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A core outcome set for childhood epilepsy treated with ketogenic diet therapy (CORE-KDT study): international parent and health professional consensus

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Data availability statement

The data sets are available from the corresponding author on reasonable request.

Ethics approval statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Abstract

Objective: Ketogenic diet therapy (KDT) can result in benefits (seizure and non-seizure related) for children with drug resistant epilepsy. However, clinical trials report a wide range of outcomes making synthesis of evidence difficult, and do not adequately reflect parent views on important outcomes for their child. To address this, we established the first international parent, health professional and researcher consensus to develop a core outcome set, guided by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative (COMET registration #1116).

Methods: Ethical approval was granted (London-Surrey REC19/LO/1680). A scoping review and interviews with parents identified a comprehensive list of potentially important outcomes, followed by a two-round online Delphi survey of parents and health professionals to prioritise outcomes of importance for inclusion in a core outcome set. This informed a stakeholder consensus meeting and consultation process to finalise the core outcome set.

Results: In total, 97 outcomes were identified; 90 from the scoping review and seven from parent interviews. These were rationalised to 77 by the study advisory group, then rated in the first Delphi round by 49 parents and 96 health professionals who suggested 12 new outcomes for rating in round two. 66% of participants (30 parents and 66 professionals) completed round two, where 22 outcomes met criteria for inclusion. In the consensus meeting (9 parents and 13 professionals), 27 undecided outcomes were discussed and scored; one further outcome reached consensus for inclusion. After consultation and ratification, 14 outcomes across five domains were included in the core outcome set.

Significance: A core outcome set for childhood epilepsy treated with KDT has been developed, incorporating the views of international parents and professionals. Implementation in research and clinical settings will standardise outcome selection and reporting, facilitate data synthesis and ultimately enhance the relevance of outcomes to parents, researchers and health professionals.

Key words: Delphi, ketogenic diet, paediatric epilepsy, outcomes, core outcome set

Key points

1. Studies report a wide range of outcomes, making evidence synthesis challenging and they do not adequately reflect parent views on important outcomes for their child
2. The CORE-KDT core outcome set is the first international Delphi consensus on outcomes for childhood epilepsy treated with ketogenic diet
3. The core outcome set encompasses parents, health professionals, researchers, charity and industry views from 33 countries in an inclusive and transparent manner
4. Implementation in research and clinical settings will standardise outcome selection and reporting, facilitate data synthesis and enhance relevance of outcomes
5. Future work will focus on identifying appropriate outcome measurement instruments

Introduction

Epilepsy is one of the most common, serious neurological conditions of childhood,[1] estimated to affect 1 in 418 children in the first three years of life.[2] A significant proportion (35%) of children will develop drug resistant epilepsy, experiencing regular debilitating seizures despite treatment with multiple anti-seizure medications (ASMs).[3,4] There is a high risk of cognitive and behavioural comorbidity[5] and early mortality.[6] The burden of which extends to the broader family, where parents describe a cycle of uncertainty, characterised by changing symptoms, behaviours and uncertain futures.[7,8]

Ketogenic diet therapy (KDT) is considered when two or more ASMs have failed to control seizures.[9] Meta-analyses suggest that children treated with KDT are five[10] to six times[11] more likely to achieve at least 50% seizure reduction. than those treated with usual care. Seizure freedom is recommended as the primary outcome, followed by seizure reduction, cognitive function and quality of life as secondary outcomes.[12,13] However, there is considerable variation and a lack of consistency in reported outcomes, definitions, and measurement approaches.[8] Physiological outcomes including seizure control and adverse effects of KDT dominate, while few studies consider functional and quality of life outcomes. Furthermore, outcomes traditionally used in research do not adequately reflect parents' priority outcomes.[8] These issues hamper the evidence base in KDT, limit comparison between studies, risk duplication of research efforts and excludes parents views. These challenges in outcome reporting are not unique to childhood epilepsy and are replicated in other clinical areas. A potential solution is a core outcome set (COS), a minimum group of outcomes that should be measured and reported in all trials for a specific clinical area.[14]

This can reduce outcome heterogeneity, facilitate evidence synthesis and increase the relevance of research by involving stakeholders in the development.[15,16] Martin-McGill et al.[11] in their recent Cochrane review, concluded that a COS would help improve future outcome measurement and reporting in trials of epilepsy and KDT.

To date, there is no consensus among health professionals, researchers and parents regarding outcomes to be measured and reported for childhood epilepsy treated with KDT. 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) [8,17] was undertaken to develop a COS, motivated by the necessity to identify seizure and non-seizure related outcomes of importance and incorporate parents' views on priority outcomes for the first time. This will inform future clinical trials and support outcome selection and reporting in clinical practice via routine data collection, audit or service evaluation. It is advantageous for clinical and trial data to be consistent, particularly in this area where one unique treatment (KDT) is under investigation. We identified potentially important outcomes via a scoping review (phase 1) and semi-structured parent interviews (phase 2).[8] The identified outcomes were ratified (phase 3), and consensus sought on inclusion in a COS through an international Delphi survey and stakeholder consensus meeting (phase 4). Here, we report our study in line with the Core Outcome Set-STAndards for Reporting (COS-STAR) guidance.[18] (Checklist Appendix S1)

Methods

Study overview

The scope of the COS was defined according to criteria recommended by the Core Outcome Measures in Effectiveness Trials Initiative (COMET).[14] The health condition was drug resistant (refractory) epilepsy in a paediatric population treated with the intervention of KDT. The COS would likely include a range of outcomes that span the physiological, functioning and resource use domains and hence be relevant to both research and clinical practice settings. The study was conducted in line with COMET methodological recommendations[14] and conformed to standards guiding COS development (Core Outcome Set-STAndards for Development: COS-STAD,[19] Core Outcome Set-STAndardised Protocol items: COS-STAP.[20]) Figure 1 outlines the stages of development of the COS.

Study registration and protocol

The CORE-KDT study was registered on the COMET database.[21] The study protocol[17] and scoping review protocol[22] were described previously.

Patient and Public Involvement and Engagement (PPIE)

From the outset, we have recognised the importance of parents and carers as stakeholders, ensuring representation in each phase. Two parent partner co-investigators (EW, VA) were actively engaged throughout the study. Both had personal experience with epilepsy and KDT and support families with KDT at Matthew's Friends, where they serve as trustees (VA) and chief executive officer (EW). A PPIE consultation with two parents informed the design of the interview schedule, highlighting that time and competing demands would be the most significant challenges for parents. We therefore offered interviews seven days a week early to late, via telephone, videocall or home visit (UK only). A study advisory group (SAG) including parent, health professional and charity representatives provided study oversight, reviewed key documentation, and participated in the phase 3 consultation process.

Stakeholder participants and eligibility

Parents, health professionals (consultant paediatric neurologists, paediatricians, ketogenic dietitians, epilepsy specialist nurses and neuropsychologists), researchers, industry and charity representation were sought. Charity and industry representatives would likely be professionals, so were allocated to the health professional and researcher group. Participation was open internationally to stakeholders with lived experience of providing KDT for their child or experience supporting families. Participants were English speaking (parent interviews and consensus meeting) or proficient with written English (Delphi survey). Parents were recruited from nine UK KDT centres operating as Participant Identification Centres (UK participants), charity organisations (Matthew's Friends, Young Epilepsy and Epilepsy Action), Epilepsy the Ketogenic Way and social media – Twitter and Facebook (UK and international participants). Health professionals were recruited internationally via professional networks (Matthew's Friends Professionals list, Ketogenic Dietitians Research Network, Ketogenic Professional Advisory Group, Epilepsy Nurses Association) and social media.

Phase 1-3: Identification of outcomes

Outcomes were identified via a scoping review of studies involving children with epilepsy treated with KDT, using methods described previously.[22] All reported outcomes were extracted verbatim together with the assessment tool or measurement method. Considerable repetition existed in outcomes and terminology used to describe them, so the verbatim list was stratified into composite outcomes, then categorised into domains according to the COMET taxonomy.[23] Outcomes of importance to parents were identified through semi-structured interviews, using open-ended questions to facilitate parent led

discussion. Outcomes were identified directly by asking parents to identify and then prioritise important outcomes for their child, and indirectly by undertaking a content analysis of the interview transcripts. Outcomes identified from the scoping review and parent interviews were combined to generate an outcomes list for a consultation process involving the research team and the SAG.[8] This included content validation of new outcomes identified by parents, using representative quotes to illustrate the context and naming of each new outcome. Plain language descriptors were derived from the definitions of outcomes used in previous studies and the language parents used.

Phase 4: Prioritisation of outcomes

Delphi Survey

Parents, health professionals and researchers were invited to participate in a two-round international Delphi survey to prioritise outcomes to include in the COS. DelphiManager software facilitated both rounds (R1 and R2) where participants were asked to rate the importance of each outcome on a Likert type scale ranging from 1-9 (1-3 not important; 4-6 important but not critical and 7-9 critically important). In R1, participants could propose additional outcomes not addressed by existing outcomes. These were reviewed and added to R2 if not already represented. The scores for each stakeholder group, (i) parents and (ii) health professionals and researchers, were analysed separately to ensure both were equally represented. Scores from participants who partially completed the survey were included to ensure their views were integrated. Descriptive statistics summarised the results of each group, in each round, including the percentage of participants scoring 1-9 for each outcome. All were invited to participate again in R2, where their individual R1 score and group scores of both stakeholder groups were presented on histograms. Participants were asked to reflect on collective scores, rescore each outcome and share reasoning for any changed scores. Consensus criteria for inclusion or exclusion from the COS were defined a priori.[14] Outcomes scored critically important (7-9) by 70% or more and not important (1-3) by 15% or less in both stakeholder groups were categorised for inclusion in the COS. Conversely, outcomes scored not important by 70% or more and critically important by 15% or less were excluded. Outcomes that failed to reach a consensus for inclusion or exclusion were categorised as undecided.

Consensus meeting

Participants were invited to attend an online (Zoom) stakeholder consensus meeting, purposely sampled to ensure representation of all stakeholders. The aim of the meeting was

to share the Delphi results, and review and score undecided outcomes to identify if they should be included in the COS. The meeting was chaired and facilitated by an independent female academic and dietitian.

Many outcomes remained undecided after the Delphi. Discussion and scoring of all in the online meeting was not possible due to the level of focus required.[24] Therefore, priority was given to the scoring of undecided outcomes where 70% or more of one stakeholder group scored it critically important. Arguably these had the greatest likelihood of achieving consensus. This decision and list of outcomes was shared with participants prior to the meeting in their information pack. Participants were asked to review the remaining undecided outcomes and propose any additional outcomes for review at the consensus meeting.

The chair presented each outcome for discussion with its lay descriptor, scores from each stakeholder group and similar outcomes (if any) already included in the COS. Discussion and contrasting views were invited followed by voting (Zoom polling). The same Likert type scale was used as in the Delphi. Scores were calculated separately for both stakeholder groups to mitigate the imbalance in numbers. Typically, voting results are shared immediately with participants. However, there was concern that doing so may lead to frustration among parent participants, that their views were not being heard if outcomes they perceived to be important failed to reach consensus if health professionals scored them less important. This risked introducing bias to the discussion and scoring. Therefore, the decision was taken to analyse scores after the meeting and share the provisional COS within one week. Participant feedback was sought (JISC online survey) following the meeting to assess satisfaction with the process and again, following review of the proposed COS to gather final feedback.

Ethical approval

Ethical approval was granted by the NHS Health Research Authority (London-Surrey REC, reference 19/LO/1680). Written consent was gathered prior to the interviews and from participants attending the consensus meeting. Participating in the Delphi was regarded as implicit consent.

Protocol deviations

Our protocol[17] was prepared prior to the covid pandemic and included an in-person consensus meeting. A virtual online meeting was instead convened to reduce risk for participants who may be shielding. It enabled international participation and efficient and

cost-effective use of time for all, particularly health professionals who were under significant clinical pressures. Following R2, no outcomes met the criteria for exclusion from the COS. Fish et al.[25] encountered similar in their anal cancer COS and proposed revised criteria, whereby outcomes were excluded if 50% or less of participants in both groups scored the outcome as critically important. We applied this criterion to reduce the number of undecided outcomes going forward to the consensus meeting. Finally, the protocol stated that all undecided outcomes would be addressed in the consensus meeting and voting results shared with participants immediately after voting.

Results

Identification of outcomes

The scoping review and interviews with parents have been described elsewhere[8] and summarised in Figure 1. Ninety outcomes were identified in the scoping review, together with seven new parent identified outcomes. During the consultation process, 97 outcomes were rationalised to 77, however parent identified new outcomes remained unchanged.

Prioritisation of outcomes

Parent interviews

We gained a deeper understanding of the outcomes parents valued most through the interviews.[8] Some struggled to choose just one outcome and instead suggested multiple important outcomes. 'Seizure reduction' and '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 (Table 1). At this stage in the study 'learning and cognition' were grouped together to reflect the descriptor often used by parents. A quote from one mother illustrates the importance of cognition.

> *"The cognitive ones for me were the biggest…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).*

Delphi Survey

In total, 145 participants from 33 countries (49 parents, 96 health professionals and researchers) participated in R1. Table 2 summarises participant characteristics. Most professional participants were paediatric dietitians or paediatric neurologists with 40% of

these professionals reporting >10 years' experience with KDT. For parents, 90% were mothers, a similar pattern of recruitment to the interviews.

Eight participants submitted incomplete sets of scores, six of whom were parents: the smaller of the stakeholder groups. Therefore, their partial scores were included. Participants could choose an 'unable to score' option, which resulted in fluctuations in the total number of participant scores for each outcome, so the inclusion of partial datasets would not adversely influence the results. Table 3 summarises R1 and R2 results. Participants proposed 68 additional outcomes during R1, of which 12 were added to R2 for scoring (total N=89 outcomes). The remaining proposed outcomes (N=56) were duplicates or influencing factors rather than outcomes (Appendix S2).

Scores from 96 R2 participants were analysed (30 parents, 66 health professionals and researchers). Two parents and three health professionals partial R2 scores were included. The attrition rate between R1 and R2 was 34% (49 participants: 19 of 49 parents [39%] and 30 of 96 health professionals and researchers [31%]). Twenty-two outcomes reached consensus for inclusion in the COS. No outcomes met the original criteria for exclusion, so we applied the criterion proposed by Fish et al.[25] which excluded 17 outcomes from the COS. The remaining 50 outcomes were classified as 'undecided'.

Consensus Meeting

The online consensus meeting was held on February 23rd 2022. Nine parents and 13 health professionals participated, representing nine countries. Appendix S3 lists contributors and roles. Fourteen (seven parents and seven health professionals) had completed both rounds of the Delphi. Of the remaining eight, three were voting members of the research team, one represented Young Epilepsy and four were members of an expert working group developed to explore the measurement of outcomes. Three participants were unable to attend (two parents and one epilepsy specialist nurse).

Following the Delphi, 19 of the 50 undecided outcomes were scored critically important by ≥70% of one stakeholder group only. It would not be feasible to discuss and score all 50 outcomes, so these 19 outcomes were prioritised. The remaining 31 outcomes were not deemed to be critically important by the majority of either group but prior to the meeting, participants proposed eight of these for discussion and scoring, resulting in a final total of 27 outcomes put forward to the consensus meeting. One additional outcome reached consensus for inclusion in the COS - 'Unplanned hospital admissions' (Table 4). Fourteen

outcomes reached consensus for exclusion when the 50% exclusion criterion was applied. During the consensus meeting, participants shared opinions on outcomes that could be merged to reduce the overall number in the COS. Interestingly, following the Delphi, three broad adverse effects outcomes were voted into the COS; side effects that affect (i) 'the heart', (ii) 'the liver' and (iii) 'the respiratory system'. Yet arguably as important and more frequently occurring side effects such as 'growth', 'constipation', 'reflux' and 'kidney stones' were excluded or undecided. Parents argued that all side effects should be considered as they felt reassured by the monitoring of these. Health professionals felt there were additional potential renal concerns beyond renal stones alone and the value of respiratory side effects was questioned. In response to these valuable insights, the research team ratified the provisional COS (Appendix S4), which was shared with the participants one week later. The final COS (Table 5) includes 14 outcomes across five domains of the COMET taxonomy.[23]

Participant feedback was sought following the meeting (18 completed; seven parents, 11 health professionals) and on reviewing the COS (20 completed; eight parents, 12 health professionals). All (100%) participants were satisfied with the process and felt able to contribute. 94% felt comfortable to communicate their views. When asked if the consensus meeting produced a fair result 56% agreed or strongly agreed, likely because the provisional COS had not yet been shared. The same question was repeated one week later when the provisional COS was shared, and all participants (100%) agreed or strongly agreed that the meeting produced a fair result. These quotes illustrate participants' feedback:

> *'I think the core outcome set is a very good compromise to avoid a long list of outcomes but capture the highest priority outcomes. Well done'*

> *'I found the discussion really useful. I think both health professionals and parents benefited from the open discussion.'*

Discussion

The CORE-KDT core outcome set provides the first international consensus on outcomes for children with epilepsy treated with KDT. It has been developed encompassing the views of parents, health professionals, researchers, charity and industry representatives from 33 countries. A significant strength of the study is that the mixed methodology is informed by consensus guidelines,[14] defined in an a priori protocol,[17] and transparently conducted and reported. The Delphi consensus methodology facilitated differing viewpoints and avoided potential over-influence from one type of stakeholder. Consequently, the COS is a valid

framework for selecting outcomes in future research involving KDT for drug-resistant childhood epilepsy. The COS reflects the outcomes of greatest importance to both parents and health professionals so it should also inform routine data collection, monitoring and decision making in the clinical setting. With routine implementation of the CORE-KDT set, both settings will benefit from improved consistency in outcome selection and reporting.

The COS includes commonly reported outcomes including 'seizure reduction' 'seizure freedom' and 'quality of life' in line with existing guidelines for children with epilepsy.[12,26] There are shared outcomes with the CHOICE COS for Rolandic epilepsy[27] and outcome criteria for ASM use.[28] Unlike drug resistant epilepsy, Rolandic epilepsy is often well managed with ASMs and many children will outgrow the condition. In contrast, we hypothesised that the CORE-KDT set would capture additional outcomes relevant to the complexity of drug resistant epilepsy, the severity of associated co-morbidities and monitoring of KDT. As expected, the CORE-KDT set includes outcomes specific to KDT which are not adequately captured in any existing published COS. Although no guidance exists on the ideal number of outcomes, it is likely that larger COS will be difficult to implement and less likely adopted. We reduced 89 outcomes to just 14, the majority of which are routinely used to monitor children with epilepsy treated with KDT and so the COS should be easily implemented in research and clinical practice.

With the inclusion of six physiological outcomes (four prioritised by interviewed parents) and three functional outcomes (all prioritised by interviewed parents), the COS now better reflects the priorities of all stakeholders. Furthermore, three of the seven new outcomes identified during the parent interviews are represented: 'parental confidence with KDT', 'rescue medication use for status epilepticus', and 'seizure duration' was merged with seizure severity. There were however, some unexpected exclusions including sleep and cognition outcomes. Children with epilepsy have shorter sleep times and more sleep difficulties when compared with those without epilepsy.[29] Consequently, learning, mood, behaviour, seizures and parents' quality of life may all be affected.[30] KDT has been shown to improve sleep quality and reduce daytime sleep for children with epilepsy.[31] Consequently, it was surprising that sleep was not included in the COS. It may be that poor sleep is somewhat expected and accepted for children and parents, due to the seizure burden and complex care requirements. This may influence parents perceived importance but warrants further investigation. Our findings are similar to Murugupillai's[28] outcomes study where sleep was not prioritised. However, five sleep-related outcomes were included in the CHOICE COS.[27] For now, we have suggested that sleep pattern be considered as a factor of quality of life, until the relationship between KDT and sleep is better understood.

Interviewed parents prioritised ‘learning and cognition’ outcomes equally with ‘seizure reduction’ so the exclusion of three cognition outcomes from the COS was surprising. In the Delphi, cognition outcomes failed to reach consensus in either stakeholder group. When offered the opportunity to propose undecided outcomes for discussion in the consensus meeting, only one parent proposed a related outcome – ‘educational attainment and progress’. However, this did not reach consensus for inclusion. Prior to the Delphi, the learning and cognition outcome was expanded to three composite outcomes: ‘learning’, ‘memory’ and ‘speech and language’, to improve clarity and reduce ambiguity. In the Delphi, the domain descriptor stated that these were cognition outcomes, but possibly these outcomes no longer resonated as strongly with some participants. This demonstrates the difficulty of creating composite outcomes, if over stratified they may lose meaning and relevance. Robust, repeated review of the outcomes and descriptive terminology by the research team and SAG can go some way to mitigating this challenge. ‘Alertness’ was voted into the set following the Delphi and while parents voted ‘concentration’ in at the consensus meeting, it failed to reach consensus for inclusion as only 62% of professionals scored it critically important. It was noted at the meeting, however, that the terms 'alertness' and 'concentration' are sometimes used interchangeably, especially by parents, so the decision was made to combine both outcomes. It was argued that if alertness or concentration were improving, it was a sign that “things might improve further”, such as social interactions and academic performance.

Defining outcomes with standard terminology and standardised definitions requires careful consideration. The plain language descriptors (Table 5) were refined in consultation with the SAG and feedback from consensus meeting participants. Feedback will be sought from researchers and clinicians who implement the COS to determine the need for further refinement.

COMET encourages researchers to include patients with lived experience of the studied condition as members of the research team, in order to develop a COS that is relevant and trusted by patients.[32] Parent co-investigators played a critical role, supporting parent recruitment, which increased parent engagement and helped identify parent-important outcomes. The consensus meeting brought together parents and health professionals for the first time to discuss outcomes openly and participant feedback emphasised the value of hearing each other’s viewpoints. The PPIE consultation predicted that parents would experience time constraints and competing demands, challenges further compounded by the COVID pandemic, particularly when home-schooling or having difficulty accessing carer

support. For the consensus meeting, finding a time that worked for all participants was particularly challenging. We chose a weekday during school hours to accommodate parents. However, the resultant time difference then limited international participation. Time differences, work commitments and pandemic related pressures prevented some professionals from attending. Future studies need to consider these challenges when planning.

Limitations

The study was conducted in English, limiting international participation to English speakers. The decision to rely on parental proxy reporting of patient experience was made in recognition that many children with cognitive impairments would not be able to participate. Although recruitment strategies varied, our sample included mainly mothers; an issue not unique to our study but perhaps represents the parent who has most to say on the topic. The parent group may be biased towards the beneficial effects of KDT as all children experienced seizure reduction. However, their viewpoints can be generalised to children with epilepsy who trial and continue KDT. Significant participant attrition occurred from Delphi R1 to R2 (34%), despite many extensions and personalised reminder emails. Intervention, in the form of emails from parent representatives increased parent participation slightly. The sampling frame guiding interview recruitment considered the epilepsy diagnosis but omitted developmental status and learning difficulties. Collation of this data may have provided further insights to the study population.

Conclusion

The CORE-KDT core outcome set has identified 14 outcomes which should guide outcome selection in future clinical trials and practice. Measurement of these multi-dimensional outcomes will require careful consideration, and this will be the focus of future work. We have convened a group of international experts to review the appropriateness of existing validated outcome measurement instruments, guided by the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN).[33] Future work will also explore the potential to adapt the CORE-KDT set for other settings where KDT is utilised, including paediatric metabolic disorders and adult drug resistant epilepsy.

Figure and table legends

Figure 1. Overview of core outcome set development
Table 1. Interviewed parents' prioritisation of outcomes

Table 2. Delphi participant characteristics and demographic data
Table 3. Delphi Round 1 and 2 percentage scores for both stakeholder groups.
Outcomes highlighted in grey were scored as critically important (7-9) by ≥70% of one stakeholder group and represent those prioritised for discussion and scoring at the stakeholder consensus meeting.
Table 4. Summary of consensus meeting voting results in order of decreasing importance
Table 5. The CORE-KDT core outcome set for children with epilepsy treated with ketogenic diet therapy

Supplementary data

1. Appendix S1 COS-STAR checklist
2. Appendix S2 Additional outcomes proposed in round 1 and justification for inclusion or exclusion
3. Appendix S3 Consensus meeting participants and their roles
4. Appendix S4 Proposed core outcome set and justification for amendments following consensus meeting

Author contributions

JH Carroll: conceptualisation, methodology, investigation, resources, data curation, writing original draft, project administration. JH Cross, M Hickson, A Collinson: conceptualisation, methodology, writing review and editing, supervision. E Williams, V Aldridge: conceptualisation, validation, writing review and editing.

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TABLE 1. Interviewed parents' prioritisation of outcomes

Domain[23]	Outcome	N identified
Physiological Clinical	Seizure reduction	6
Cognition	Learning and cognition	6
Physiological Clinical	Anti-seizure medication 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

TABLE 2. Delphi participant characteristics and demographic data

Stakeholder group	Variable	Round 1 (%)	Round 2 (%)
Parents	**All**	**49**	**30**
	Sex		
	F	44 (90)	26 (86)
	M	3 (6)	2 (7)
	Not stated	1 (2)	1 (3)
	Prefer not to say	1 (2)	1 (3)
	Origin		
	UK	33 (67)	22 (73)
	Europe	8 (16)	3 (10)
	N America	4 (8)	2 ((7)
	Australia & New Zealand	4 (8)	3 (3)
	Ethnicity		
	White	45 (92)	27 (89)
	Mixed or Multiple ethnic groups	2 (4)	2 (7)
	Asian or Asian British	1 (2)	0 (0)
	Prefer not to say	1 (2)	1 (3)
	Age of Child (years)		
	0-2	2 (4)	1 (3)
	2-6	9 (18)	4 (13)
	6-12	18 (37)	12 (40)
	12-18	15 (31)	10 (33)
	Not stated	5 (10)	3 (10)
	Type of KD		
	Classical KD	26 (53)	15 (50)
	Modified Atkins Diet or Modified KD	15 (31)	11 (36)
	Medium chain triglyceride (MCT) KD	6 (12)	4 (13)
	Not stated	2 (4)	0 (0)
	Duration of KD Treatment		
	≤ 3 months	3 (6)	1 (3)
	4 mths – 1yr	9 (18)	4 (13)
	1-2yrs	14 (29)	11(36)
	>2yrs	21 (43)	14 (46)
	Not stated	2 (4)	0 (0)
Health Professionals and researchers	**All**	**96**	**66**
	Sex		
	F	73 (76)	51 (77)
	M	18 (19)	13 (20)
	Not stated	5 (5)	2 (3)
	Origin		
	UK	31 (32)	24 (36)
	Europe	23 (24)	14 (21)
	North America	20 (21)	13 (20)
	South America	5 (5)	4 (6)
	Asia	9 (9)	7 (11)
	Australia & New Zealand	7 (7)	4 (6)
	Africa	1 (1)	0 (0)
	Ethnicity		
	White	73 (76)	52 (79)
	Asian or Asian British	10 (10)	9 (14)
	Mixed or Multiple ethnic groups	5 (5)	3 (5)
	Prefer not to say	5 (5)	1 (1)
	Other ethnic group	2 (2)	1 (1)
	Black; African; Caribbean/Black British	1 (1)	0 (0)
	Profession		
	Dietitian	48 (50)	33 (50)
	Dietitian and researcher	2 (2)	1 (1)
	Nutritionist	2 (2)	2 (3)
	Paediatric neurologist	15 (16)	9 (14)
	MD neurology	6 (6)	5 (8)
	Neuropaediatrician	1 (1)	1 (1)

	Paediatrician	4 (4)	3 (5)
	Physician	2 (2)	2 (3)
	Prof of paediatric neurology	1 (1)	1 (1)
	Clinical fellow paediatric epilepsy	1 (1)	1 (1)
	Clinical/epilepsy specialty nurse	5 (5)	3 (5)
	Paediatric nurse practitioner	1 (1)	1(1)
	Academic	3 (3)	1(1)
	Researcher	2 (2)	1(1)
	Neuropsychiatrist	1 (1)	1(1)
	Neuropsychologist	1 (1)	1(1)
	Food manufacturer	1 (1)	0 (0)
	Professional Experience		
	<1 yr	9 (9)	8 (12)
	2-5 yrs	21 (22)	16 (24)
	6-10 yrs	27 (28)	15 (23)
	>10yrs	38 (40)	26 (39)
	Not stated	1 (1)	1 (1)

TABLE 3. Delphi Round 1 and 2 percentage scores for both stakeholder groups

Outcomes	Round 1 Parent (N=49)			Round 1 HP (N=96)			Delphi Rd 1 consensus	Round 2 Parent (N=30)			Round 2 HP (N=66)			Delphi Rd 2 consensus
	1-3 (%)	4-6 (%)	7-9 (%)	1-3 (%)	4-6 (%)	7-9 (%)		1-3 (%)	4-6 (%)	7-9 (5)	1-3 (%)	4-6 (%)	7-9 (%)	
Physiological Clinical Outcomes														
1. Seizure reduction	0	6	94	0	2	98	IN	0	3	97	0	0	101	IN
2. Seizure freedom	4	21	75	2	15	83	IN	0	21	79	0	13	88	IN
3. Seizure duration	4	15	81	3	20	77	IN	0	18	83	0	11	89	IN
4. Spasm reduction	8	14	79	0	16	84	IN	5	18	78	0	9	93	IN
5. Spasm freedom	8	22	70	2	24	74	IN	5	27	69	0	14	86	UNDECIDED
6. Seizure severity	6	6	87	0	13	86	IN	0	11	89	0	5	96	IN
7. Status epilepticus	9	2	88	0	6	93	IN	4	0	96	0	2	98	IN
8. Use of rescue medication for status epilepticus	12	7	79	2	22	75	IN	4	12	84	0	16	85	IN
9. Antiseizure medication (ASM) use	4	21	75	0	25	75	IN	0	21	78	0	13	88	IN
10. Antiseizure medication (ASM) blood concentrations	9	25	65	17	48	34	UNDECIDED	0	46	54	17	62	21	UNDECIDED
11. Side effects of antiseizure medications	4	24	72	1	48	52	UNDECIDED	0	16	85	2	50	48	UNDECIDED
12. Non antiseizure medication use	23	34	43	12	54	34	OUT	18	56	26	12	71	17	OUT
13. Cerebrospinal fluid (CSF) concentrations of neurotransmitters	28	36	36	53	34	13	OUT	38	45	16	69	27	4	OUT
14. Electroencephalogram (EEG) findings	8	27	65	4	39	57	UNDECIDED	4	50	46	4	39	57	UNDECIDED
15. Growth	6	38	56	2	22	77	UNDECIDED	7	54	39	0	16	85	UNDECIDED
16. Cholesterol levels	8	44	48	2	46	52	UNDECIDED	0	60	41	4	59	37	OUT
17. Gastro oesophageal reflux	11	36	52	3	43	53	UNDECIDED	8	47	46	2	44	54	UNDECIDED
18. Constipation	12	35	52	3	39	58	UNDECIDED	11	40	50	0	37	62	UNDECIDED
19. Gut bacteria	15	35	50	20	55	25	OUT	12	52	36	17	73	12	OUT
20. Ketogenic rash	13	45	42	14	59	26	OUT	13	56	30	11	78	10	OUT
21.Kidney stones	11	33	56	2	28	69	UNDECIDED	4	40	56	0	22	78	UNDECIDED
22. Prophylactic potassium citrate use	17	23	60	5	52	43	UNDECIDED	17	39	44	0	57	44	OUT
23. Bone health	6	32	63	1	41	58	UNDECIDED	0	37	62	0	37	63	UNDECIDED
24. Bone fractures	9	36	55	2	41	56	UNDECIDED	8	35	58	2	32	66	UNDECIDED
25. Side effects that affect the liver	4	31	66	4	27	68	UNDECIDED	0	29	71	0	20	81	IN
26. Side effects that affect the heart	7	28	66	3	31	65	UNDECIDED	0	29	70	2	20	78	IN
27. Side effects that affect breathing	7	28	66	6	29	63	UNDECIDED	0	27	73	2	21	77	IN
28. Side effects that affect hormones	9	33	59	8	46	45	UNDECIDED	0	39	61	4	56	41	UNDECIDED
29. Thyroid function tests	11	38	53	21	46	33	UNDECIDED	12	36	52	24	58	20	UNDECIDED

Diet and Nutrition Outcomes														
30. Appetite	5	47	48	3	49	48	**OUT**	4	64	32	4	55	41	**OUT**
31. Dietary adherence	7	24	69	0	5	94	UNDECIDED	0	20	81	0	0	99	**IN**
32. KD duration	11	43	45	0	23	76	UNDECIDED	16	47	39	0	22	78	UNDECIDED
33 Onset of ketosis	9	30	61	5	38	58	UNDECIDED	11	30	60	5	39	58	UNDECIDED
34. Ketone levels	0	26	75	1	28	70	**IN**	0	22	78	0	20	81	**IN**
35. Time to respond to KD	0	42	58	1	34	65	UNDECIDED	0	50	51	2	26	73	UNDECIDED
36. Tolerability of KD	2	30	67	0	8	92	UNDECIDED	4	18	79	0	3	97	**IN**
37. Parents or primary carers confidence with KD	4	30	67	1	24	75	UNDECIDED	4	32	64	2	12	86	UNDECIDED
38. Palatability of KD formula and supplements	4	23	72	3	35	62	UNDECIDED	4	28	68	4	27	70	UNDECIDED
39. Food preference	4	44	51	4	38	59	UNDECIDED	12	51	38	5	41	54	UNDECIDED
40. Physical feeding difficulties	10	29	61	1	31	69	UNDECIDED	8	37	54	0	26	74	UNDECIDED
41. Behavioural feeding difficulties	8	28	64	1	28	72	UNDECIDED	9	26	65	0	18	83	UNDECIDED
42. Efficacy of ketogenic parenteral nutrition	3	26	70	2	32	65	UNDECIDED	5	20	75	2	22	76	**IN**
43. Side effects of parenteral nutrition	3	23	71	3	32	64	UNDECIDED	5	32	63	0	23	77	UNDECIDED
44. Resting energy expenditure (REE)	12	42	46	14	49	36	**OUT**	12	62	24	10	69	23	**OUT**
45. Energy utilisation	6	31	62	17	48	35	UNDECIDED	17	39	44	10	62	29	**OUT**
46. Vitamin and mineral blood concentrations	2	26	71	4	33	63	UNDECIDED	4	27	70	2	33	65	UNDECIDED
Global Quality of Life Outcomes														
47. Quality of life for child on KD	0	18	83	0	9	91	**IN**	0	15	86	0	5	96	**IN**
48. Parent or primary carers quality of life	9	29	62	0	18	82	UNDECIDED	11	32	57	2	8	90	UNDECIDED
49. Parent or primary carers health	13	27	60	2	40	58	UNDECIDED	15	36	50	4	37	60	UNDECIDED
50. Family life	9	27	64	0	39	61	UNDECIDED	7	32	61	0	41	58	UNDECIDED
Social & Emotional Functioning Outcomes														
51. Alertness	0	13	87	1	33	65	UNDECIDED	0	15	86	0	24	76	IN
52. Behaviour	0	19	82	1	35	63	UNDECIDED	0	25	76	0	29	72	**IN**
53. Concentration	0	13	86	1	38	61	UNDECIDED	0	19	82	0	39	62	UNDECIDED
54. Social skills	0	26	75	1	46	52	UNDECIDED	0	39	61	2	52	47	UNDECIDED
55. Hyperactivity	6	34	61	3	47	50	UNDECIDED	4	58	39	2	56	43	**OUT**
56. Participation in everyday life	0	7	93	1	36	62	UNDECIDED	0	18	83	0	31	70	**IN**
57. Independence	2	25	74	2	48	51	UNDECIDED	4	38	59	0	54	46	UNDECIDED
58. Mood	0	17	83	1	44	55	UNDECIDED	0	29	71	2	51	48	UNDECIDED
59. Emotional development	2	21	78	2	47	51	UNDECIDED	4	29	68	2	57	42	UNDECIDED
Cognition Outcomes														
60. Memory	2	29	69	1	44	55	UNDECIDED	0	35	66	2	50	50	UNDECIDED
61. Speech and language	5	22	73	1	39	59	UNDECIDED	0	40	60	0	52	48	UNDECIDED
62. Learning	2	22	76	1	35	63	UNDECIDED	0	34	67	0	46	54	UNDECIDED
63. Developmental milestones	7	33	59	0	27	72	UNDECIDED	0	54	47	0	31	70	UNDECIDED

V1.2 Tables and figures adjusted as requested

Physical Functioning Outcomes														
64. Activities of daily living	2	42	55	2	46	51	UNDECIDED	0	40	60	0	60	40	UNDECIDED
65. Movement ability	5	41	55	3	49	47	UNDECIDED	0	51	50	0	69	33	**OUT**
66. Coordination and balance	5	44	51	2	52	46	UNDECIDED	0	66	35	0	71	30	**OUT**
67. Manual ability	5	46	48	2	56	42	**OUT**	0	69	31	0	75	25	**OUT**
68. Fatigue	0	38	63	1	41	58	UNDECIDED	0	38	63	2	48	51	UNDECIDED
69. Time spent asleep	4	40	57	2	44	54	UNDECIDED	0	42	58	3	51	46	UNDECIDED
70. Daytime sleepiness	2	41	58	1	45	55	UNDECIDED	0	51	50	2	57	41	**OUT**
Resource Use														
71. Accident & Emergency Department attendance	4	29	65	2	30	67	UNDECIDED	4	25	70	0	20	80	**IN**
72. Unplanned hospital admissions	4	38	58	2	26	71	UNDECIDED	4	31	66	0	20	81	UNDECIDED
73. Length of hospital stays	7	40	52	2	36	61	UNDECIDED	4	40	56	0	38	62	UNDECIDED
74. Cost of hospital stays	31	30	39	14	45	42	**OUT**	30	39	32	9	58	32	**OUT**
75. Cost effectiveness of KD	30	28	42	4	29	67	UNDECIDED	29	35	36	2	25	73	UNDECIDED
76. Quality adjusted life years for child on KD	2	28	69	1	34	66	UNDECIDED	4	23	74	0	23	77	**IN**
77. Quality adjusted life years for parent or primary carer of child on KD	11	37	51	2	38	59	UNDECIDED	22	29	50	2	36	63	UNDECIDED
Participant Proposed Outcomes added to Round 2														
78. Hyperuricaemia							-	13	47	40	5	68	27	**OUT**
79. Electrolyte deficiency							-	10	48	43	3	35	62	UNDECIDED
80. Carnitine deficiency							-	5	50	45	3	34	64	UNDECIDED
81. Recovery time following a seizure (Postictal State)							-	4	36	60	2	53	45	UNDECIDED
82. Blood glucose levels							-	4	46	50	5	33	62	UNDECIDED
83. Financial burden of KD therapy							-	24	44	32	2	44	55	UNDECIDED
84. Parents feel supported to manage KD							-	4	19	78	2	13	86	**IN**
85. Parental stress associated with the management of KD therapy							-	7	37	55	2	27	72	UNDECIDED
86. Onset of therapeutic ketosis							-	4	60	38	3	45	52	UNDECIDED
87. Educational attainment and progress							-	0	48	52	2	56	43	UNDECIDED
88. Use of outpatient services and appointments							-	19	59	22	5	58	38	**OUT**
89. Use of Emergency Services							-	4	54	43	2	30	68	UNDECIDED

Outcomes highlighted in grey were scored as critically important (7-9) by ≥70% of one stakeholder group and represent those prioritised for discussion and scoring at the stakeholder consensus meeting.

TABLE 4. Summary of consensus meeting voting results in order of decreasing importance

Outcomes	Parent (N=9)			HCP (N=13)			Consensus
	1-3 (%)	4-6 (%)	7-9 (%)	1-3 (%)	4-6 (%)	7-9 (%)	
Unplanned hospital admissions	0	24	75	0	8	92	IN
KD duration	0	44	55	0	0	99	NO CONSENSUS
Concentration	0	11	89	8	31	61	NO CONSENSUS
Growth	22	44	33	0	23	77	NO CONSENSUS
Cost effectiveness of KD	22	33	44	0	23	76	NO CONSENSUS
Time to respond to KD	0	44	55	0	31	69	NO CONSENSUS
Parents confidence with KD	0	37	63	16	23	62	NO CONSENSUS
Mood	11	22	66	23	53	23	NO CONSENSUS
Speech and language	12	24	62	46	38	16	NO CONSENSUS
Parents quality of life	12	49	37	0	39	61	NO CONSENSUS
Kidney stones	0	44	55	0	46	54	NO CONSENSUS
Developmental milestones	0	33	66	30	31	39	NO CONSENSUS
Vitamin & mineral blood concentrations	11	33	55	8	77	16	NO CONSENSUS
Spasm freedom	12	50	37	16	39	46	OUT
Side effects of anti-seizure meds	37	36	25	61	38	0	OUT
EEG findings	28	71	0	39	46	15	OUT
Palatability of KD formula and supplements	49	37	12	30	38	31	OUT
Physical feeding difficulties	55	44	0	39	31	31	OUT
Behavioural feeding difficulties	22	44	33	31	38	31	OUT
Side effects of parenteral nutrition	55	44	0	31	38	30	OUT
Family life	0	50	50	23	62	15	OUT
Independence	12	50	37	47	38	16	OUT
Quality adjusted life years (parent)	75	24	0	39	30	31	OUT
Blood glucose levels	25	50	24	39	54	8	OUT
Parental stress associated with the management of KD therapy	12	36	49	0	54	46	OUT
Onset of therapeutic ketosis	62	37	0	54	30	16	OUT
Educational attainment and progress	12	74	12	30	47	23	OUT

TABLE 5. The CORE-KDT core outcome set for children with epilepsy treated with ketogenic diet therapy

Domain[23]	Outcome	Descriptor
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
	Seizure freedom	Not having seizures
	Seizure severity	The duration and severity of seizures considering the impact on the child during and afterwards. For example, injuries, falls, incontinence, confusion and time to recover
	Status epilepticus and use of rescue medication	The frequency of status episodes and the number of rescue medications administered
	Antiseizure medication use	The number and dose of antiseizure medications
	Adverse effects of ketogenic diet	Adverse effects of ketogenic diet such as gastrointestinal, growth, renal, cardiac, hepatic and respiratory effects. Classified as short and longer term as appropriate
Diet and Nutrition outcomes	Ketone levels	Monitoring of ketosis to include: - urine or blood concentrations of ketones - hyperketosis - time point at which target therapeutic ketosis is reached
	Dietary adherence or compliance	Compliance with the agreed dietary and monitoring plan
	Tolerability of ketogenic diet	Tolerance of ketogenic diet including consideration of: - the challenges of ketogenic diet - tolerance of prescribed ketogenic formula, supplements and foods - duration of treatment with ketogenic diet - behavioural feeding difficulties
	Parents feel supported to manage ketogenic diet	Parents feel supported and enabled to manage and provide the ketogenic diet for their child. This support will may come from the keto team, charity organisations, peers or the clinical trial team. Consider assessment of parent's confidence with the provision of ketogenic diet
Global Quality of Life outcomes	Quality of life for child on ketogenic diet	Childs general well-being in terms of health, comfort and happiness, including consideration of: - change in their ability to participate in everyday life and joining in activities like school - sleep pattern and quality - calculation of quality adjusted life years
Social and Emotional Functioning outcomes	Alertness and concentration	Change in level of alertness, concentration or ability to interact with those around them. Being awake, aware, attentive and ability to focus. The fog' lifting and being more present.
	Behaviour	Change in behaviour and their ability to adapt to surroundings and situations. Childs actions, reactions and functioning in response to everyday environment and situations.

Resource Use	Accident & Emergency Department attendance and unplanned hospital admissions	Epilepsy or ketogenic diet related issues leading to visits to the Accident & Emergency department and or being admitted to hospital. Excludes outpatient department visits and planned, elective hospital admissions.

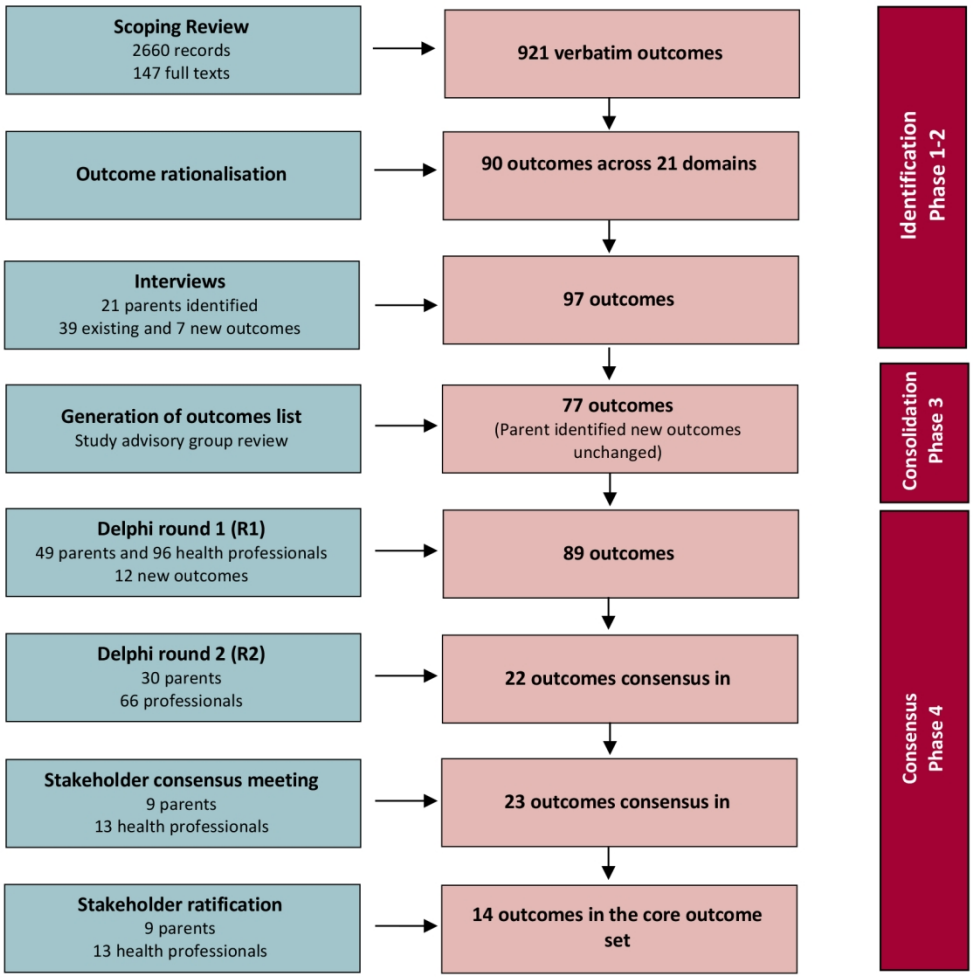

Figure 1. Overview of core outcome set development

152x152mm (300 x 300 DPI)