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Mapping epilepsy-specific patient-reported outcome measures for children to a proposed core outcome set for childhood epilepsy

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ABSTRACT

Objective: The objectives of the study were to (1) map questions in epilepsy-specific patient-reported outcome measures (PROMs) of children's health-related quality of life (HRQoL) to a proposed core outcome set (COS) for childhood epilepsy research and (2) gain insight into the acceptability of two leading candidate PROMs.
Method: We identified 11 epilepsy-specific PROMs of children's HRQoL (17 questionnaire versions) in a previous systematic review. Each item from the PROMs was mapped to 38 discrete outcomes across 10 domains of the COS: seizures, sleep, social functioning, mental health, cognition, physical functioning, behavior, adverse events, family life, and global quality of life. We consulted with three children with epilepsy and six parents of children with epilepsy in Patient Public Involvement and Engagement (PPIE) work to gain an understanding of the acceptability of the two leading PROMs from our review of measurement properties: Quality of Life in Childhood Epilepsy (QOLCE-55) and Health-Related Quality of Life Measure for Children with Epilepsy (CHEQOL).
Results: Social Functioning is covered by all PROMs except DISABKIDS and G-QOLCE and *Mental Health* is covered by all PROMs except G-QOLCE and Hague Restrictions in Childhood Epilepsy Scale (HARCES). Only two PROMs (Epilepsy and Learning Disability Quality of Life (ELDQOL) and Glasgow Epilepsy Outcome Scale (GEOS-YP)) have items that cover the *Seizure* domain. The QOLCE-55 includes items that cover the domains of *Physical Functioning*, *Social Functioning*, *Behavior*, *Mental Health*, and *Cognition*. The CHEQOL parent and child versions cover the same domains as QOLCE-55 except for *Physical Functioning* and *Behavior*, and the child version has one item that covers the discrete outcome of *Overall Quality of Life* and one item that covers the discrete outcome of *Relationship with parents and siblings*. The QOLCE-55 parent version was acceptable to the parents we consulted with, and CHEQOL parent and child versions were described as acceptable to our child and parent advisory panel members.
Significance: Mapping items from existing epilepsy-specific PROMs for children is an important step in operationalizing our COS for childhood epilepsy research, alongside evaluation of their measurement properties. Two leading PROMS, QOLCE-55 and CHEQOL, cover a wide range of domains from our COS and would likely be used in conjunction with assessment tools selected for specific study objectives. The PPIE work provided practical insights into the administration and acceptability of candidate PROMs in appropriate context. We promote our COS as a framework for selecting outcomes and PROMs for future childhood epilepsy evaluative research.

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1. Introduction

Epilepsy is defined by the tendency for recurrent seizures [1] and covers a range of different age-related clinical syndromes and

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etiologies. In children, epilepsy is the most common, chronic, neurological condition, affecting around 3.2/1000 in Europe [2,3]. Much of its impact is due to the medical, psychological, social, and cognitive implications of seizures and antiepileptic medications [4–6] and consequently, health-related quality of life (HRQoL) has become an important emphasis for childhood epilepsy research. Health-related quality of life can be assessed using patient-reported outcome measures (PROMs). However, PROMs cannot simply be selected "off-the-shelf". Evidence of robust measurement properties is important, and also, the salience and acceptability of items to people completing the questionnaires must also be considered [7].

When choosing a childhood epilepsy PROM for a specific objective, essential properties to consider, in addition to validity and reliability, include how well items map onto aspects of health; how the questions and response options are received by the respondents; and the importance of the items to children with epilepsy and their families. Previously, Sadeghi et al. [8] mapped epilepsy-specific PROMs for children to domains in the World Health Organization's International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) [8,9]. Although the ICF-CY is a comprehensive classification system of health for children, its domains are not specific to epilepsy and do not classify broader aspects of wellbeing and quality of life. Therefore, it is important to evaluate how PROMs of interest map to all the outcomes perceived as more important for children with epilepsy, — and this has not previously been done.

We have proposed a core outcome set (COS) for childhood epilepsy research [10,11]. Our COS development was uniquely child- and family-centered, involving iterative Delphi surveys, and a face-to-face meeting with young people with epilepsy, parents, and health professionals. Stakeholders reached consensus on 38 outcomes across ten health domains: (1) Seizures, (2) Sleep, (3) Physical functioning, (4) Social functioning, (5) Behavior, (6) Mental Health, (7) Cognition, (8) Family functioning, (9) Adverse events, and (10) Global quality of life. Our COS captured commonly reported outcomes such as 'seizure frequency' that are consistent with existing tools such as the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements [12–15]. However, our COS also highlights nonseizure-related, child-centered outcomes including "feelings about epilepsy" (emotions or reactions to having epilepsy such as embarrassment or stigma), which suggests that the seizure-focused view is not the only important outcome for HRQoL in young people with epilepsy. Therefore, our COS is unique in its representation of stakeholders' views.

The next stage of the COS development work is to establish how to measure the core outcomes [16]. One approach would be to conduct systematic reviews within each of the ten health domains, though the resulting battery of measures might be burdensome for respondents and would have required more resources than available to us. Therefore, we took a pragmatic approach to map the content of 11 epilepsy-specific PROMs for children to our COS, using a broadly similar method by which PROM questions have been mapped to the ICF-CY [8].

Subsequently, we focused on two leading candidate PROMs with better evidence of robust measurement properties from our prior systematic review [17]: Quality of Life in Childhood Epilepsy 55-item version (QOLCE-55) parent report and the Health-Related Quality of Life Measure for Children with Epilepsy (CHEQOL) child and parent report [18,19]. The QOLCE-55 is part of the QOLCE family of PROMs, which has four questionnaire versions with different numbers of items (QOLCE 76, QOLCE-55, QOLCE-16, and G-QOLCE) [19–25]. Both QOLCE and CHEQOL have been used internationally for numerous evaluative studies and have been translated into other languages for use [26–51]. We consulted our Patient Public Involvement and Engagement (PPIE) Research Advisory Panel of children with epilepsy and their parents on the acceptability of the two leading PROMs.

2. Methods

2.1. Epilepsy-specific PROMs

Our previous systematic review identified 11 epilepsy-specific PROMs of children's HRQoL (Table 1). Two PROMs have parent and child report versions with slightly different items (Quality of Life in Pediatric Epilepsy (QOLPES) and CHEQOL); the Impact of Childhood Illness Scale (ICI; parent-only report) was developed from a prior questionnaire version (Modified Impact of Epilepsy Schedule (MIOES)); and the QOLCE (parent-only report) family of PROMs has four questionnaire versions with differing numbers of items (G-QOLCE, QOLCE-16, QOLCE-55, QOLCE-76). The different versions result in 17 questionnaires to map (Table 1), and so we use the term 'questionnaire' from here onwards to reflect this. Sadeghi et al. [8] found thirteen epilepsy-specific PROMs for children in their review, and we identified nine of the same PROMs. The PROMs that we did not include from the Sadeghi et al. [8] review were the Epilepsy Foundation of America Concerns Index (EFA), the Glasgow Epilepsy Outcome Scale (GEOS-C), The Impact of Childhood Neurologic Disability Scale (ICNDS), and the Epilepsy and Children Questionnaire (ECQ). We did not include the EFA and GEOS-C as they are PROMs for adults. The ICNDS is not condition-specific but may be useful in epilepsy. The ECQ was validated in an Italian population. We found two further PROMs that were the GEOS-YP (child-only report) and Pediatric Quality of Life Inventory™ *Epilepsy* Module (*PedsQL™ Epilepsy* Module) (parent and child report).

2.2. Mapping

Mapping refers to the process of deciding where the content of a PROM fits in relation to a specific framework. Two reviewers (HC and AC) collaboratively discussed and mapped the 17 questionnaires to our COS outcomes and definitions, item-by-item (Table 2; supplementary 1). We mapped items that did not match a discrete outcome definition but broadly covered a domain area to one of the 10 COS domains (Table 2). We excluded items that did not fit the COS or were too broad. For example, we excluded the items that asked about 'general health' from the QOLIE-AD-48 questionnaire as this is not covered in our COS. Similarly, we excluded the item 'In the past 4 weeks, how often have these problems (physical or emotional) caused you to do fewer things than you would have liked to do?' because 'fewer things than you would have liked to do' is too broad and not within the conceptual framework of our COS. Disagreements about where an item should be mapped were arbitrated by a third reviewer (CM).

2.3. Patient, Public Involvement and Engagement (PPIE)

INVOLVE, an organization funded by the National Institute of Health Research (NIHR) in the UK, defines PPIE as "research being carried out 'with' or 'by' members of the public and patients rather than 'to', or 'about', or 'for' them" [52]. Patient and Public Involvement and Engagement involves patients as active partners in research and can lead to greater quality and relevance of research due to the unique patient perspective that PPIE members can bring. It can refer to a diverse range of activities including consulting Advisory Panels of patients and the public. This study is reported in line with the GRIPP2 short form for PPIE (supplementary 2) [53]. We consulted with a subset of members from our established Advisory Panel, consisting of children with epilepsy and parents, about the two leading candidate questionnaires from our systematic review [17], QOLCE-55 and CHEQOL. The members of our Advisory Panel responded to a call through national epilepsy charities and clinical services for people with experience of childhood epilepsy to join our Advisory Panel. The aim of our Advisory Panel consultation was to help further gain insight into the acceptability of the PROMs as well as to assess their real-life functionality such as the speed of

Table 1
Epilepsy-specific patient reported outcome measures (PROMs) of children's HRQoL.

No.	Instrument version	Author	Purpose	No. of items and domains	Age range	Country/Origin	Respondent
1a	Adult's Attitudes to Children with Epilepsy: Visual Analogue Scale	Hoare (1986) [58]	Assess adult's attitudes to children with epilepsy	47 items, 7 domains: Physical consequences of a single fit; Etiology of epilepsy; Problems for the child at present and in the future; Side effects of drugs; Problems for the child's parents; Social restrictions or the child and his family; Adverse effects of family life	10	Edinburgh, UK	Parent
1b	Modified Impact of Epilepsy Schedule	Hoare (1993) [59]	Assess adult's attitudes to children with epilepsy and the impact on adults	39 items, 3 domains: The medical care and treatment of epilepsy; The child's adjustment and development; Effects on family life	5–15 years	Edinburgh, UK	Parent
1c	The Impact of Childhood Illness Scale (ICI)	Hoare et al., (2000) [57]	Assess the impact of epilepsy/long-standing childhood illness on QoL on the child and family	30 items, 4 domains: impact on the child's development and adjustment; impact on the parents; and impact on the family and a combined total score. The instrument is scored on two dimensions: Frequency and Importance.	6–17 years	Edinburgh, UK	Parent
2	The Hague Restrictions in Childhood Epilepsy Scale (HARCES)	Carpay et al., (1997) [61]	Quantify restrictions due to disability in childhood epilepsy	10 items, including 2 global items	4–16 years	Hague, Rotterdam	Parent
3	Quality of Life in Epilepsy Inventory for Adolescents (QOLIE-AD-48)	Cramer et al., (1999) [62]	Assess HRQoL in adolescents with epilepsy	48 items, 8 domains: Epilepsy impact; Memory/concentration; Attitudes towards epilepsy; Physical functioning; Stigma; Social support; School behavior; Health perceptions and a total summary score.	11–17 years	USA & Canada	Child
4	Quality of Life in Pediatric Epilepsy (QOLPES)	Arunkumar et al., (2000) [63]	To assess HRQoL in children with epilepsy	20 items	3 months – 18 years	USA	Parent & child
5a	Quality of Life in Childhood Epilepsy (QOLCE)	Sabaz et al., (2000) [20] & Sabaz et al., (2003) [21]	Assess HRQoL for children with epilepsy	Australian version: 73 items, 16 subscales, covering 7 domains: cognition, physical activities, social activities, emotional wellbeing, behavior, general health, general quality of life and a total score USA version: 76 items, 16 subscales, covering 7 domains: cognition, physical activities, social activities, emotional wellbeing, behavior, general health, general quality of life and a total score	4–18 years	New South Wales, Australia & USA	Parent
5b	QOLCE 55	Goodwin et al., (2015) [19]	Assess HRQoL for children with epilepsy, in a shortened version	55 items, 4 domains: Cognitive; Emotional; Social and Physical	4–18-years	Canada	Parent
5c	QOLCE 16	Goodwin et al., (2018) [25].	Assess HRQoL for children with epilepsy, in a shortened version	16 items, 4 domains: Cognitive; Emotional; Social and Physical	4–18-years	Canada	Parent
5d	G-QOLCE	Conway et al., (2018) [24].	Assess HRQoL for children with epilepsy with 1-item	1 item	4–18 years	Canada	Parent
6	Impact of Pediatric Epilepsy Scale (IPES)	Camfield et al., (2001) [64]	Assess the influence of epilepsy on the major aspects of the family and child's life	11 items	2–16 years	Canada	Parent
7	Health-Related Quality of Life Measure for Children with Epilepsy (CHEQOL-25)	Ronen et al., (2003) [18].	Measure the HRQOL of preadolescent children with epilepsy	25 items, 5 domains: Interpersonal/Social Consequences; Worries and Concerns; Intrapersonal/Emotional Issues; Epilepsy My Secret and Quest for Normality	6–15 years	Canada	Parent & child
8	DISABKIDS (Epilepsy Module)	Baars et al., (2005) [65]	Assess the HRQoL of children and adolescents with epilepsy and their families	10 items, 2 domains: Impact and Social	4–16 years	Collaboration of seven European countries (Austria, France, Germany, Greece, the	Child and parent report (parent proxy for 4–7-year

(continued on next page)

Table 1 (*continued*)

No.	Instrument version	Author	Purpose	No. of items and domains	Age range	Country/Origin	Respondent
						Netherlands, Sweden and the United Kingdom)	olds)
9	Epilepsy and Learning Disability Quality of Life (ELDQOL)	Buck et al., (2007) [66]	Assess HRQoL in children with both epilepsy and learning disabilities	70 items, 4 domains: Behavior; Seizure severity; Mood and Side effects	2–18 years	UK	Parent
10	Glasgow Epilepsy Outcome Scale (GEOS-YP)	Townshend et al., (2008) [67]	Assess the impact of epilepsy on an adolescent's QoL that is based on exploration of adolescent's views	50 items, 9 domains: Peer Acceptance; School/work; Development of Autonomy; Future focus; Epilepsy as part of Me; Medication issues; Seizures, Knowledge about Epilepsy; Sense of Uncertainty	10–18 years	Glasgow, UK Tertiary epilepsy centers	Child
11	PedsQL Epilepsy Module	Follansbee-Junger et al., (2016) [68]	Validate a brief and reliable epilepsy-specific, health-related quality of life (HRQOL) measure in children with various seizure types, treatments, and demographic characteristics.	29 items, 5 domains: Impact; Cognitive; Sleep; Executive Function and Mood/Behavior	2–18 years	USA	Parent only report (2–4-year olds), and child and parent proxy report (aged 5–18)

completion. This was not qualitative research [54] but was aimed at improving the quality and relevance of our research.

Two Family Engagement Officers (SL and RM), respectively based in the South East and North of England led the PPIE consultation. Members of our Advisory Panel were invited to provide their personal views on the PROMs. We adopted a structured approach using clear guidance and simple feedback forms that asked questions on the length of time taken to complete the questionnaire and the acceptability of the items and response options. Advisory Panel members provided feedback via email, post, or face-to-face and were offered reimbursement for their time following payment guidance from INVOLVE [55].

Six parents of children with epilepsy from the Advisory Panel provided feedback on the CHEQOL parent version and QOLCE-55. Three parents attended a face-to-face meeting held at a venue in Central London facilitated by a FEO (SL). Three parents returned feedback via post/email. Three children with epilepsy aged 12 to 15 from the Advisory Panel provided feedback on the CHEQOL child version and returned their feedback forms through email. The parents and children who assisted with this work are from locations across the UK, white British and English-speaking, and have a range of experience of childhood epilepsy.

Ethics approval and formal consent is not appropriate or required for PPIE as the people are involved as partners in the research not as participants.

3. Results

3.1. Mapping

We mapped items from each epilepsy-specific PROM of children's HRQoL to our COS of 38 outcomes across 10 domains (Tables 3 and 4). Mapping each PROM item-by-item to our COS was not straightforward. Some PROMs had items that could map to multiple aspects of the COS (Table 2). Some of the more difficult PROMs to map included the ICI [56,57]. The ICI was developed by merging two prior scales, the Adult Attitudes To Children With Epilepsy (AATCWE) and the MIOES [58,59]. We did not map the items of the AATCWE as it does not measure a child's HRQoL at a moment in time but instead asks questions about hypothetical situations and the respondent's general attitudes. The ICI was developed from items in the AATCWI and the MIOES. The ICI has two scoring options of 'frequency' and 'importance'. The two scoring options meant that each item could map to a specific discrete outcome but also be mapped to the discrete outcome of *parental health* because every item was to be rated on an 'importance' scale to the parent, regardless of the frequency.

3.1.1. Seizures domain

Two questionnaires (Epilepsy and Learning Disability Quality of Life (ELDQOL) and GEOS-YP) cover the *Seizure* domain. The GEOS-YP has four items that cover *Seizures*, while ELDQOL has one item that covers *Seizures* and 13 items that cover the discrete outcome of *Seizure Severity*.

3.1.2. Sleep domain

Both ELDQOL and PEDSQL are the only questionnaires that cover the *Sleep* domain. The ELDQOL has one item that broadly covers *Sleep*. The PEDSQL covers the broad domain of *Sleep* but also contains two items that cover the discrete outcomes of *Awakenings from Sleep* and *Daytime Sleepiness*.

3.1.3. Physical Functioning domain

More than half of the questionnaires (Hague Restrictions in Childhood Epilepsy Scale (HARCES), QOLIE-AD-48, QOLPES Parent and child, QOLCE-76, QOLCE-55, QOLCE-16, ELDQOL, GEOS-YP, and PEDSQL) broadly capture *Physical functioning*. Only ELDQOL captures the two discrete outcomes within the *Physical Functioning* domain of *Gross Motor Function* and *Fine Motor Function*.

3.1.4. Social Functioning domain

Fifteen questionnaires (not DISABKIDS and G-QOLCE) have items that capture an aspect of *Social functioning*. The QOLCE-76 is the only PROM that also covers all four discrete outcomes within the *Social Functioning* domain. The ELDQOL has only one item that covers *Ability to join activities with others*, and the PEDSQL has only one item that covers the broad domain of *Social Functioning*.

3.1.5. Behavior domain

Seven questionnaires measure at least one aspect of *Behavior* (MIOES, QOLIE-AD-48, QOLPES parent, QOLCE-76, QOLCE-55, ELDQOL, PEDSQL). Four questionnaires measure the discrete outcome of *Behavioral Concerns* (MIOES, QOLPES parent, QOLCE-76, QOLCE-55), and only two questionnaires measure the discrete outcome of *Impulsivity* (PEDSQL and QOLCE-76). The QOLCE-76 is the only questionnaire that has items that cover the main domain of *Behavior* but also measures the two discrete outcomes of *Behavioral concerns* and *Impulsivity*.

Table 2
Core outcome set (COS) for childhood epilepsy research.

Outcome	Description	Domain
Seizure freedom	Not having seizures	SEIZURES
Seizure frequency	How often seizures occur	
Seizure duration	How long a seizure lasts	
Seizure severity	How bad seizures are in terms of effects on the person during and after seizures — such as falls or injuries, incontinence, confusion, and time to recover afterwards	
Total time spent asleep at night	Total time spent asleep each night	SLEEP
Total time spent asleep in 24 h	Total time spent asleep in 24 h	
Awakening from sleep	Wakings in the night that parents/carers are aware of	
Breathing difficulties	May include snoring or gasping for breath	
Daytime sleepiness	Feeling sleepy or actually sleeping during the day	
Movement ability – Gross motor function	Using parts of the body together and efficiently, such as to ride a bike, or stand on one leg, catching and throwing	PHYSICAL FUNCTIONING
Manual ability – fine motor function	Dexterity in handling objects, handwriting	
Ability to join in activities with others	Joining in with people, such as playing out with friends, doing sports, joining in things	SOCIAL FUNCTIONING
Friendships	Forming and maintaining friendships	
Engagement in school life	Feeling part of the school community	
Experience of other people's attitudes towards epilepsy	Bullying, social exclusion	
Behavioral concerns	Being able to control emotions and respond to situations in context	BEHAVIOR
Impulsivity	Acting without thinking	
Feelings about having epilepsy	Emotions or reactions to having epilepsy, such as embarrassment, shame, stigma	MENTAL HEALTH
Self-esteem	Overall feelings about yourself	
Self-harm	Thinking about hurting yourself on purpose or wishing you were dead	
Fears of having a seizure	Having a seizure in public, being injured during a seizure, dying during a seizure, what other people will do during a seizure	
Mood swings	Quick unexplained changes of mood	
Concealment	Not telling people about epilepsy	
Learning	Gaining new skills & knowledge generally	COGNITION
Literacy	Reading, writing, spelling	
Speech & Language	Making yourself understood and understanding when spoken to	
Memory	Short & long term	
School attendance	Being and engaging in school curriculum	
Academic attainment	Reaching personal potential through studying and completing assigned tasks and projects, and advancing to next stages of education	
Concentration	Focusing on something for the required period of time	
Executive functioning	The ability to plan and organize activities. Executive functions help you manage life tasks of all types. For example, executive functions let you organize a trip, a research project, or a paper for school effectively	
Relationships with parents & siblings	Getting along well with and feeling close to other members of family	FAMILY FUNCTIONING
Family life	Impact of epilepsy on family life such as parent work opportunities and/or leisure time	
Parental health	Parent's physical and emotional wellbeing	
Epilepsy specific attendance at A&E and/or unplanned admission to the ward	Visiting the hospital due to an acute medical emergency	ADVERSE EVENTS
Adverse events or reactions	Any unintended effects of treatments, side effects	
Drug treatment failure events (adverse events or poor seizure control)	Stopping medication because it's not working or causing problems	
Overall quality of life	How you feel your life is generally	GLOBAL QUALITY OF LIFE

3.1.6. Mental health domain

Fifteen questionnaires (not G-QOLCE or HARCES) have items that cover *Mental health* as a broad domain. The QOLCE-76 has 17 items that measure *Mental Health* broadly, three items that cover the discrete outcome of *self-esteem* specifically and one item that covers *self-harm*. The QOLCE-55 has seven items that cover *Mental Health* broadly and two items that measure the discrete outcome of *self-esteem*. The CHEQOL child report has six items that broadly cover *Mental Health* and two items that cover the discrete outcome of *Feelings about having epilepsy*.

3.1.7. Cognition domain

Fourteen questionnaires (not HARCES, G-QOLCE, or DISAKBIDS) broadly cover *Cognition*. *Memory* and *Concentration* are the two discrete outcomes measured most frequently with QOLCE-76 and QOLCE-55 having six items each specifically measuring *Memory*, and 4 items each specifically measuring *Concentration*.

3.1.8. Family Functioning domain

Nine questionnaires cover some aspect of *Family Functioning* (MIOES, ICI, QOLIE-AD-48, QOLPES parent and child version, QOLCE-76, IPES, CHEQOL child, and ELDQOL). Every item in the MIOES and ICI cover *Parental health* due to the way the PROM response items are phrased around parental concern. In the ICI, there are two scales of *Frequency* and *Importance*, which ask about the impact of all these questions on parent health.

3.1.9. Adverse events domain

Three questionnaires (ICI, ELDQOL, and GEOS-YP) have at least one item that covers *Adverse events or reactions*.

3.1.10. Global Quality of Life domain

Seven questionnaires include one item that measures *Global Quality of Life* (QOLPES child and parent, G-QOLCE, QOLCE-76, IPES, CHEQOL child, and ELDQOL).

3.2. PPIE consultation on the acceptability of two leading candidate PROMs

3.2.1. QOLCE-55

The QOLCE-55 is a parent-report questionnaire for young people with epilepsy aged between 4 and 18 years old with 55 items split

Table 3
Number of items from 11 epilepsy-specific PROMs for children represented in a proposed core outcome set for childhood epilepsy.

	1a. MIoES	1b. ICI	2. HARCES	3. QOLIE-AD-48	4a. QOLPES (Parent)	4b. QOLPES (Child)	5a. G-QOLCE	5b. QOLCE-76	5c. QOLCE-55	5d. QOLCE-16	6. IPES	7a. CHEQOL (child)	7b. CHEQOL (parent)	8. DISABKIDs	9. ELDQOL	10. GEOS-YP	11. PEDSQL
SEIZURES (total)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14	4	0
Seizure freedom																	
Seizure frequency																	
Seizure duration																	
Seizure severity															13		
General seizures															1	4	
SLEEP (total)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	3
Total time spent asleep at night																	
Total time spent asleep in 24 h																	
Awakenings from sleep																	1
Breathing difficulties																	
Daytime sleepiness																	1
General sleep															1		1
PHYSICAL FUNCTIONING (total)	0	0	4	4	1	1	0	9	5	3	0	0	0	0	3	1	1
Movement ability – Gross motor function								1							1		
Manual ability – fine motor function															2		
General Physical Functioning			4	4	1	1		8	5	3						1	1
SOCIAL FUNCTI ONING (total)	2	2	3	2	2	2	0	9	8	4	2	7	4	0	1	6	1
Ability to join activities with others			2					2	3						1		
Friendships	2	1				1		1		1	1	1	1			1	
Engagement in school life			1					1	2	1		1					
Experience of other people's attitudes towards epilepsy		1			1	1		1	1		1	4	2			5	
General Social Functioning				2	1			4	2	2		1	1				1
BEHAVIOR (total)	3	0	0	2	1	0	0	8	6	0	0	0	0	0	1	0	2
Behavioral concerns	2				1			3	3								
Impulsivity								1									1
General Behavior	1			2				4	3						1		1
MENTAL HEALTH (total)	2	2	0	13	1	5	0	18	9	4	1	10	9	10	1	13	8
Feelings about having epilepsy		1		6		2						2	1	6		6	2

Self-esteem				6	1			1	2		1						1	
Self-harm								1										
Fears of having a seizure						2						1	2	4			4	1
Mood swings	2	1																
Concealment												1	1				1	
General Mental Health				1		1		16	7	4		6	5			1	1	5
COGNITION (total)	3	2	0	12	2	3	0	20	22	4	1	2	2	0		3	2	6
Learning																		1
Literacy	1					1		1	1									
Speech & language				2				3	2							1		
Memory				1		1		6	6	1		1	1					1
School attendance				2													1	
Academic attainment				1							1						1	1
Concentration	1			2	1	1		4	4			1	1			1		1
Executive functioning				2				2	2									1
General Cognition	1	2		2	1			4	7	3						1		1
FAMILY FUNCTIONING (total)	19	8	0	1	5	1	0	1	0	0	4	1	0	0		4	0	0
Relationships with parents and siblings				1		1					2	1				1		
Family life	6	5			1						1							
Parental health	7[b]	1[a]			4						1					2		
General Family Functioning	6	2						1								1		
ADVERSE EVENTS (total)	0	2	0	0	0	0	0	0	0	0	0	0	0	0		2	1	0
Epilepsy specific attendance at A&E and/or unplanned admission to the ward																		
Adverse events or reactions		2														2	1	
Drug treatment failure events (adverse events or poor seizure control)																		
General Adverse Events																		
GLOBAL QUALITY OF LIFE (total)	0	0	0	0	1	1	1	1	0	0	1	1	0	0		1	0	0
Overall quality of life					1	1	1	1			1	1				1		
Too broad/vague		1	1	7	1	4		1	5							3		
Do not fit the COS:	10	13	2	7	6	3		9		1	2	4	10			10	18	7

1a. Modified Impact of Epilepsy Schedule (MIOES), 1b.Impact of Childhood Illness Scale (ICI), 2.The Hague Restrictions in Childhood Epilepsy Scale (HARCES), 3.Quality of Life in Epilepsy Inventory for Adolescents (QOLIE-AD-48), 4.Quality of Life in Pediatric Epilepsy (QOLPES),5a-5d.Quality of Life in Childhood Epilepsy (QOLCE), 6.Impact of Pediatric Epilepsy Scale (IPES), 7.Health-Related Quality of Life Measure for Children with Epilepsy (CHEQOL-25), 8.DISABKIDS Epilepsy Module, 9.Epilepsy and Learning Disability Quality of Life (ELDQOL), 10.Glasgow Epilepsy Outcome Scale (GEOS-YP), 11.PEDSQL Epilepsy Module.

[a] The ICI has a 'frequency' scale and an 'importance' scale. The importance scale asks about the impact of all these questions on parental health.

[b] The MIoES assesses parental worry about each question.

Table 4
Number of items from 11 epilepsy-specific PROMs for children represented in the 10 domains of a proposed core outcome set for childhood epilepsy.

	1a. MIoES (39)	1b. ICI (30)	2. HARCES (10)	3. QOLIE-AD-48 (48)	4a. QOLPES -Parent (20)	4b. QOLPES -Child (20)	5a. G-QOLCE	5b. QOLCE-76 (76)	5c. QOLCE-55 (55)	5d. QOLCE-16 (16)	6. IPES (11)	7a. CHEQOL -Child (25)	7b. CHEQOL-Parent (25)	8. DISABKIDs (10)	9. ELDQOL (44)	10. GEOS-YP (45)	11. PEDSQL (28)
SEIZURES	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14 (32%)	4 (9%)	–
SLEEP	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1 (2%)	–	3 (11%)
PHYSICAL FUNCTIONING	–	–	4 (40%)	4 (8%)	1 (5%)	1 (5%)	–	9 (12%)	5 (9%)	3 (19%)	–	–	–	–	3 (7%)	1 (2%)	1 (4%)
SOCIAL FUNCTIONING	2 (5%)	2 (7%)	3 (30%)	2 (4%)	2 (10%)	2 (10%)	–	9 (12%)	8 (15%)	4 25%	2 (18%)	7 (28%)	4 (16%)	–	1 (2%)	6 (13%)	1 (4%)
BEHAVIOR	3 (8%)	–	–	2 (4%)	1 (5%)	–	–	8 (11%)	6 (11%)	–	–	–	–	–	1 (2%)	–	2 (7%)
MENTAL HEALTH	2 (5%)	2 (7%)	–	13 (27%)	1 (5%)	5 (25%)	–	18 (24%)	9 (16%)	4 25%	1 (9%)	10 (40%)	9 (36%)	10 (100%)	1 (2%)	13 (29%)	8 (29%)
COGNITION	3 (8%)	2 (7%)	–	12 25%	2 (10%)	3 (15%)	–	20 (26%)	22 40%	4 25%	1 (9%)	2 (8%)	2 (8%)	–	3 (7%)	2 (4%)	6 (21%)
FAMILY FUNCTIONING	19 (49%)	8 (27%)	–	1 (2%)	5 (25%)	1 (5%)	–	1 (1%)	–	–	4 (36%)	1 (4%)	–	–	4 (9%)	–	–
ADVERSE EVENTS	–	2 (7%)	–	–	–	–	–	–	–	–	–	–	–	–	2 (5%)	1 (2%)	–
GLOBAL QUALITY OF LIFE	–	–	–	–	1 (5%)	1 (5%)	1 (100%)	1 (1%)	–	–	1 (9%)	1 (4%)	–	–	1 (2%)	–	–
OTHER/DOES NOT FIT TO COS	10 (26%)	14 (47%)	3 (30%)	14 (29%)	7 (35%)	7 (35%)	–	10 (13%)	5 (9%)	1 (6%)	2 (18%)	4 (16%)	10 (40%)	–	13 (30%)	18 (40%)	7 (25%)

1a. Modified Impact of Epilepsy Schedule (MIOES), 1b.Impact of Childhood Illness Scale (ICI), 2.The Hague Restrictions in Childhood Epilepsy Scale (HARCES), 3.Quality of Life in Epilepsy Inventory for Adolescents (QOLIE-AD-48), 4.Quality of Life in Pediatric Epilepsy (QOLPES),5a-5d.Quality of Life in Childhood Epilepsy (QOLCE), 6.Impact of Pediatric Epilepsy Scale (IPES), 7.Health-Related Quality of Life Measure for Children with Epilepsy (CHEQOL-25), 8.DISABKIDS Epilepsy Module, 9.Epilepsy and Learning Disability Quality of Life (ELDQOL), 10.Glasgow Epilepsy Outcome Scale (GEOS-YP), 11.PEDSQL Epilepsy Module.
Bracket underneath the PROM name indicates the number of items in the PROM.
Percentage underneath item number has been rounded to 1 decimal place.

across four domains (Cognitive; Emotional; Social; Physical). The questions ask the respondent to rate on a 6-point Likert-scale (*Very Often*, *Fairly Often*, *Sometimes*, *Almost Never*, *Never*, *Not applicable*) how often during the past four weeks the respondent's child has done something e.g., *had trouble remembering things*. The QOLCE-55 is a shortened version of the QOLCE-76. The items of the QOLCE-76 were derived from a focus group of patients with epilepsy [20,21].

Advisory Panel parents completed the QOLCE-55 in 3–7 min. The questionnaire was deemed easy to understand with clear instructions. One question that was difficult to understand for one parent was '*how often has your child been able to do physical activities other children his/her age do?*'. It was suggested that "*activities*" is a broad concept that could be broken down into specific activities to make the question easier to answer. Some questions asked about '*how your child feels*', and parents commented that for some questions you can intuit an answer, but for other more subjective questions about feelings their answer may not be an accurate reflection of their child's feelings.

3.2.2. CHEQOL

The CHEQOL has child self-report and parent proxy report versions for children with epilepsy aged between 6 and 15 years old. It has 25 items across five domains (Interpersonal/Social consequences; Worries and concerns; Intrapersonal/Emotional Issues; Epilepsy My Secret; Quest for Normality). The items are presented as two polar statements such as '*some kids with epilepsy say kids won't play with them*' and '*other kids with epilepsy say other kids always play with them*'. The child or parent respondent is asked to decide which statement is '*most like them*' by circling it and to also decide if this is '*really true*' or '*sort of true*' by ticking a box. The items of the CHEQOL were developed using focus group discussions involving children with epilepsy and their parents [60]. Parents from our Advisory Panel completed CHEQOL in 4–9 min and children from our Advisory Panel completed CHEQOL in 15–18 min. The parent and child version ask mostly the same questions except for questions about the future, driving a car and jobs, which are only in the parent version.

One Advisory Panel parent commented that the two different statements e.g., '*some kids with epilepsy say kids won't play with them*' seemed to be 'pessimistic' and '*other kids with epilepsy say other kids always play with them*' seemed to be 'optimistic' indicating that choosing a response option may not be a straightforward decision depending on the respondent's viewpoint. The statements were deemed appropriate but there was no context to the questionnaire such as the recall period (e.g., over the last week) for answering the questions, and the questions referred to an abstract child.

Children commented that they '*liked*' the CHEQOL and the content of questions. One child from the Advisory Panel stated that the question about 'medication' should have a 'not applicable' option. The response options of '*some kids*' and '*other kids*' could be '*confusing*' at times.

3.2.3. Comparing QOLCE-55 and CHEQOL

For parents in our Advisory Panel, the QOLCE-55 questionnaire was preferable to the CHEQOL. Parents found that the QOLCE-55 items and response options were in a recognizable Likert style format. All parents commented that the CHEQOL asked important and relevant questions about epilepsy, but the response options that ask about an abstract child could be confusing to interpret. Overall, our consultation suggests that CHEQOL was acceptable to children with epilepsy and their parents and QOLCE-55 is acceptable to parents.

4. Discussion

We have described how the content of 11 epilepsy-specific PROMs of children's HRQoL map to the 10 domains and 38 discrete outcomes of our proposed COS. Our COS items have been prioritized as most important to measure by children with epilepsy, their parents, and professionals in the UK [11]. All 11 PROMs (17 questionnaire versions) cover a range of our COS outcomes but none cover them all. Most PROMs cover aspects of *Social Functioning* and *Mental Health*, while others neglect items on *Seizures* or *Sleep*. Members of our Advisory Panel found the two leading PROMs from our prior systematic review, QOLCE-55 (parent-report) and CHEQOL (parent and child report), to be acceptable for research use in the context of the UK National Health Service (NHS).

The PROMs measure a *subjective perception* of health, wellbeing, and QOL, and they constitute one of several available evaluative tools. Hence, although only two PROMs mapped to the *Seizure* domain, seizures might be more appropriately measured objectively using video-electroencephalography, or more systematically using a specific rating scale. Similarly, *Cognition* and *Mental health* could be measured using a variety of domain-specific and well-validated instruments. Therefore, it is not appropriate to judge the HRQoL PROMs on how well they fit to our COS, which contains outcomes and domains that may be better measured in other ways.

At the same time, some PROM items were not mapped to our COS as they did not fit within its conceptual framework e.g., items reflecting *independence*, *future concerns*, or *worries*. The COS development is a method of defining which outcomes are of *most importance* to stakeholders, but it does not mean that other outcomes may not also be important to measure. We are not suggesting that a new PROM should be developed that is inclusive of all domains of our proposed COS, or that the extent to which a PROM measures the domains makes it 'better' than others. Rather, we are promoting the uptake of our COS as a *framework* for selecting outcomes and PROMs for childhood epilepsy research, not as a rigid set of outcomes to be measured.

Mapping to our COS is an important step for childhood epilepsy research as our COS is unique in its representation of stakeholders' views, unlike other tools and frameworks [12–15]. The COS outcomes were decided through a transparent process using Delphi methodology that avoids overinfluence of one type of stakeholder (young person with epilepsy vs parent vs professional) over another [11]. Our COS includes child-centered outcomes such as *school attendance*, *concealment*, and *relationship with parent and siblings* that are not solely seizure or health-focused, highlighting how important it is to measure outcomes that are relevant and of concern to children with epilepsy. Although unique, our COS mapping is a useful adjunct to the Sadeghi et al. [8] analysis that mapped the items of epilepsy-specific PROMs to the ICF-CY framework and also made clear their biopsychosocial content. Sadeghi et al. found that regardless of the PROM title, most of the PROMs measured biopsychosocial health, as opposed to a subjective assessment of health (HRQoL) or a subjective perception about the respondent's life (QoL). To measure outcomes validly in research, it is essential to utilize a PROM that conceptually matches the outcome(s) of interest, otherwise, it could result in a study falsely concluding an intervention is ineffective.

We highlighted CHEQOL and QOLCE-55 as leading PROMs because they measured salient items from our COS and have robust measurement properties. Both CHEQOL and QOLCE-55 are north American PROMS that cover a range of our COS domains, with considerable overlap. They have more emphasis on the domains of *Mental Health* and *Social Functioning*. To our knowledge, both the QOLCE-55 and CHEQOL PROMs have not been mapped to any other kind of framework except for the ICF-CY. The QOLCE-55 belongs to the QOLCE PROM family that consists of four questionnaire versions with different numbers of items (QOLCE-76, QOLCE-55, QOLCE-16, and G-QOLCE) [19–25]. Of all the versions, the QOLCE-55 questionnaire has good and replicated evidence for structural and construct validity and internal consistency [22,23]. In comparison, the CHEQOL questionnaire has both child (aged 6–15 years) and parent-reported versions and good evidence of content, structural, and construct validity [18].

Acceptability is an essential property of a PROM as it is important that items do not cause distress, are relevant and important, and respondents can easily complete it [7]. The acceptability test is an essential final feasibility step in deciding how to measure an outcome, once the outcomes of interest and candidate instruments have been decided.

The items of the QOLCE were derived from a focus group of patients with epilepsy [20], and professionals reviewed the questionnaire for content and clarity. Similarly, the items of the CHEQOL were developed using focus group discussions involving children with epilepsy and their parents [60]. The QOLCE and CHEQOL versions have also been used internationally for numerous evaluative studies and have been translated into other languages [25–50]. However, although the item development work involved relevant stakeholders, it is not clear if further validation work looked at the 'real-life' use of a PROM such as the time to complete, or if other studies that translated the PROMs had further assessed their acceptability. Our Advisory Panel members considered both CHEQOL and QOLCE-55 to be acceptable for real-life use in a UK context.

Patient and Public Involvement and Engagement in health research is becoming increasingly important to make sure that research is as relevant and useful as possible to patients [52]. It is less concerned with the methods used to seek people's views and more about what PPIE members are asked to contribute, what recommendations they make and, importantly, what action is taken in response. Consulting Advisory Panels on the acceptability of a PROM to clarify any misunderstandings could lead to a considerable impact on the future research use of the PROM such as during scoring and analysis. For example, Love et al. [45] found when using the QOLCE in an evaluative study on children with epilepsy that the 'Not Applicable (N/A)' box resulted in missing data. Love et al. suggest that this could be due to the different interpretation of 'N/A' between parent respondents and from clinicians, e.g., parents may tick 'N/A' because their child does not engage in that behavior, whereas a clinician could argue that '0' would be the better item scoring. The QOLCE-55 is a shorter version of the QOLCE, and so does not include all the items of the QOLCE 76. However, the 'N/A' is still an item scoring option and it is important to consider. Parents in our Advisory Panel found the 'N/A' option useful, but it needs to be ensured that respondents fully understand how to answer the questions to avoid missing data and misinterpretation of items and their scoring. Our Advisory Panel's comments about the familiarity of the Likert rating for the QOLCE-55, and parents' lack of confidence in intuiting their child's feelings, are valuable insights to aid researchers or clinicians in making final decisions about deploying an instrument.

4.1. Conclusion

When deciding which PROM to use for a specific purpose, it is essential to consider (a) matching the implicit conceptual framework to the outcomes of research interest; (b) robust evidence of measurement properties; and (c) the appropriateness and acceptability of the questionnaire and individual questions to the respondents in the same context that the research will be conducted. We recommend researchers consult with families in the context of PPIE to ensure measures are acceptable for their settings and their research questions. In our case, both QOLCE-55 (parent-report) and CHEQOL (parent and child report) were considered acceptable and mapped well to our COS. This exercise was an important first step in applying our recently developed COS as a framework for selecting outcomes for evaluative research in childhood epilepsy in the UK.

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Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

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