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Core outcome set development for childhood epilepsy treated with ketogenic diet therapy: Results of a scoping review and parent interviews

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ABSTRACT

Purpose: Clinical trials on childhood epilepsy treated with ketogenic diet (KD) use a wide range of outcomes, however, patients and decision-makers often do not perceive the outcomes used as the most important. We sought parental opinion on outcomes of importance and compared these to outcomes reported in published research.

Methods: Ethical approval (London-Surrey-REC19/LO/1680). A scoping review identified outcomes reported in previous studies of childhood epilepsy and KD. Parents were recruited from nine KD centres (UK), charities and social media (international), then interviewed (Jan-April 2020) to explore priority outcomes. Content analysis identified all outcomes in transcripts. Parent identified outcomes were compared with those in the scoping review. Outcomes were collated and grouped into domains according to the COMET Taxonomy.

Results: Of 2663 articles;147 met inclusion criteria. 921 verbatim outcomes were sorted into 90 discrete outcomes, reduced to 70 in consultation with the study advisory group, then classified into 21 domains. Parents (n = 21) identified 39 outcomes as important from the scoping review and seven new outcomes. They prioritised both physiological and functional outcomes in contrast to past studies, which prioritised physiological outcomes.

Conclusion: Little consistency exists in the outcomes used in childhood epilepsy and KD research. Those traditionally used do not adequately reflect parents' important outcomes for their child. Clinical trials should consider the broader priorities of parents when choosing outcomes, in particular, functional outcomes. Identified outcomes will inform an international two-round Delphi-study with parent, professional and researcher participants to develop a core outcome set for this clinical area (COMET registration #1116).

1. Introduction

Epilepsy is a neurological disorder characterised by recurrent epileptic seizures. Up to 67% of children with epilepsy will have seizures controlled by anti-seizure medication or enter spontaneous remission [1]. Early control of seizures is associated with better developmental outcome [2], but many childhood epilepsies have a poor prognosis for seizure control [3]. Up to 35% of children will be refractory to standard anti-seizure medication [4] and continue to experience regular debilitating seizures. Developmental delay is common in infants and young children leading to severe disability in older children and adults [5]. Non-pharmacological treatments such as ketogenic diet (KD) therapies are considered when anti-seizure medications fail to control seizure activity.

KDs are high fat, restricted carbohydrate regimens in use since the 1920s [6] when the classical KD was first described. The medium chain triglyceride KD followed in the 1970s [7] with the modified Atkins diet [8] and low glycaemic index treatment [9] protocols developed in the 2000s. KDs are well-established treatments for paediatric refractory epilepsy, with an increasing number of randomised controlled trials (RCT's) demonstrating efficacy [10–18]. Meta-analyses suggest that children treated with KD are five [19] to six [20] times more likely to achieve at least 50% seizure reduction than those treated with usual care. Yet, the mechanisms underlying the clinical effects of KD therapy

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are not yet fully understood [21]. Typically, seizure reduction or seizure freedom are the primary outcomes in clinical trials, with tolerability and adverse effects usually considered secondary outcomes.

The National Institute for Health and Care Excellence (NICE) guidance (CG137) recommends seizure freedom as the primary outcome and seizure reduction, cognitive function and quality of life as secondary outcomes when treating epilepsy [22]. van Berkel et al. [23] in a systematic overview, identified 33 studies that considered cognitive outcomes. However, over half of these were retrospective and parent reports. Subjective reporting of cognitive improvement dominated with fewer studies using objective measures. Similarly, a recent Cochrane review [20] identified only one RCT [17] which assessed the effect of KD therapy on quality of life, cognition and behaviour, highlighting the need to assess these outcomes objectively in future clinical trials.

To date, there has been no unified attempt to assess patient and parent views into the choice of outcomes, and consequently there is no consensus among healthcare professionals, patients, parents and researchers regarding what should be measured and reported. The CORE-KDT study (**C**ore **O**utcomes in **R**efractory childhood **E**pilepsy treated with **K**etogenic **D**iet **T**herapy- www.plymouth.ac.uk/core-kdt) aims to address this issue by developing a core outcome set – a minimum group of outcomes that should be consistently measured and reported in all future clinical trials [24–26].

This study aims to identify a comprehensive set of potentially important outcomes which will be prioritised by parents, health professionals and researchers in an international two-round Delphi study to achieve consensus on a core set of outcomes. The scoping review aims to systematically identify a list of outcomes reported in published studies of childhood epilepsy treated with KD therapy. It is not yet known to what extent outcomes reported in prior published studies represent the priorities of parents to a child with epilepsy. As such, relying on the systematic scoping review as a single source to populate a comprehensive set of outcomes may overlook potentially important and relevant outcomes to parents. The qualitative study, therefore, aims to identify the outcomes of importance to parents and any new outcomes not previously identified in the scoping review. A consultation process with the study advisory group will agree the final set of outcomes for inclusion in the future Delphi study.

1.1. Patient and public involvement

From the outset, we have recognised the value and importance of parents and carers as stakeholders and worked closely with our lay research partners at Matthew's Friends, (a charity supporting families with KD therapies), to guide the design and delivery of the CORE-KDT study. A patient and public involvement consultation was undertaken, where two parents with experience with epilepsy and KD therapy were interviewed. They felt this study of outcomes was worthwhile research and welcomed the inclusion of parents as participants in each phase. A study advisory group was convened which included parent, charity, and health professional representation. They provided oversight for the study, reviewed key documentation, and participated in the phase 3 consultation process. Their feedback guided the ratification of the set of outcomes including lay outcome descriptions, in preparation for an international two-round Delphi study.

2. Methods

2.1. Systematic scoping review

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [27]. It was registered on the Joanna Briggs Institute systematic review register and the Core Outcome Measures in Effectiveness Trials Initiative (COMET) online database [28]. The full inclusion and exclusion criteria, search strategy, approaches to study screening, data extraction and synthesis were stipulated *a priori* in the published protocol [29]. Owing to the large number of included articles; data extraction was undertaken by the lead author (JC) only. However, the findings were verified by a second reviewer (KMMG) who independently extracted data from 10% of included articles with agreement. This study focussed on the reporting of outcomes rather than the incidence or value of these outcomes, hence study quality nor risk of bias were relevant or assessed. The only deviation from protocol was to develop and use a standardised data extraction proforma instead of JBI SUMARI® (Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information) as this necessitates quality assessment of included studies.

2.2. Qualitative study design

Qualitative research methods play a significant role in the development of core outcome sets [30] ensuring the outcome lists being considered for prioritisation are exhaustive and reflect the views of key stakeholders [24]. Our qualitative descriptive study used a semi structured interview approach to achieve the primary objective of identifying outcomes of importance to parents and the secondary objective of exploring the families' experiences of epilepsy and KD therapy (manuscript in preparation).

2.3. Ethical approval

Ethical approval was granted by the National Health Service (NHS) Health Research Authority (London-Surrey Research Ethics Committee, reference 19/LO/1680).

2.4. Sampling

Participants were eligible if they were a parent or carer to a child aged ≤18 years with refractory epilepsy being treated with KD therapy or had weaned from KD in the past year, were English speaking and able to consent and participate in the interview. Parents or carers of a child being treated with KD therapy for a condition other than epilepsy or weaned from KD over one year ago were excluded. Maximum variation sampling strategies were employed to ensure diversity in terms of the following characteristics: age, epilepsy diagnosis, country of residence, type and duration of KD therapy and response to treatment with KD.

Participants were recruited from the UK and internationally from three sources:

1 Nine KD centres operated as Participant Identification Centres. An information sheet was shared with prospective families by their care team (UK participants).
2 Charity organisations: Matthew's Friends, Young Epilepsy and Epilepsy Action shared the study information across a range of mediums including webpages, social media, newsletters and forums (UK and international participants).
3 Epilepsy – the Ketogenic way: a family support group on Facebook. The group administrator shared the study information with group members (UK and international participants).

Posts and information sheets directed interested participants to the CORE-KDT study webpage where the participant information sheet was available and a contact form to register interest. JC contacted all interested participants and offered an informal discussion to answer questions and provide an overview of the research.

2.5. Data collection

Interviews were undertaken between January and April 2020 by JC, a female registered dietitian and doctoral researcher with approximately 12 years' experience with KD therapy. Particpants were aware of the

researchers experience and planned body of research. They were offered the opportunity to have their interview via telephone, video call or in their own home (UK participants only). Written consent was taken prior to the interview and participants reminded that they could stop the interview or withdraw from the study at any point. The following demographic data were collected: gender of parent and child, country of residence, age of child, type of epilepsy if known, number of anti-seizure medications trialled prior to KD, method of feeding (oral, enteral or mixed), type of KD and duration of treatment.

A range of open questions were used to facilitate parent led discussion (Table 1). The researcher adopted a conversational approach to encourage and enable parents to articulate their stories with little tension [31]. A reflective research diary was used to document reflections and findings post interview to support later analysis. The first two interviews were transcribed and analysed to enable iterative changes to the interview schedule. Participants struggled to understand the word outcome, therefore 'results' was used as a term to enhance understanding and context. Outcomes were identified by asking participants to identify the important results for children with epilepsy treated with KD therapy. Participants who listed multiple outcomes were asked to prioritise, to help us to understand the outcomes they value most. Alone, this approach may have resulted in a narrow view on outcomes, identifying only those outcomes that parents understood to be results or outcomes. To mitigate this, outcomes were also identified indirectly via a content analysis of the full interview transcripts. Together, this enabled all possible outcomes to be identified.

2.6. Data analysis

All interviews were audio-recorded, professionally transcribed (intelligent verbatim transcription), and uploaded to NVivo 12 for analysis. The theoretical framework underpinning the analysis was aligned with directed content analysis, described by Hseih and Shannon [32]. The set of outcomes identified in the scoping review became the template for the outcome categorization matrix. Any newly identified outcomes were coded inductively and their domain categorised according to the COMET taxonomy [33]. JC coded all transcripts and AC reviewed 10% for accuracy of coding. There were no new additional outcomes identified by the second reviewer and no disagreements regarding the coding.

2.7. Consultation with the study advisory group

Outcomes generated from the scoping review and parent interviews were reviewed and ratified by the study advisory group and research team. This included content validation of the newly identified outcomes using representative quotes to demonstrate the context and naming of each new outcome. Plain language outcome descriptors were informed by the definitions of outcomes in the scoping review and parents' descriptions in the interviews. For each outcome the group considered (i) face validity, understanding and acceptability (ii) merging with closely related items, (iii) exclusion if agreed to be an influencing factor rather than a true outcome and (iv) expansion of existing outcomes.

Table 1
Semi structured interview schedule.

1.	Please start by telling me the story of your child's epilepsy
2.	Could you tell me how your child's epilepsy has affected you and your family?
3.	Thinking back to before your child started ketogenic diet, can you tell me what your expectations or hopes of the diet were?
4.	Were those expectations delivered? (what has changed with ketogenic diet?)
5.	Can I ask, how did that make you feel?
6.	Has that changed - do you still feel that way now?
7.	As you are aware we are interested in the results or outcomes that parents believe are important to assess in clinics and research, what results do you think are important when using the KD?
8.	If you were asked to prioritise, what would be the most important result or outcome?
9.	Can you tell me about the day-to-day management of the KD?
10.	What might help to make KD easier for families?
11.	Do you think a buddy or mentoring programme would be helpful where parents support each other with KD?

3. Results

3.1. Overview of systematic scoping review

The search identified a total of 2663 articles (Fig. 1); 2660 through electronic databases and three through hand search of reference lists of included full text studies. British Library e-theses service and Open Grey returned no relevant articles. Trial registers and OAlster returned relevant articles, though all were duplicates of those already identified in database searches. 1921 articles remained after duplicates were removed. Titles and abstracts were screened against the inclusion criteria, yielding a total of 163 articles for full text analysis. 147 articles met the inclusion criteria. There was almost an equal number of articles arising from prospective ($n = 73$) and retrospective study designs ($n = 74$). Recently there appears to be an increase in the number of studies published indicating the urgent need for a core outcome set. Most studies are relatively small with only 40 participants. The Classical KD was used in most studies as the sole KD offered (65%) or as an option alongside other KD's (19%). Specification of outcomes *a priori* is important for study quality yet 72% of articles failed to do so.

3.2. Overview of qualitative study

In total, 21 parents were interviewed (19 individuals and 1 couple), representing 21 children with epilepsy treated with KD therapy. Semi structured interviews lasted a median of 72 min (35–131mins). Table 2 summarises demographic data for parents and their child together with treatment related characteristics. No participants withdrew from the study. In contrast to the literature, the modified ketogenic diet was most often used ($N = 13$), followed by the classical KD ($N = 6$) and medium chain triglyceride KD ($N = 1$). Children had trialled between one to seven anti-seizure medications prior to commencing KD therapy. Nine children achieved complete seizure freedom and the remaining 12 experienced seizure reduction.

3.3. Identification of outcomes

A total of 921 verbatim outcomes were measured and reported in 147 articles [10–17,34–172] Considerable repetition and overlap existed in outcomes and the terminology used to describe these, so these were stratified into 90 discrete outcomes. Only 52% of identified outcomes were reported in more than one study. In total, parents identified only 39 outcomes from the scoping review. They identified seven new outcomes not previously identified in the scoping review, listed in Table 3 with sample anonymised quotes to provide context. Three of these outcomes were particularly family centred, impacting on the day to day functioning of the family; (1) parents confidence with KD, (2) parent or primary carers health and (3) family life. Outcomes generated from the scoping review ($N = 90$) and interviews with parents ($N = 7$) were presented to the SAG and research team for review and ratification (Fig. 2). Parent identified outcomes remained unchanged. Fourteen outcomes were merged owing to overlap with other outcomes. Nineteen outcomes were removed as they were influencing or predictive factors rather than true outcomes. 13 outcomes were expanded to reduce ambiguity for participants, for example cognition was expanded to three outcomes: speech and language, memory, and learning. The consultation process concluded with 77 outcomes and representative plain language descriptors (Table 4).

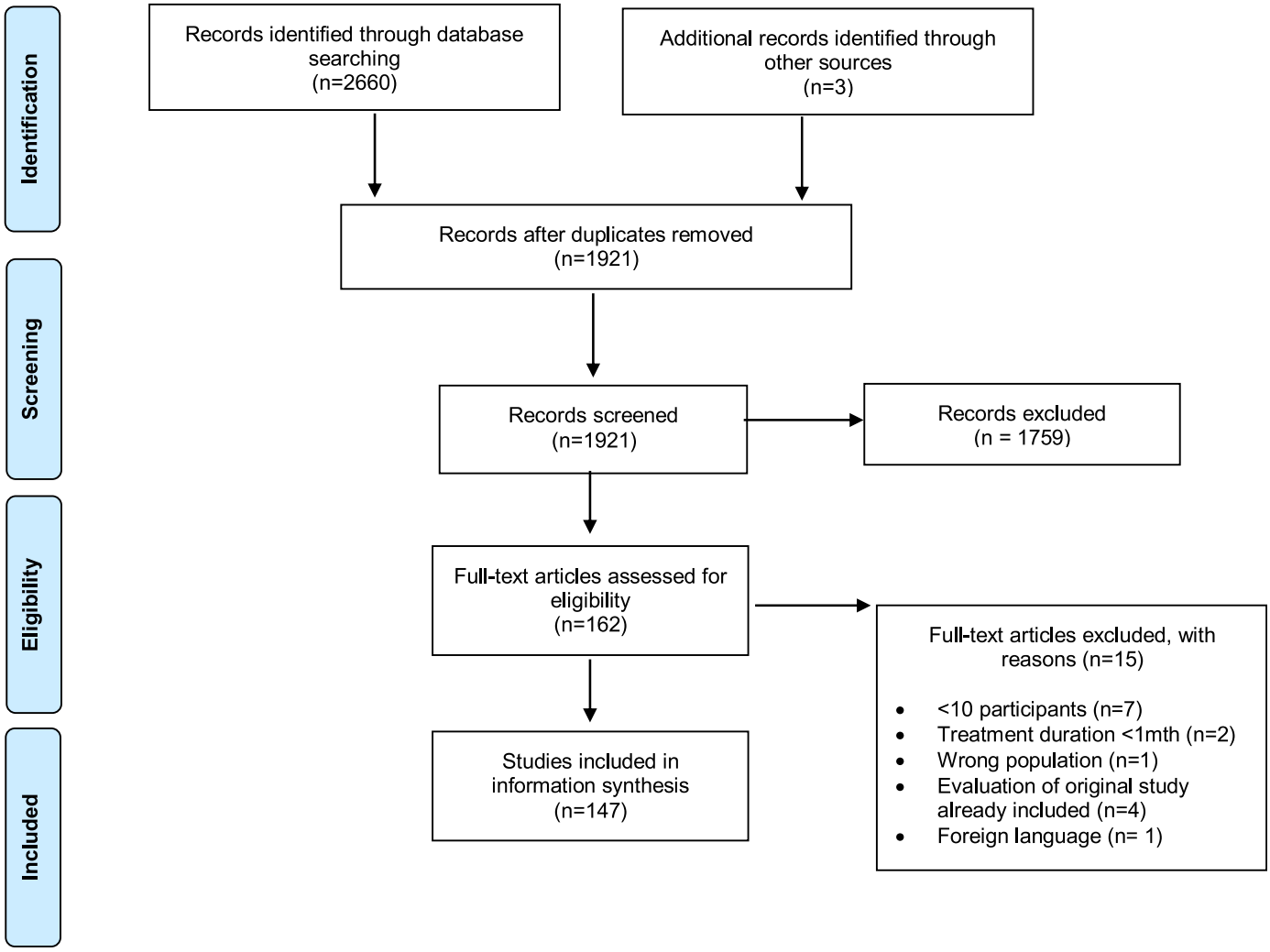

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of scoping review.

3.4. Outcome classification

Outcomes were classified into 21 relevant domains of the COMET taxonomy [33]. The taxonomy addresses five core areas including Death, Physiological/Clinical, Life impact - Functioning, Resource Use and Adverse Effects, across 38 outcome domains. Death was the only core area not represented as no deaths were attributed to treatment with KD therapy. Adverse side effects were initially grouped according to the system affected, for example adverse effects gastrointestinal. The principal reason being that it could prove overly onerous for participants in a Delphi study to rate a list of hundreds of outcomes if each individual adverse effect was listed as a discrete outcome. It could be argued that this approach risks loss of specificity, with the final core outcome set being open to interpretation. However, a compromise employed by Fish et al. [173] in the development of a core outcome set for anal cancer was to name any side effect as a discrete outcome if it was identified in the parent interviews alone or in the parent interview and scoping review together. We utilised this approach to ensure the inclusion of side effects parents felt were important in the Delphi study. Side effects identified by parents and listed individually as a discrete outcome included fatigue, bone health, bone fractures, renal stones, cholesterol, gastro oesophageal reflux disease, constipation, ketogenic rash and feeding difficulties.

4. New outcomes identified by parents

4.1. Global quality of life outcomes

All parents interviewed described the impact of their child's epilepsy on their physical, mental health and wellbeing, suggesting the need to consider parental health as an outcome. FP11 and FP17 described the 'mental burden' that many parents report feeling, a process similar to grieving trying to process their child's diagnosis and what the future holds for their family.

> *"it kind of changes the way that you attack everything. It's kind of a grieving period of, well our lives are not going to be the way we thought they were" (FP11)*

The majority of participants described how their child's epilepsy had impacted wider family life. While there are similarities with the parental health outcome, family life encompasses broader aspects of the household including relationships, career and the impact for siblings.

It is challenging for couples to spend quality alone time together; instead, families tend to do activities together. This is further compounded when families are isolated and don't have extended family close by. Some have seen their relationship fail, while others feel it has brought them closer together. Parents work and careers were often adversely affected. This predominantly affected mothers who took career breaks, worked part-time or left their job. The reasons cited were to spend time with their child/ren, the burden of balancing caring

Table 2
Participant characteristics and demographic data.

Participant	Type of interview	Country of residence	Gender parent	Gender child	Age of Child (Y, M)	Diagnosis	Type of KD	Feeding route	KD Therapy duration (Y, M)	Response to KD	ASMs trialled pre KD
FP1	Telephone	UK	F	M	12y 3m	Juvenile epilepsy	MKD	Oral	6m*	Seizure reduction	2
FP2	Video call	UK	F	M	5y 10m	Tetrasomy 18p	MKD	Oral	6m	Seizure reduction	4
FP3	Telephone	Ireland	F	F	12y 11m	Benign focal epilepsy	MKD	Oral	4m	Seizure reduction	7
FP4	Telephone	UK	F	M	3y 3m	Infantile spasms	Classical →MKD	Oral	1y classical 1y MKD*	Seizure free	3
FP5	Video call	UK	F	M	8y 7m	Doose syndrome	Classical	Oral	4y	Seizure free	3
FP6	Telephone	UK	F	M	9y 7m	Drug resistant epilepsy	Classical	Oral	2y*	Seizure reduction	4–5
FP7	Telephone	UK	F	M	17y 2m	Idiopathic generalised refractory epilepsy	MKD	Oral	5y 3m	Seizure reduction	6
FP8	In person	UK	F	F	12y 9m	Subcortical band heterotopia	Classical	Oral	2y 4m	Seizure reduction	4
FP9	Video call	UK	F	M	5y 6m	Myoclonic astatic epilepsy	MKD	Oral	1y 10m	Seizure free	5
FP10	Telephone	New Zealand	F	M	14y 7m	Drug resistant epilepsy	MKD	Oral	4y 6m	Seizure free	6
FP11	Telephone	USA	F	M	2y 4m	Dravet syndrome	Classical	Oral	1y 2m	Seizure reduction	1
FP12	Telephone	New Zealand	F	M	13y 4m	Lennox Gastaut syndrome	MKD	Oral & Gastrostomy	6m	Seizure reduction	4
FP13	Telephone	UK	F	M	2y 9m	PLCB1 related epilepsy	Classical → MKD	Oral	1y classical 8 m MKD	Seizure free	3
FP14	Telephone	UK	F	M	3y 7m	Angelman Syndrome	MKD	Oral	1 y 2m	Seizure reduction	3
FP15	Telephone	Australia	F	F	5y 0m	Doose syndrome	MKD	Oral	1y 10m	Seizure free	2
FP16	Telephone	Australia	F	F	6y 3 m	Drug resistant epilepsy	MKD	Oral	6 m	Seizure free	-
				F	9yr 0m	Drug resistant epilepsy	MKD	Oral	6m	Seizure free	4
FP17	Telephone	UK	F	F	2y 3m	Dravet syndrome	Classical	Oral	7m	Seizure reduction	3
FP18	Telephone	UK	F	M	12y 11m	Complex Drug resistant epilepsy	MKD	Oral	6m	Seizure reduction	6
FP19 § MP2	Video call	UK	M F	M	7y 9m	Drug resistant epilepsy	Classical	Oral	1y 10m	Seizure reduction	4
MP1	Telephone	UK	M	F	14y 6m	Drug resistant epilepsy	MCT	Oral	2y 6m*	Seizure free	4

FP: female participant MP: Male participant.
*Weaning in progress or weaned from KD.
§ joint interview with participant FP19 and MP2.
MKD: Modified ketogenic diet, MCT: Medium Chan Triglyceride ketogenic diet, ASM: anti-seizure medication.

responsibilities alongside the workload KD creates and the uncertainty that epilepsy brings, having to 'drop everything and go' if they received an emergency call about their child. Over half of parents interviewed referred to their child's siblings and how epilepsy and KD have affected them. There was a general sense of siblings having to be 'more responsible' and watch out for their brother or sister with epilepsy. This support was often invaluable for parents, but with it came the worry that they were 'neglecting' their child/ren by not paying them enough attention or expecting too much of them.

> *"They really do look after her. …I think actually we take it harder than them. I think we worry that they are missing out…I don't feel they hold any grudges against us which is what you worry about" (FP17)*

4.2. Social and emotional functioning outcomes

Participation is defined 'as involvement in a life situation' [174] and represents how one functions in society with a health condition. Twelve parents discussed participation as an outcome for their child. The majority did so in the context of taking part in activities like school trips, sleepovers and sports. It was challenging for parents to balance the risk of an activity like swimming with the enjoyment their child was missing out on. Parents described independence in the context of freedom and making choices. Like participation, it often involved an activity or task, yet distinct in that the child was doing it independently, unsupervised, and alone.

> …"*the other thing for us is independence…I would like to get to a place, and I don't know if it will ever happen where he can walk to school" (FP1)*

MP1 described how their hopes for their daughter's future independence now included independent living, employment and an almost 'normal life' since becoming seizure free with KD therapy.

4.3. Diet and nutrition outcomes

Almost half of parents interviewed identified that their confidence with preparing and managing the KD should be considered. It is a

Table 3
New outcomes identified by parents.

Domain [33]	Outcome	Sample quote	N parents
Global Quality of Life	1. Parent or primary carers health	*I haven't slept, genuinely haven't had a night's sleep since October. I cannot – my body won't let me sleep because I have heard him, every seizure he's had, has woken me up… So, it's a huge impact. (FP1)*	21
	2. Family life	It means we don't always do things that we thought we were going to do…it impacts on her sister obviously because things can be changed at the last minute. (FP8)	16
Social and Emotional Functioning	3. Participation in everyday life	*Doesn't matter the diagnosis, it's about your child achieving as best they can…we started the trampoline lessons, he loves it. So, whatever is out there, albeit the risk involved, I just want him to have as many opportunities. (FP19 +MP2)*	12
	4. Independence	He's his own person. He's independent. He walks to the train station every day, catches a train, then catches the bus and gets himself to school. He wouldn't have done that if he was having seizures. That just wouldn't have been an option. (FP10)	8
Diet and Nutrition	5. Parent's confidence with KD	*I find we're just more confident in our knowledge of the diet and recipe's and how it works and things. It has become much easier as times gone on, definitely. (FP13)*	9
Physiological Clinical	6. Use of rescue medication for status epilepticus	*If I cannot have to midaz [rescue medication] and he can reduce the seizures to a manageable level where we're not exhausted from it, then I was kind of happy. (FP12) W*	4
	7. Seizure duration	We did have a decrease in seizure times, slightly. (FP6)	4

significant undertaking for parents, and the responsibility of preparing every meal and snack correctly can be 'daunting'. The KD offered parents the opportunity to regain some control in the management of their child's epilepsy, and it was something they could 'actively' do. This was a strong thread throughout the interviews.

> *"Yes, it's something I've been able to do. It's not a doctor telling me there's this pill; give him that…It's bloody hard work, but at the same time it's something I've done and actually I'm quite good at it now…It's given me a little bit of control" (FP7)*

FP19 and MP2 agreed; however, with that control comes additional pressure, feeling like 'you are his medicine'. As parents became more comfortable with KD, their confidence to try new things improved, such as eating out for the first time and going on holidays. They gained a sense of achievement and improved self-efficacy from these firsts that enhanced their confidence and ease with KD.

4.4. Physiological clinical outcomes

Four parents highlighted the importance of monitoring the use of rescue medication, as a reduction in use would suggest an improvement in seizure control. FP11 and FP14 described how this resulted in fewer Accident and Emergency department visits and subsequent unplanned hospital admissions.

> *"…even when he does have them [seizures], they're so much more responsive to rescue medication too…We haven't had to call ambulances" (FP11)*

Reduced seizure duration is closely linked to the use of rescue medications but yet distinct, as parents discussed seizure duration without connecting it to rescue medication use. FP14 described how her sons nocturnal hyper motor tonic seizures have reduced from 45 to 10 min in duration when treated with KD therapy.

4.5. Parents priority outcomes

When asked to prioritise the outcomes they identified (Table 5), some parents struggled to choose just one and instead suggested multiple. Seizure reduction, learning and cognition were prioritised by an equal number of parents ($N = 6$) suggesting these were two of the most important outcomes for their children. Functional outcomes ($N = 9$) that affect daily life were most often prioritised by parents and included learning, quality of life, independence and participation.

"For me progress, just the cognitive ones for me were the biggest… That was worth anything we go through. The seizures are never going to be controlled… but their livable. The cognitive benefits for him were my biggest step forward and that was just amazing" (FP7)

While parents prioritised a range of both physiological and functioning outcomes, past clinical trials focussed predominately on physiological outcomes and adverse effects.

5. Discussion

Our study sought to identify the range of outcomes reported in research involving children with epilepsy treated with KD therapy and assess to what extent these outcomes represented parents' priorities for their child. An important issue emerging from our findings is the lack of consistency in outcome reporting, with only 52% of identified outcomes reported in more than one study in the scoping review. The inconsistent use of outcome measures hampers the evidence base for KD therapy, limiting meta-analysis of data from several trials. Martin-McGill et al. [20] could only include four trials in a meta-analysis undertaken in their recent Cochrane systematic review, leading the authors to conclude that a core outcome set would help to improve future outcome measurement and reporting. This present study is part of a larger body of work to identify a core outcome set for childhood epilepsy treated with KD therapy, guiding outcome measurement and reporting in future clinical trials, audit and service evaluation in clinical practice.

Parents lead the provision of KD therapy in addition to the complex daily management of their child's epilepsy and care needs. These experiences provide unique perspectives that should be considered in order to make research and health decisions relevant [175]. To our knowledge, this is the first in depth qualitative study, exploring parents' views on outcomes of importance. Our study demonstrates that the clinical outcomes traditionally used in research do not adequately reflect parents' important outcomes for their child. This was evident in two key findings: (1) parents identified only 39 of the 90 outcomes from the scoping review, suggesting that the remaining outcomes are less important; (2) parents identified seven new, previously unidentified outcomes, despite the existing wide range of outcomes identified in the scoping review. This is consistent with findings from other core outcome set studies where interviews with patients [176–178] and parents [179] highlighted new outcomes not previously identified through systematic

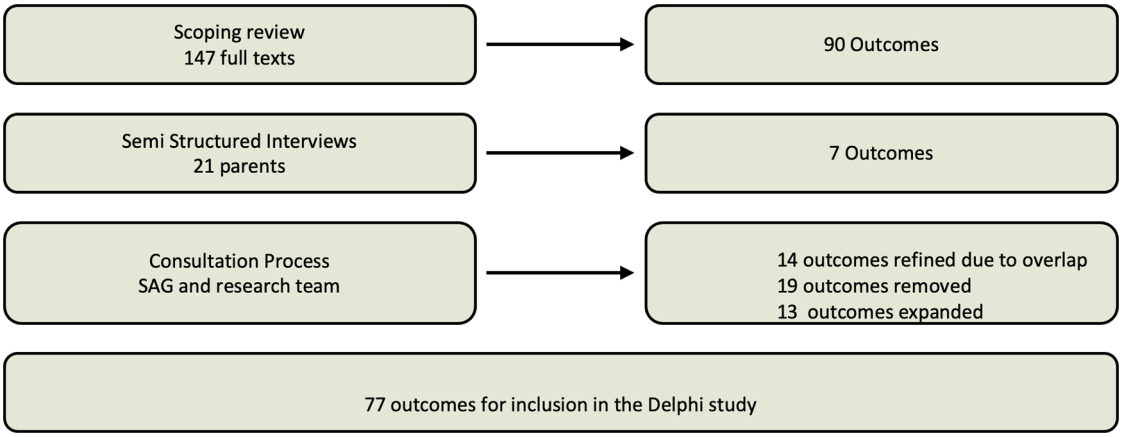

Fig. 2. Overview of identification and ratification of outcomes for inclusion in a Delphi Study.

review of published studies.

Parents of children with epilepsy have higher rates of stress, anxiety and depression owing to the additional burden of care associated with having a child with a complex illness [180]. All parents interviewed shared the profound impacts of a diagnosis of drug-resistant epilepsy and the experiences that followed for their family. These insights sensitise professionals to the challenges families experience and provide context for the newly identified family centred outcomes that emerged from interviews with parents. These included *parental health, family life* and *parental confidence with KD*. Woodgate et al. [181] describe a state of intense parenting, where parents of children with complex care needs took on more roles than parents of healthy children and had to work more intensely at these roles. Parental health and well-being are often deprioritised as they focus on caring for their child with complex needs, trying to cope with uncertainty, anxiety, exhaustion and frustration [182]. While KD therapy offered hope when other treatments had failed; it imposed additional roles and burdens for parents and affected wider family life. Findings in the present study are consistent with the findings of Webster [183] who explored intense parenting with 12 parents who undertook KD for their child with epilepsy and the subsequent impacts on family life. The gendered nature of KD was highlighted where mothers predominantly led the management and implementation of the diet. While fathers contributed in different ways, mothers often gave up their jobs to prioritise their caring role within the family. For some parents we interviewed, the impacts on family life extended to their other children. Parents expressed their concerns regarding the burden of care siblings of a child with epilepsy face. Siblings often provided assistance and support in the daily care and management of their brother or sister with epilepsy. Parents were proud of their children's good nature but worried that this may have a lasting negative impact or limit their experiences compared to their peers. Our findings are somewhat limited by parent proxy reporting; however, similar themes were uncovered in a study exploring siblings caring roles in epilepsy and KD therapy, where both parents and siblings were interviewed [184]. Our sample consisted largely of mothers ($N = 19$ mothers, $N = 2$ fathers), however this issue is not unique to our study.

When describing the daily management and challenges of KD therapy, parents tended to focus more on their ability and confidence to provide KD for their child and less on the technical aspects such as daily monitoring of ketosis and dietary adequacy. Outcomes which professionals might prioritise. With time, parents confidence grew, and pride in their ability to attain the expertise and skills required to cope with epilepsy and KD [185]. These family centred outcomes can affect the families' coping, well-being, and functioning, thereby influencing their ability to support the child with epilepsy treated with KD therapy. Health professionals need to equip parents with the essential knowledge, skills and support to build their confidence and self-efficacy to undertake KD. Consistent measurement of family centred outcomes would provide insight to the challenges families may be facing and enable keto teams to take a holistic approach by offering support and signposting to relevant services. It is plausible to suggest that this may positively impact parents' motivation to continue with KD despite the challenges faced.

Seizure reduction was prioritised as a primary outcome in both published research and interviews with parents, suggesting that both parents and researchers agree that it is a priority outcome to assess the efficacy of KD therapy. Thereafter though, priorities diverged. In published research, physiological and clinical domain outcomes were most often reported, focusing predominantly on seizure control and adverse effects. While two physiological and clinical domain outcomes were prioritised by multiple parents (*seizure reduction* and *anti-seizure medication reduction*), others including *growth, seizure freedom, and fatigue* were each prioritised only once suggesting these outcomes do not represent the whole picture for parents. Measuring physiological and clinical outcomes alone risks overlooking outcomes that can profoundly affect day-to-day functioning and quality of life for the child and wider family. Parents prioritised functioning outcomes such as *learning and cognition, quality of life, independence*, and *participation* highlighting the importance of these. While the numbers are small owing to the qualitative nature of the study, the findings do suggest that the secondary outcomes assessed in published research do not reflect parents' priority outcomes. Future trials should consider a broader range of efficacy outcomes beyond seizure control and adverse effects. In addition, choosing to assess functional outcomes related to activities or gains meaningful to the child and family in everyday living, such as quality of life, cognition, independence, and participation.

6. Conclusion

Our findings justify the need to measure outcomes that are important to families and, in particular, to seek agreement between stakeholders on the prioritisation of the set of 77 outcomes. The outcomes identified in this study will inform a two-round international Delphi study to seek consensus on a core outcome set for this clinical area. The 77 outcomes will be presented for prioritisation to parents, health professionals and researchers. A consensus meeting with representation from all stakeholder groups will ratify the results of the Delphi study and agree on the final core outcome set for dissemination, informing outcome reporting in future clinical trials and clinical practice.

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Table 4
77 Outcomes classified according to the COMET Taxonomy [33] with associated descriptors, mapping of parent identified outcomes (P) and newly identified parent outcomes (*).

Domain	Outcome Name	Descriptor	Parent identified outcome
Physiological Clinical Outcomes	Seizure reduction	With reduction classified as: greater than or equal to 90% reduction, greater than or equal to 50% reduction or less than 50% reduction in seizure activity.	P
	Seizure freedom	Not having seizures	P
	*Seizure duration	How long a seizure lasts	P
	Spasm reduction	With reduction classified as: greater than or equal to 90% reduction, greater than or equal to 50% reduction or less than 50% reduction in clusters of spasms	
	Spasm freedom	Not having spasms	
	Seizure severity	How bad seizures are in terms of effects on the child during and after a seizure. For example, injuries, falls, incontinence, confusion and time to recover afterwards	
	Status epilepticus	How often this occurs. Sometimes seizures do not stop, or one seizure follows another without the person recovering in between. If this goes on for 5 min or more it is called status epilepticus or 'status'.	
	*Use of rescue medication for status epilepticus	How often rescue medication is used	P
	Anti-seizure medication (ASM) use	Number and dose of anti-seizure medications to reflect recent changes such as weaning from an ASM	P
	Anti-seizure medication (ASM) blood concentrations	The concentration or level of anti-seizure medications in the blood	
	Side effects of anti-seizure (ASM) medications	Side effects experienced with the use of anti-seizure medications	P
	Non anti-seizure medication use	Name and dose of other non-anti-seizure medications including recent changes. For example, medication to help manage side effects of KD.	
	Cerebrospinal fluid (CSF) concentrations of neurotransmitters	Concentration (level) of key neurotransmitters in the cerebrospinal fluid, for example dopamine, serotonin and norepinephrine	
	Electroencephalogram (EEG) findings	Changes in the EEG. An EEG looks at what is happening in the brain – the activity of the brain cells.	P
	Growth	Changes in weight, length, height or growth centile	P
	Cholesterol levels	The concentration or level of cholesterol in the blood. This can increase for some children treated with KD	P
	Gastro oesophageal reflux	High fat intake can exacerbate existing reflux for some children	P
	Constipation	Difficulty in passing a stool (poo) or going to the toilet less often	P
	Gut bacteria	Changes in the types and proportions of bacteria in the gut	
	Ketogenic rash	Rash can present as redness on the skin and may give a sensation of itchiness. Most likely to present around the neck, chest, armpits, back and shoulders.	P
	Kidney stones	Hard deposits that form inside the kidney, the incidence can be higher in very young, immobile children treated with KD and certain medications	P
	Prophylactic potassium citrate use	If potassium citrate is used, does it reduce the incidence of kidney stones	
	Bone health	Examining bone health through DEXA scanning, a high precision xray that measures bone mineral density and bone loss.	P
	Bone fractures	Experiencing a broken bone	
	Side effects that affect the liver	For example, deranged liver function blood tests and gallstones	
	Side effects that affect the heart	For example, high blood pressure and associated heart problems	
	Side effects that affect breathing	For example, respiratory tract infections, pneumonia and aspiration	
	Side effects that affect hormones	For example, hormones that control mood, growth, development and metabolism	
	Thyroid function tests	A blood test to check levels of thyroid hormones	

(*continued on next page*)

Table 4 (*continued*)

Domain	Outcome Name	Descriptor	Parent identified outcome
Diet and Nutrition outcomes	Appetite	Change in the desire to eat food or drink	P
	Dietary adherence	How closely the patient follows the agreed dietary and monitoring plan	
	Food preference	Change in preferred foods while on KD or when weaned from KD	P
	Physical feeding difficulties	For example, difficulty swallowing or unable to consume the necessary volume and hence requires tube feeding	P
	Behavioural feeding difficulties	Challenges with feeding, for example food fussiness, food refusal, difficulty with textures and long mealtimes	P
	Tolerability of KD	How well the child can manage the KD and its challenges	
	*Parents confidence with KD	Parents feelings towards being able to cope and manage the KD	P
	Palatability of KD formula and supplements	Acceptability of the taste of prescribed KD formula, supplements or additives (for example ready meals, snacks, milkshakes, desserts, vitamins and minerals, fat, protein or carbohydrate shots and powders)	P
	Efficacy of ketogenic parenteral nutrition	How well the effects of KD achieved via oral or enteral (tube feeds) feeding are sustained when changed to parental nutrition (feeding into a vein; not oral or tube feeding)	
	Side effects of parental nutrition	Side effects experienced when having ketogenic parental nutrition (feeding into a vein; not oral or tube feeding)	
	Resting energy expenditure (REE)	Change in resting energy expenditure (calories or energy needed to maintain normal function)	
	Energy utilisation	Change in breakdown of fat and carbohydrate measured using a respirometer	
	Vitamin and mineral blood concentrations	Blood tests to check the concentration (levels) of vitamins, minerals and associated markers; aiding diagnosis of deficiency or toxicity	
	KD duration	Length of time on KD	
	Onset of ketosis	The time taken to achieve ketosis after commencing KD	
	Ketone levels	Urine or blood concentrations (levels) of ketones including excess ketosis (hyperketosis)	P
	Time to respond to KD	The point at which improvement in epilepsy is seen after commencing KD	
Global quality of life outcomes	Quality of life for child on KD	Childs general well-being in terms of health, comfort and happiness	P
	Parent or primary carers quality of life	Parent or primary carers general well-being in terms of health, comfort and happiness	
	*Parent or primary carers health	Parent or primary carers emotional and physical wellbeing	P
	*Family life	Impact of epilepsy and KD on family life including siblings, parents relationship, work and career opportunities	P
Social and emotional functioning outcomes	Alertness	Change in level of alertness. Being awake, aware, attentive and prepared to act or react. The fog' lifting and being more present	P
	Behaviour	Change in behaviour. Childs actions, reactions and functioning in response to everyday environment and situations. Ability to adapt to surroundings and situations for example home versus school	P
	Concentration	Change in ability to focus on a given task while ignoring distraction	P
	Social skills	Change in ability to engage and interact with others, for example siblings and friends	P
	Hyperactivity	Change in level of hyperactivity which is described as being unusually and extremely active	
	*Participation in everyday life	Change in ability to join in and undertake activities, for example swimming, playing with friends, joining nursery and playgroups.	P
	*Independence	Child becoming as independent as they can, for example; needing less	P

(*continued on next page*)

Table 4 (*continued*)

Domain	Outcome Name	Descriptor	Parent identified outcome
		supervision or walking to school alone	
	Mood	Change in general sense of positive or negative mood	P
	Emotional development	Change in child's understanding of who they are and what they are feeling	P
Cognition outcomes	Memory	Change in short and long-term memory	P
	Speech and language	Change in ability to make oneself understood & understanding when spoken to	P
	Learning	Change in ability to gain new skills and knowledge	P
	Developmental milestones	Progress in meeting milestones such as smiling, sitting without support, responding to requests, sorting shapes and colours	P
Physical functioning outcomes	Activities of daily living	Change in ability to carry out activities like feeding, toileting, washing	P
	Movement ability	Change in ability to sit, crawl, walk, run or jump	P
	Coordination and balance	Change in ability to use parts of body together & efficiently, e.g. riding a bike	P
	Manual ability	Change in dexterity in handling objects like cutlery and toys	P
	Fatigue	Lacking in energy, feeling more tired or 'drained' than usual	P
	Time spent asleep	Total time spent asleep in each 24 h period	P
	Daytime sleepiness	Feeling sleepy or actually sleeping during the day	P
Resource Use	Accident & Emergency Department attendance	Epilepsy or KD related issues leading to visits to the Accident & Emergency department but not admitted to hospital as an inpatient	P
	Unplanned hospital admissions	Unexpectedly needing to be admitted to hospital for epilepsy or KD related issues	P
	Length of hospital stays	Number of inpatient days in hospital in a given period, e.g. last year	
	Cost of hospital stays	Estimated cost of the medical care provided during attendance at Accident & Emergency Department and/or hospital admissions (not including costs incurred by the family through loss of earnings, taxi use etc.)	
	Cost effectiveness of KD	is KD a cost-effective treatment for epilepsy	P
	Quality adjusted life years for child on KD	A 'quality adjusted life year' takes account of how a treatment affects a child's quantity and quality of life. It can be used to assess the cost effectiveness of treatments.	
	Quality adjusted life years for parent or primary carer of child on KD	A 'quality adjusted life year' takes account of how a treatment (for their child with epilepsy) affects the parent or primary carers quantity and quality of life. It can be used to assess the cost effectiveness of treatments.	

Table 5
Parents priority outcome.

Domain [33]	Outcome	N identified
Physiological Clinical	Seizure reduction	6
Cognition	Learning and cognition	6
Physiological Clinical	Anti-epileptic drug reduction	4
Global quality of life	Quality of life (child)	4
Social and emotional functioning	Independence	3
Social and emotional functioning	Participation	3
Social and emotional functioning	Alertness	1
Cognition	Speech and language	1
Physiological Clinical	Seizure freedom	1
Physical functioning	Fatigue	1
Physiological Clinical	Growth	1
Physical functioning	Mobility	1
Social and emotional functioning	Improved behaviour	1

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Appendix 1. Search strategy for PubMed

Diet, Ketogenic [MeSH] OR ketogenic diet [tiab] OR low carbohydrate diet [tiab] OR high-fat [tiab] OR modified atkins [tiab] OR MCT diet [tiab]

AND

Epilepsy [MeSH] OR seizure* [tiab] OR epilep* [tiab]

AND

Child* [MeSH] OR adolescen* [MeSH] OR infant [MeSH] OR paediatric [tiab] OR child [tiab] Or infant [tiab] OR adolescen* [tiab] OR teen [tiab]

Limits: 10 years. Search returned 461 records.

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