequently across all levels of impairment (Table 3 and Table S1).

## Anticipated impacts of described meaningful changes

The 493 open-text responses yielded one to three codes each. For example, in the expressive communication domain, the rationale 'Behaviour challenges are tied closely to frustration with unmet needs' was coded as 'Behavioural regulation'. In the independent eating domain, the rationale 'Would allow my child independence in a key arena of self-care, free up considerable time for her caregivers, and allow my child to eat when hungry and stop eating when full' was coded as 'Independence', 'less care time', and 'eat at own pace and stop when full'. Codes described impacts on health and well-being for child and family (Table 4).

For the child, meaningful change codes were classified as important for the child's mental and physical health, independence, social well-being, safety, personal growth, and quality of life. Impacts for the child's physical health, independence, personal growth, and quality of life were described for each functional area. Meaningful change codes in communication and motor skills were anticipated to impact the child's social well-being, reduce frustration and improve behavioural regulation, and improve physical health (Table 4).

For the family, meaningful change was anticipated as important for parents' mental health, daily care regimens, and family joy and quality of life. Family joy was anticipated from hearing their child's voice, greater family connections at mealtimes, and ability to engage more in community activities (Table 4).

# DISCUSSION

Psychometric evidence for reliability and validity is accumulating in COAs for populations with severe impairments (see, for example, Berg et al.[22] and Saldaris et al.[23]) yet there is limited understanding of what change is meaningful to patients.[11] We surveyed 267 parents of children with severe developmental impairments, most with a genetic variant associated with a DEE, and described meaningful change codes in functional domains. Common codes described being able to communicate preferences and emotions, express pain and discomfort, gain sitting and walking skills, and grasp objects for eating or play. Meaningful change was anticipated to support health, independence and safety, care regimens, and quality of life of both the affected individuals and their families.

Expressive and receptive communication were frequently prioritized, consistent with priorities described for other conditions (see, for example, Neul et al.[24]). Communication in CDKL5 deficiency disorder, a severe DEE condition, has been described as multi-dimensional comprising multiple modes, purpose and meaning, and reciprocal exchanges.[25] This aligns well with the codes in our study. Illustrating divergence from expectations, parents described meaningful change in terms of better communication of purpose and meaning, such as indicating yes or no and communicating pain, across the levels of impairment.

Gross motor skills build incrementally during development, as represented in gross motor assessments for cerebral palsy[26] and CDKL5 deficiency disorder.[23] Illustrating convergence with the developmental sequence, meaningful change codes varied with the level of gross motor impairment. For example, codes for those unable to walk included gaining head control or leg strength to assist transfers, whereas codes for individuals with less impairment referred to independent walking. Codes such as finishing chewing before taking the next bite were described in children with better eating skills, also illustrating convergence with the developmental sequence. However, other codes such as 'avoiding choking' (eating safely) or 'finger feeding' or 'eating with utensils' (eating independently) were described across impairment levels, illustrating divergence.

In our previous qualitative study, meaningful change described smaller developmental steps in children with more limited skills and more complex steps for children with better skills.[10] Our current data set is more extensive, and we have identified a more nuanced set of patterns with commonalities and differences in meaningful change across levels of impairment.

We previously described a family of change-related constructs,[10] comprising reliability, minimal clinical important difference, and individual worthwhile change. Here, we sought to expand our understanding of individual worthwhile change beyond our previous study,[11] preferred by the US Food and Drug Administration over minimal clinical important difference values which are average group changes.[9] As documented in the International Classification

**TABLE 4** Categories explaining why meaningful change was anticipated to be important to the child and family, alongside sample codes for each functional domain.

| | | Sample codes in each functional area | | | | | |
|---|---|---|---|---|---|---|---|
| | **Category** | **Expressive communication** | **Receptive communication** | **Gross motor** | **Fine motor** | **Eating safely** | **Eating independently** |
| Child | Mental health | Behavioural regulation | Less social anxiety | Less frustration and fear of movement | — | Less distress from suctioning | Better sleep |
| | Physical health | Rapid meeting of needs | — | Better management of respiratory secretions | Preserve wrist joints | Reduced risk of aspirating | Less illness and fewer seizures if better hydrated |
| | Independence | Choice and control | Able to follow routines | Achieve new motor skills | More dignity with self-care | Eating orally | Eat at own pace and stop when full |
| | Social well-being | Two-way communication | Increase social engagement and connections | Participation and play with siblings and peers | Use signs or device for communication | — | — |
| | Safety | To say stop | Safety | Less falls | — | Safety | — |
| | Personal growth and quality of life | More social joy | Greater learning | Participate in activities in the community | Engaging with objects in the world | To taste delicious foods | — |
| Family | Mental health | Less parent worry and stress | More harmonious home | — | — | Less parental anxiety | Less stress |
| | Day-to-day care | Knowing appropriate solutions | Knowing the child understands | Less equipment needed | Child self-feeding for parent to enjoy own meals | More efficient feeding and drinking | Less care time, less things to pack |
| | Family joy and quality of life | To celebrate the child's voice | Easier family activities and outings | Easier to travel | — | Family connections at mealtimes | Eat together as a family |

of Functioning, Disability and Health,[27] impairments relate to day-to-day activities and participation, which are each influenced by personal and environmental factors.[27] Consistently, parents explained why a meaningful reduction in impairments and increase in activities would be important for the child's health, activities, and participation, and could enable personal joy. Parents also explained the potential for positive impacts for the family, namely better mental health, easier or reduced provision of day-to-day care, and more opportunities for joyful activities and quality of life. Achieving meaningful change in functional abilities for the child could enable parents to participate in more enjoyable activities including self-care[28] and in turn enable better family functioning. In combination, meaningful change was perceived as facilitating better quality of life.[29] There are two implications for measurement. First, COAs must have appropriate elements to validly measure meaningful change.[6] Second, COAs of functioning should be accompanied by broader COAs, such as quality of life, to indicate whether the meaningful change has achieved wider impact in how the child lives.

The sample size was large and enabled a comprehensive examination of meaningful change in DEE and other conditions with severe communication impairments. Accordingly, our findings are limited in their transferability to other patients where communication skills are not severely impaired. The mixed-methods study design generated maximal insights into meaningful change in this population for specific domains and levels of impairment. However, this was a convenience sample which might not be representative of the population. We were unable to probe the expressed concepts. Some responses were non-specific which reduced our ability to understand meaningful change more fully. With small numbers of individuals with each genetic aetiology, we were unable to examine between-group consistencies or differences. Similarly, we had limited data to describe the epilepsy phenotype and compare across epilepsy syndromes,[30] which are also associated with complex neurodevelopmental phenotypes.

## CONCLUSION

Our findings will guide the development and selection of COAs that are best able to measure meaningful trial endpoints and ensure effective and meaningful testing of the efficacy of new treatments. Irrespective of diagnosis, our findings will inform interpretation of developmental progress in clinical care for children with severe developmental impairments.

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## CONFLICT OF INTEREST STATEMENT

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

## DATA AVAILABILITY STATEMENT

Raw research data are not shared, noting that the coding tree is shown in Supplementary Table 1.

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## SUPPORTING INFORMATION

The following additional material may be found online:
**Figure S1:** Procedural flowchart.
**Table S1:** Tables showing all 86 codes for each functional domain, categorized by the level of impairment.

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