2023

CORE OUTCOMES FOR REFRACTORY CHILDHOOD EPILEPSY TREATED WITH KETOGENIC DIET THERAPY: THE CORE-KDT STUDY

Carroll, Jennifer

UNIVERSITY OF
PLYMOUTH

CORE OUTCOMES FOR REFRACTORY CHILDHOOD EPILEPSY TREATED WITH KETOGENIC DIET THERAPY: THE CORE-KDT STUDY

by

JENNIFER CARROLL, BSc MSc.

A thesis submitted to the University of Plymouth in partial fulfilment for the degree of

DOCTOR OF PHILOSOPHY

School of Health Professions

May 2023

Acknowledgements

When I was appointed to lead a ketogenic diet service for children with epilepsy, I believed that nothing could top it and I would remain in clinical practice for the remainder of my career. I never imagined I would move into academia and pursue a PhD, but I am extremely glad that I did. It has undoubtedly been one of the most enjoyable and rewarding challenges of my career to date. Throughout my doctoral studies, I have realised how much I miss working with children and their families, and in many ways, I have now come full circle by returning to clinical work alongside research and consulting.

I would like to express my gratitude to my supervisory team; Dr Avril Collinson, Professor Mary Hickson and Professor Helen Cross for their unwavering support. You gave me the freedom, time and independence I needed to advance my research and contribute to the keto research community in a manner I am proud of. I look forward to working with each of you again. Thank you to the organisations who provided funding in support of this research; The British Dietetic Association General Education Trust Fund, University of Plymouth and Nutricia Danone.

It was through this research that I was able to reconnect with colleagues and the brilliant team at Matthew's Friends. Special thanks go to Emma Williams and Val Aldridge for coming on board as research partners, I truly appreciate your support with the planning and execution of this research project. There is no limit to your enthusiasm and dedication to improving access and provision of ketogenic diet therapy to individuals with epilepsy. It is an honour for me to be able to play a small part in that by continuing to support the outstanding work of

the charity. I am very grateful to all who participated in and supported the development of this core outcome set, especially the parents, who gave up their precious time to share their family's experiences with me. It was a privilege to listen to your stories. The contributions you made to the CORE-KDT project have been invaluable but have also made me a better dietitian and for that I am grateful.

Thank you to my wonderful parents, Mary and Tom, as well as my sister Laura, for all your support and encouragement, the Bloom and Wild deliveries, and the La Bougie candles which brightened the office on PhD days. Lastly, I would like to thank my husband Sean, who planted the seed of doing a PhD and encouraged me to believe I could accomplish it. The endless coffees, motivational pep talks, and unwavering belief in my abilities kept me going, and without you, I would not be where I am today. We are a team that tackles everything together, and I cannot wait for our next adventure.

Authors Signed Declaration

At no time during the registration for the degree of *Doctor of Philosophy* has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee. This thesis has been proofread by a third party; no factual changes or additions or amendments to the argument were made as a result of this process. A copy of the thesis prior to proofreading will be made available to the examiners upon request. Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment.

This study was financed with the aid of a studentship from the University of Plymouth, and grants from the British Dietetic Association General Education Trust Fund and Nutricia Danone.

Publications

1. Carroll, J.H., Cross, H., Hickson, M. Williams, E., Aldridge, V., & Collinson, A. (2023) 'A Core outcome set for childhood epilepsy treated with ketogenic diet therapy (CORE-KDT study): international parent and health professional consensus', *Epilepsia*, 64(4), pp. 919-36. DOI: 10.1111/epi.17513

2. Carroll, J.H., Cross, H., Hickson, M. Williams, E., Aldridge, V., & Collinson, A. (2022a) 'The CORE-KDT study: A mixed methods protocol to establish core outcomes for refractory epilepsy treated with ketogenic diet therapy' *Trials,* 23(1),675. DOI: 10.1186/s13063-022-06629-7

3. Carroll, J.H., Cross, H., Hickson, M. Williams, E., Aldridge, V., & Collinson, A. (2022b) 'Core outcome set development for childhood epilepsy treated

with ketogenic diet therapy: Results of a scoping review and parent interviews', *Seizure,* pp. 99, 54-67. DOI: 10.1016/j.seizure.2022.05.009

4. Carroll, J.H. (2021) 'Outcomes in paediatric epilepsy treated with ketogenic diet therapy, can we achieve consensus?' *Complete Nutrition*, 21(6), pp. 31-33.

5. Carroll, J., Martin-McGill, K.J., Cross, H., Hickson, M. & Collinson, A. (2019) 'Outcome measurement and reporting in childhood epilepsy treated with ketogenic diet therapy: a scoping review protocol', *JBI Database Systematic Reviews and Implementation Reports*, 17(5), pp. 633-639. DOI: 10.11124/JBISRIR-2017-003924

Presentations

1. CORE-KDT – core outcomes for refractory childhood epilepsy treated with ketogenic diet therapy – findings from an international Delphi and parent interviews.
Presented by J Carroll at: European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 55th Annual Meeting (Vienna). May 2023.

2. Outcomes in childhood epilepsy - The CORE-KDT study.
Presented by J Carroll at: KetoCollege Advance Training Programme for Keto Professionals (East Grinstead). May 2023.

3. A mixed methods study to develop a Core outcome set for Refractory childhood Epilepsy treated with Ketogenic Diet Therapy (The CORE-KDT study).
Presented by J Carroll at: The British Dietetic Association Research Symposium (Birmingham). December 2022.

4. Outcomes in childhood epilepsy treated with ketogenic diet: Can we achieve consensus?
Presented by J Carroll at: Spotlight on New Perspectives to Manage Complex Epilepsy (virtual). June 2022.

5. A mixed methods study to develop a core outcome set for refractory childhood epilepsy treated with ketogenic diet therapy: Preliminary findings

Presented by J Carroll at: The British Dietetic Association Research Symposium (virtual). Dec 2020.

Posters

1. Carroll, J.H., Hickson, M. Cross, H., Williams, E., Aldridge, V., & Collinson, A. A core outcome set for childhood epilepsy treated with ketogenic diet therapy (CORE-KDT study).
Accepted at: i) Nutricia KetoConference 2023. Newcastle, June 2023. ii) The 35th International Epilepsy Congress. Dublin, September 2023
ii) Global Keto 8th Global Symposium on Ketogenic Therapies. San Diego, September 2023.

2. Carroll, J.H., Hickson, M. Cross, H., Williams, E., Aldridge, V., & Collinson, A. A mixed methods study to develop a core outcome set for refractory childhood epilepsy treated with ketogenic diet therapy (CORE-KDT).
Presented at: The British Paediatric Neurology Association conference (virtual). Jan 2023.

3. Williams, E., Aldridge, V., Fountain., J. & Carroll, J.H. The benefits of Patient and Public Involvement and Engagement (PPIE) in research: a charities contribution to outcome prioritisation for children with epilepsy treated with ketogenic diet therapy.
Presented at: The British Paediatric Neurology Association conference. Jan 2023.
Accepted to: Global Keto 8th Global Symposium on Ketogenic Therapies. San Diego, September 2023.

4. Carroll, J.H., Hickson, M. Cross, H., Williams, E., Aldridge, V., & Collinson, A. Beyond seizure control, a mixed methods study to develop a core outcome set for refractory epilepsy treated with ketogenic diet therapy: preliminary findings.

Presented at: i) Global Keto 7th Global Symposium on Medical Ketogenic Diet Therapies. Brighton October 2021. ii) The British Paediatric Neurology Association conference (virtual). Jan 2022.

5. Carroll, J.H., Parkin, T., Hickson, M., Cross, H., M. Williams, E., Aldridge, V., & Collinson, A. (2021) Family experiences of childhood epilepsy and ketogenic diet therapy: a qualitative study.
Presented at: i) Global Keto 7th Global Symposium on Medical Ketogenic Diet Therapies. Brighton October 2021. ii) The British Paediatric Neurology Association conference (virtual). January 2022.

Wordcount: 62,000 (excluding tables and figures)

Signed:  Date: 08.05.23

Abstract

Jennifer Carroll

Core outcomes for refractory childhood epilepsy treated with ketogenic diet therapy: the CORE-KDT study.

Background: Ketogenic diet therapy can result in seizure and non-seizure related benefits for children with drug resistant epilepsy. However, clinical trials report a wide range of outcomes which makes evidence synthesis difficult and they 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 - a minimum standardised set of outcomes that should be measured and reported. (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 international Delphi survey of parents and professionals to prioritise outcomes of importance for inclusion in a core outcome set. This informed a stakeholder consensus meeting and consultation process which finalised 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 by 49 parents and 96 health professionals in round one of the Delphi. Participants suggested 12 new outcomes for inclusion in round two, completed by 66% (30 parents and 66 professionals). Twenty-two outcomes met criteria for inclusion. Twenty-seven undecided outcomes were

discussed and scored in the consensus meeting (9 parents and 13 professionals); one further outcome reached consensus for inclusion. Following the consensus meeting and ratification, 14 outcomes across five domains were included in the core outcome set.

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

Contents

List of Tables

List of Figures

Abbreviations

ASM	Anti-Seizure Medication
BHB	Beta Hydroxybutyrate
CAU	Care as Usual
CBD	Cannabidiols
CBCL	Child Behaviour Checklist
CHO	Carbohydrate
CHOICE	Core Health Outcomes in Childhood Epilepsy
CKD	Classical Ketogenic Diet
COMET	The Core Outcome Measures in Effectiveness Trials Initiative
CORE-KDT	Core Outcomes in Refractory childhood Epilepsy treated with Ketogenic Diet Therapy
COREQ	COnsolidated criteria for Reporting Qualiatative research
COS-STAD	Core Outcome Set-STAndards for Development
COS-STAP	Core Outcome Set- STAndardised Protocol items
COS-STAR	Core Outcome Set - Standards for Reporting
EEG	Electroencephalogram
EThOS	British Library E-Theses Online Services
EQ-5D	EuroQol 5 Dimensions
EQ-5D-Y	EuroQol Five Dimensions Youth
FEPSY	The Iron Psyche, Neuropsychological Computerised Test Battery
FIRES	Febrile Infection-Related Epilepsy Syndrome
FP	Female Participant
GDPR	General Data Protection Regulation
GMFM	Gross Motor Function Measure
GLUT1DS	Glucose Transporter Protein 1 Deficiency Syndrome
HARCE	The Hague Restrictions in Childhood Epilepsy Scale
HOME	Harmonising Outcome Measures in Eczema
ILAE	International League Against Epilepsy
IMMPACT	The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials

ISRCTN	International Standard Randomised Controlled Trials Number
JBI	Joanna Briggs Institute
JBI-SUMARI	Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information
KD	Ketogenic Diet
LCT	Long Chain Triglyceride
LGIT	Low Glycaemic Index Treatment
MAD	Modified Atkins Diet
sMAD	simplified Modified Atkins Diet
MCT	Medium Chain Triglyceride
MKD	Modlifed Ketogenic Diet
MP	Male Participant
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NHS HRA	National Health Service Health Research Authority
NHS3	National Hospital Seizure Severity Scale
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
SIGLE	System for Information on Grey Literature in Europe
PARS	The Personal Adjustment and Role Skills Scale
PDHD	Pyruvate Dehydrogenase Deficiency
PedsQL	Pediatric Quality of Life Inventory
PIC	Participant Identification Centre
PIS	Participant Information Sheet
POMS	The Profile of Mood States
PROMS	Patient Reported Outcome Measure
PPIE	Patient and Public Involvement and Engagement
PPVT-III	Peabody Picture Vocabulary Test
PRISMA-SCR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
QoL	Quality of Life
QALY	Quality Adjusted Life Years
R&D	Research and Development

RCT	Randomised Control trial
SAG	Study Advisory Group
SDQ	The Strengths and Difficulties Questionnaire
SEV	The Social Emotional Questionnaire
SIDAED	Side effects of Anti-Epileptic Drugs
SUDEP	Sudden Unexpected Death in Epilepsy
VNS	Vagus Nerve Stimulation
TAPQOL	TNO-AZL Preschool Children's Quality of Life
TACQOL	TNO-AZL Children's Quality of Life
WHO	Word Health Organisation
WHOQOL-BREF	Word Health Organisation Quality of Life – Brief Version

Chapter 1: Introduction and literature review

Preface

The goal in completing this thesis was to solve the problem of inconsistent and inappropriate outcomes used in research to evaluate ketogenic diet (KD) therapy. Drug-resistant childhood epilepsy can be effectively treated with KD therapy, however selecting appropriate outcomes to measure can be a significant challenge, both in the clinical and research setting. The current consensus is that a core outcome set should be developed and implemented. In this chapter, a review of the problems with the outcomes used in studies to date are presented, as well as an argument for the development of a core set of outcomes for use in childhood epilepsy treated with KD therapy. An overview of childhood drug-resistant epilepsy and KD therapy is provided, along with the impacts of the disease and associated treatments on children and their families. It will become evident that little is known about how parents experience KD therapy and their views on important outcomes for their child. Finally, the phases of the research study are presented, along with an outline of the aims and objectives of the study.

1.1 The motivations for this project

I am a specialist ketogenic dietitian, with many years' experience educating and supporting families to undertake KD therapy for their child. The parents I work with often report that, "they have got their child back" as a result of treatment with KD therapy. They often see improvement in seizure control but also non-seizure related outcomes such as cognition, behaviour, overall well-being, and

quality of life, all of which can result in positive outcomes for the whole family. In 2012, I was appointed to lead the KD service at a large National Health Service (NHS) Trust, and I set about redesigning the service offered to children with drug resistant epilepsy. Identification of appropriate clinical outcomes was an essential part of this process so that the effectiveness of the treatment could be monitored. Ultimately answering the question 'are we making a difference?'. This was my first introduction to the process of outcome selection, which was followed by the challenge of identifying appropriate validated outcome measurement tools for a population of children with complex needs. On reflection, my colleagues and I in the keto team (consultant paediatric neurologist, specialist ketogenic dietitian and epilepsy specialist nurse), did what many health professionals and researchers do and elected to measure very clinical, 'numbers driven' outcomes. These included i) seizure frequency, ii) crisis epilepsy related admissions and iii) biochemistry. All outcomes that were relatively straightforward to count or track, but which failed to capture the broader non-seizure related benefits of KD therapy as reported by parents. It became apparent that there was no existing outcome measurement tool which met the specific needs of this population. We concluded that use of The Paediatric Quality of Life Inventory (Varni, Seid, & Rode, 1999), could provide some insight into the potential effects of KD therapy on health-related quality of life in children so we trialled it with families. Interestingly, some parents reported that the questionnaire took a long time to complete, and some felt it reinforced their child's limitations rather than highlighting the skills he or she had acquired. This reinforced a sense of helplessness among parents. Consequently, compliance was low, and we returned to relying on parental or clinician reporting for these difficult to measure non-seizure related outcomes. While it

was difficult to obtain reliable, subjective and consistent service level data, we were at least able to get a sense of how individual parents felt about KD therapy and its effect on their children.

Some years later, I transitioned into academia as a dietetics lecturer and began to plan my doctoral research project. The challenges of selecting, measuring, and reporting outcomes for this population remained unresolved and it was of particular interest to me to try to address some of these issues. In the literature, there is a strong emphasis on seizure related outcomes, with little focus on non-seizure related outcomes such as behaviour, cognition and quality of life. There is also a lack of consistency between studies in how these outcomes are measured and reported. It is therefore challenging for dietitians and keto teams to determine which outcomes to monitor as part of routine clinical care.

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 to make research and health decisions relevant (Washington and Lipstein, 2011). Yet, parents' experiences of KD therapy are rarely described in the literature, as well as the challenges they may encounter and strategies that may help them overcome them. I was therefore very keen to involve parents in this project, in order to gain a deeper understanding of their experiences, and to identify recommendations that may be beneficial to families who are using KD services. Furthermore, parents' perspectives on outcomes have not yet been explored, so little is known about what they consider to be the most significant outcomes for their children. Consequently, there is no consensus among parents, health

professionals and researchers regarding what outcomes should be measured and reported for drug resistant childhood epilepsy treated with KD therapy. The inconsistency that exists in both research and clinical settings hampers the evidence base in KD therapy, limiting comparison between studies and KD services. It risks duplication of research efforts and excludes the views of parents who are arguably the most important stakeholder group advocating for their children. However, these challenges in outcome measurement and reporting are not unique to childhood epilepsy and are replicated in other clinical areas.

To address the challenges of outcome selection and reporting, I undertook the CORE-KDT study (**C**ore **O**utcomes in **R**efractory childhood **E**pilepsy treated with **K**etogenic **D**iet **T**herapy) to develop a core outcome set. For the first time, seeking the consensus opinion of parents, health professionals, researchers, industry and charity representatives regarding the most important outcomes for children with drug-resistant epilepsy treated with KD therapy.

1.2 Childhood epilepsy

Epilepsy, characterised by recurrent epileptic seizures, is one of the most common serious neurological conditions of childhood (Joint Epilepsy Council, 2011). A systematic review of 33 studies worldwide estimated the median incidence of epilepsy to be 50.4 per 100,000 (33.6-75.6) people per year when including both adult and paediatric studies (Ngugi *et al.*, 2011). In the UK, epilepsy is thought to affect 600,000 individuals, 122,500 of which are children under the age of 18 years (Joint Epilepsy Council, 2011). While these estimates are over ten years old, they continue to be cited today to indicate the

approximate number of children requiring treatment for this disease. More recently, Symonds *et al.* (2021), suggest 1 in 418 children under the age of three years are diagnosed with epilepsy following a three year multicentre prospective cohort study in Scotland. An early definition of epilepsy required two unprovoked seizures to occur within 24 hours of each other, that is, seizures which are not triggered by a known cause such as hypoglycemia, trauma, infection, concussion, or fever. In 2014, the International League Against Epilepsy (ILAE) extended this to three clinical definitions of epilepsy, as shown in Table 1 (Fisher *et al.*, 2014). To better reflect typical clinical presentations, the definition was revised to include recurrence risks following a single unprovoked seizure and epilepsy syndromes. Section 1.3 discusses the classification and diagnosis of epilepsy in greater detail.

Table 1. Clinical definitions of epilepsy
(Fisher *et al.*, 2014)

	Clinical definition
Epilepsy is a disease of the brain defined by any of the following conditions	
i)	*'At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart'*
	Or
ii)	*'One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years'*
	Or
iii)	*'A diagnosis of an epilepsy syndrome'*

Anti-seizure medications (ASMs) are the first line of treatment in childhood epilepsy with the primary goal of achieving seizure freedom in the absence of side effects. Up to 65% of individuals with epilepsy will experience seizure freedom, where seizures are controlled either by medication or entering

spontaneous remission. However, up to 35% of children will continue to experience regular debilitating seizures despite being treated with multiple ASMs (Kwan, Schachter and Brodie, 2011; Wirrell *et al.*, 2012). Clinically this is described as drug-resistant or refractory epilepsy and can be defined as;

> *'a failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug schedules to achieve sustained seizure freedom'* (Kwan *et al.*, 2010).

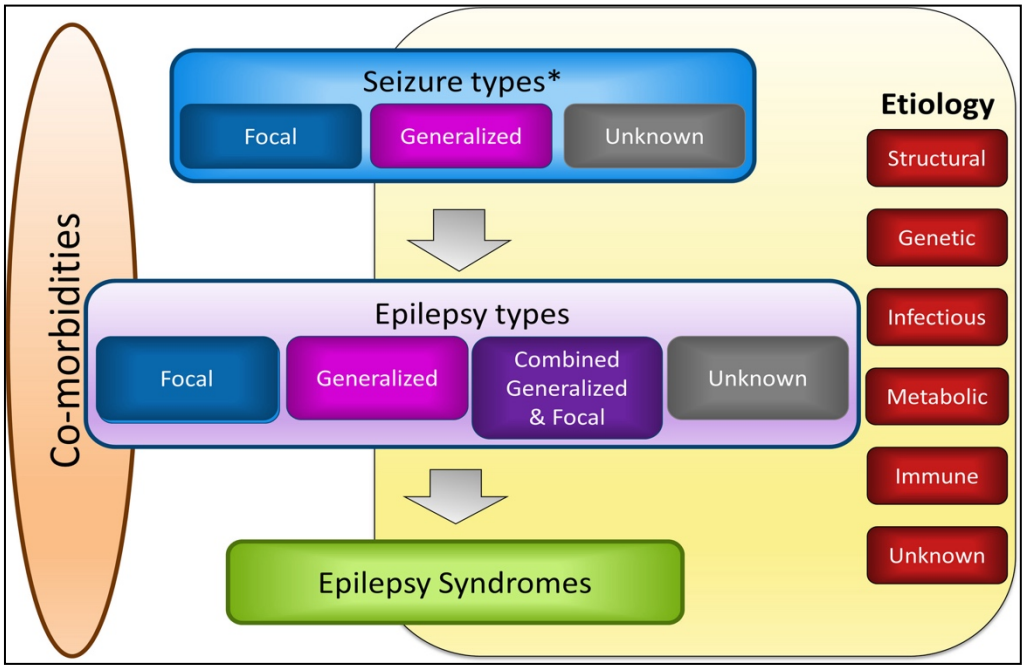
This thesis focuses exclusively on the dietary management of drug-resistant epilepsy and the associated outcomes of treatment, thus excluding epilepsies well controlled by ASMs. Ongoing, repeated seizure activity increases the risk of cognitive and behavioural comorbidities (Berg *et al.*, 2008) and early mortality (Jennum *et al.*, 2017). The burden of which extends to the broader family, where parents describe a cycle of uncertainty, characterised by changing symptoms, behaviours and uncertain futures (Webster, 2019a). When ASMs fail to control seizure activity, non-pharmacological treatments such as surgery, vagus nerve stimulation (VNS) and KD therapy are considered, often in combination with the aim of improving seizure control. ASMs and KD are most often used together, so discussion will focus on these. Surgery and VNS are quite different treatment approaches and so this chapter will only briefly discuss these.

1.3 Classification and diagnosis of epilepsy

The ILAE developed a three-level framework to guide diagnosis and classification of the epilepsies (Figure 1). This starts with a description of the

attack (seizure) and other presenting symptoms, together with neurological investigations such as magnetic resonance imaging (MRI) and electroencephalogram (EEG), to support a diagnosis of epilepsy (National Institute for Health and Care Excellence (NICE), 2012). Level one classifies the seizure type the child presents with according to the ILAE seizure classifications (Fisher *et al.*, 2017). Seizures are grouped according to where they start in the brain, whether the individual's awareness is affected or not and if the seizure involves other symptoms like movement. Level two of the ILAE framework for classifying epilepsies moves to diagnose the type of epilepsy as focal, or generalised onset, combined generalised and focal or an unknown epilepsy.

Figure 1. International League Against Epilepsy framework for classification of the epilepsies
(Scheffer et al., 2017). *Denotes onset of seizures.



Reproduced with permission

Table 2, expands on these and describes typical seizure presentations. The final level, three considers if a diagnosis of a specific epilepsy syndrome can be made. Six subgroups of etiology are considered at each level of the diagnostic pathway and a patient's epilepsy can be classified into more than one etiological category. Classification provides insights to the type of epilepsy the child presents with, how it may evolve in the future, the risk of comorbidities and potential treatment modalities. Some epilepsy syndromes are known to respond more favourably to KD therapy and it is recommended that KD therapy be considered earlier in their management (Kossoff *et al.*, 2018). These will be discussed later in section 1.7.1 and Table 6 when the efficacy of KD therapy is considered.

Table 2. Seizure classification and common presentations

Onset	Motor involvement	Common seizure presentations
Focal onset Seizures start in and affect only one part of the brain. i) Focal aware seizures do not alter consciousness. ii) Focal impaired awareness seizures alter or cause loss of awareness or thinking abilities.	**Motor onset** Visible physical movement	***Focal atonic seizure*** **–** causes a loss of muscle tone, the individual becomes limp and if standing will fall. Often referred to as a drop attack.
		Focal myoclonic seizure **–** very brief (less than one second) jerk like movement that resembles a startle.
		Focal clonic seizures **–** repeated rhythmical jerking movements of one side or part of the body.
	Non-motor onset Without any physical movement	***Focal autonomic seizure*** **–** may affect a part of the brain responsible for involuntary functions causing changes in blood pressure, bowel or bladder function and heart rhythm.
		Focal sensory seizure **–** can affect any of the five senses and present as smelling, tasting, hearing, or seeing things that aren't there, or feelings of numbness or tingling.
Generalised onset Seizures start in and affect both sides of the brain at once and happen without warning. Typically, impaired awareness & loss of consciousness.	**Motor**	***Generalised tonic-clonic seizure*** **–** muscles stiffen and the individual falls to the ground, back arches and the whole body jerks rhythmically. Breathing may be affected, control of bowels and bladder may be lost. Recovery post seizure can take minutes to hours.
		Generalised atonic seizure **–** causes a loss of muscle tone, the individual becomes limp and if standing will fall. Often referred to as a drop attack.
		Generalised myoclonic seizure **–** very brief (less than one second) jerk like movement that resembles a startle.
		Generalised clonic seizures **–** repeated rhythmical jerking movements of the whole body.
	Non-Motor	***Typical absence seizure*** **–** brief (seconds), blank vacant staring that may include eye movement or blinking.
		Atypical absence seizure **–** similar to typical absences but with pronounced jerking movements.
Unknown onset *When it is not known where in the brain the seizure starts*	**Motor**	***Tonic-clonic seizure*** **–** muscles stiffen, the individual falls to the ground, back arches and the whole body jerks rhythmically. Breathing may be affected, control of bowels and bladder may be lost. Recovery post seizure can take minutes to hours.
		Epileptic spasms **–** brief (1-3 seconds) events of arm, leg or head flexion. Tend to occur in clusters.
	Non-motor	***Behaviour arrest seizure*** **–** characterised by the person freezing or repeating words, laughing, screaming or crying

1.4 Impact of drug resistant childhood epilepsy

1.4.1 For the child

Children and adolescents with epilepsy are at risk of significant comorbidities and adverse outcomes, which will be considered further in this section. However, the most notable is the increased risk of sudden unexplained death in epilepsy (SUDEP). This refers to the sudden death of a seemingly healthy individual before, during or immediately after a tonic-clonic seizure. It is a devastating and tragic event that has lasting consequences for families and wider society. Although rare, the risk of SUDEP is higher in children with uncontrolled seizures and the incidence is reported to vary between 1.1 to 3.4 per 10,000 person-years (Saxena *et al.*, 2018). However, these findings have been challenged and may in fact be much higher, similar to the incidence reported in adult populations of 1-9 per 1000 person-years (Shorvon and Tomson, 2011; Sveinsson *et al.*, 2017).

Controlling seizure activity early in the course of epilepsy leads to better developmental outcomes for infants and children with fewer long-term adverse effects (Freitag and Tuxhorn, 2005). However, this is not always achievable, particularly for severe epilepsies including epileptic encephalopathies, which often present in infancy or childhood and have a poorer prognosis for seizure control outcomes (Wirrell *et al.*, 2012). A combination of the underlying brain disease and persistent uncontrolled seizures can result in developmental delay and neurobehavioural difficulties in infants and young children, leading to severe disabilities in older children and adults (Russ, Larson and Halfon, 2012). These difficulties include problems with cognitive development (Rantanen, Eriksson and Nieminen, 2011), communication skills (Selassie *et al.*, 2008),

social skills, difficulty focussing on a task, anxiety (Reilly *et al.*, 2014) and emotions (Davies, Heyman and Goodman, 2003). The developmental and everyday functioning abilities of a group of 48 children aged 1-7 years with epilepsy were assessed prospectively using the Griffiths Mental Development scale and Vineland Adaptive Behaviour Scales respectively (Reilly *et al.*, 2019). In total, 71% of children had significant problems with global developmental delay compared to a mean of 2% of children in the general population. Adaptive behaviours encompass real life skills such as communication, socialisation and motor skills that enable a child to undertake typical daily activities and cope in their environment. In the group of children with epilepsy, 56% exhibited significant impairments in these behaviours which was indicative of intellectual disability. Treatment with multiple ASMs was associated with lower scores on measures of adaptive behaviour and global development. This is not surprising, considering the detrimental impact of persistent seizure activity and the adverse effects of ASMs which will be discussed in section 1.5.1. and Table 3.

Children with epilepsy have shorter sleep times, more sleep difficulties and decreased sleep efficiency when compared with those without epilepsy (Pereira *et al.*, 2012; Winsor *et al.*, 2021). Parents of 48 children with epilepsy aged 1-7 years rated their child's sleep by completing the Child Sleep Habits Questionnaire (Reilly *et al.*, 2018a). Significant sleep problems were experienced by 81% of children with epilepsy, however this was also true for 71% of children with non-epilepsy related neurodisabilities. These findings suggest that sleep outcomes can be influenced by neurodisabilities and other comorbidities and not just epilepsy alone. As a consequence, learning, mood,

behaviour, seizures, and parents' quality of life can all be affected (Gibbon, Maccormac and Gringras, 2019). It is not surprising that parents of children with severe epilepsy perceive the disease to be a significant burden on their children and families' quality of life (Cianchetti *et al.*, 2015).

1.4.2 For the wider family

Parents have described childhood epilepsy as 'a cycle of uncertainty' (Webster, 2019a), where they had to fight and 'battle' to obtain a diagnosis and access adequate therapeutic support for their child (Williams *et al.*, 2012; Jones *et al.*, 2019; Reilly *et al.*, 2019). However, for some parents, facing and overcoming these challenges increased their confidence in their ability to be their child's advocate (Jensen *et al.*, 2017). Taking care of a chronically ill child places a significant burden on a family, negatively impacting the functioning of the entire family. Among 40 parents who were interviewed, 93% reported that epilepsy restricted their family's activities, decreased the wellbeing of their children, reduced their sleep quality and imposed financial difficulties (Reilly *et al.*, 2019).

In the general UK population 20% of adults score in the at-risk range for depression, 14% for anxiety and 18% for stress. In contrast, this was significantly higher for mothers of children with epilepsy, with 55% scoring in the at-risk range for depression, 47% for anxiety and 55% for stress (Reilly *et al.*, 2018b). It is interesting to note that for all three conditions, significantly more mothers scored in the at-risk range than fathers. For depression, 33% of fathers scored in the at-risk range, 26% for anxiety, and 31% for stress. Other studies which have explored the impact on fathers have reported similar findings, suggesting that the degree of negative consequences for fathers is less than for

mothers, perhaps due to the burden of care women face and differences in gender roles. (Ramaglia *et al.*, 2007; Mu, 2008; Ferro and Speechley, 2012).

Similarly, more mothers (62%) than fathers (44%) experienced significant sleep problems (Reilly *et al.*, 2018a). These were severe enough to require professional advice or support, however it was not clear if this was received. These findings are supported by Larson *et al.* (2012) who also reported 62% of mothers experienced decreased sleep quality or duration. Sleeping with their child often contributed to the sleep disturbances. Using telephone focus groups, Jensen *et al*. (2017) attempted to identify the most important domains to assess when measuring caregiver impact for caring for children with severe epilepsy. Sleep deprivation was the most common caregiver burden, driven by the uncertainty and fear that their child could have a fatal seizure in the night. Parents described the lack of sleep as torture and that they could not 'turn off' or 'punch out'; it was an endless cycle. This then led to daytime exhaustion, poor energy levels and difficulty prioritising own self-care. In addition to poor sleep, a high proportion of caregivers expressed anxiety about leaving their children with others who might not be able to cope with their child's complex needs. Due to this, they rarely took a break, spending most of their time with their child. Socially, life was very different, often friends and family struggled to understand the needs of the child or experiences the parents were facing and subsequently relationships deteriorated. One father described how they chose and accepted a new normal, forgoing social outings in order to keep their son at home in a calm and controlled environment which helped them to manage his care more safely and spend less time in the hospital.

A family's household income can be affected by epilepsy not only because of the associated higher costs of care, but also because both parents may be unable to work. In one study, American and Australian caregivers experienced greater financial worries and difficulties than European and British caregivers, most likely owing to the different structures of social support. However, mothers in all countries described the need to reduce their daily working hours and associated salary or cease employment entirely to care for their children, illustrating the often gendered nature of work (Jensen *et al.*, 2017). Similarly, among 86 parents (39 fathers and 47 mothers) of a child with epilepsy, fathers worked on average 35.3 hours per week whereas mothers worked on average only 8.6 hours per week (Reilly et al., 2018b).

It was described earlier how parents feel their children's well-being is affected, not only their child with epilepsy, but also their siblings. Everyday activities for siblings may be limited, such as going on family outings, but they also take on caring responsibilities within the family. Webster (2018) explored siblings caring roles in 24 family interviews (28 parents and 14 siblings) and also individual autodriven photo-elicitation interviews with ten of the children. Children were given a camera and encouraged to take pictures on four topics; who they lived with, what they liked to do with their family, what epilepsy meant to them, and finally, food and family meal times. They were asked to talk about their photos and describe the people and experiences in them during the interviews. In total, siblings in 20 of the 24 families provided care for their brother or sister with epilepsy categorised into three roles: alert assistant, parenting assistant and a substitute parent. Eighteen parents highlighted how grateful they were for the practical and emotional support siblings offered. They learned how to

recognise their brother's or sister's seizures and were able to alert their parents when help was needed. Interestingly this sibling support often afforded the child with epilepsy more independence from adult supervision as parents trusted the sibling to 'watch them' in the park for example. While parents appreciated the support, they did worry about the burden of responsibility.

The consequences of epilepsy for children and their families can be profound and lasting, especially in cases of severe drug-resistant epilepsies where seizure activity is not adequately controlled by treatment.

1.5 Non dietary treatments for childhood epilepsy

Anti-seizure medications (ASMs) play a vital role in trying to achieve early control of childhood seizures and they prove effective for the majority (65%) of children (Kwan, Schachter and Brodie, 2011). However, up to 35% of children will continue to experience seizures and develop drug resistant epilepsy. The management of which is complex, often requiring multiple treatment approaches which include surgery, vagus nerve stimulation (non-dietary treatment approaches) and KD therapy as adjuvant therapies alongside ASM treatment.

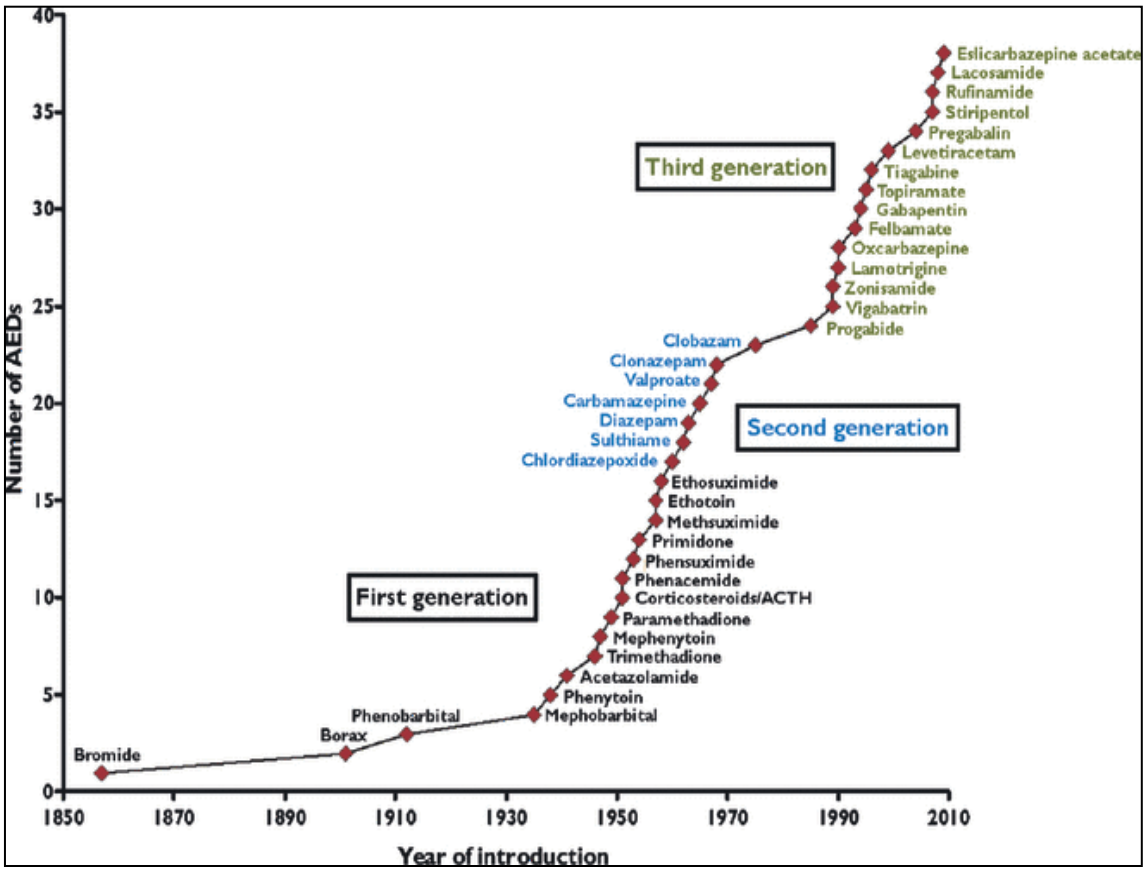
1.5.1 Anti-seizure medications

ASMs have been used for over 150 years with the primary aim of achieving control of seizure activity, while minimising the associated side effects. They are proposed to work via reduced excitability of neurons and possibly enhanced inhibition of electrical currents through the neurons (Macdonald and Kelly, 1995). It is estimated that 50% of patients will achieve seizure freedom with the

first administered ASM, 11% with the second and just 3% with the third ASM, resulting in 60-65% of children responding to drug treatment (Mohanraj and Brodie, 2006). However, each subsequent ASM trialled is estimated to work in only 0.8% of patients. Therefore, a significant proportion (up to 35%) of children will go on to develop drug resistant or refractory epilepsy, experiencing regular debilitating seizures despite treatment with multiple ASMs. Arguably, when the second ASM has failed, seizure freedom is less likely to be achieved and alternative treatment options including surgery, VNS and KD therapy should be considered.

ASMs can be classified into three generations according to when they were introduced to the market (Figure 2). The first generation were introduced between 1857 and 1958, followed by second generation ASMs between 1960-1975 (Shorvon, 2009). Since the 1980's,15 new third generation ASMs have been introduced (Liu *et al.*, 2017). Modern second and third generation ASMs are advantageous in that many do not cause adverse drug interactions (for example with contraception or other ASMs) and hypersensitivity reactions (Elger and Schmidt, 2008). However, they display only similar efficacy to older ASMs, despite costing significantly more (Kwan and Brodie, 2000; Marson *et al.*, 2007; Glauser *et al.*, 2010). It is surprising and disappointing that better seizure control cannot be achieved despite advances medically and pharmacologically.

Figure 2. History of anti-seizure medication development
(Löscher and Schmidt, 2011)



Reproduced with permission

More recently, there has been significant interest in the potential for cannabidiols (CBD) to confer seizure control. Three recent double blind randomised controlled trials (RCTs) demonstrated that 20mg/kg/day of cannabidiol induced a median percent reduction in the frequency of drop seizures of 41.9-43.6% compared to the placebo group (usual care with ASMs) of 17.2-21.8% (Devinsky *et al.*, 2018; Thiele *et al.*, 2018). Similarly in convulsive seizures the frequency was reduced by 38.9% compared to 13.3% in the placebo group (usual care with ASMs) (Devinsky *et al.*, 2017). Of note approximately two thirds of patients in these trials were also being treated with clobazam (an ASM), suggesting that clobazam and cannabidiols in combination are potentially more efficacious. NICE, therefore has recently approved

Epidyolex, a cannabidiol, as an adjuvant to Clobazam in the treatment of Lennox Gastaut syndrome and Dravet syndrome, two disorders characterized by drug-resistant seizures (NICE, 2019a, 2019b). Research into the longterm efficacy of Epidyolex is ongoing but early results look promising for improved seizure control as an adjuvant to ASMs. No comparison of cannabidiols with KD has been conducted, nor has the potential for combining both therapies to treat drug-resistant epilepsy been investigated yet.

An adverse effect of therapy is characterised by any clinical symptom, sign or deranged laboratory investigations which are deemed undesirable to the patient, medic or both (St. Louis, 2009). In epilepsy care, adverse effects of ASMs are commonly reported by parents. Table 3 outlines the broad range of adverse effects that may be experienced with ASM treatment including gastrointestinal issues, weight loss or gain, sedation, dizziness, cognitive impairments and psychomotor slowing.

Table 3. Properties and adverse effects of anti-seizure medications.
Adapted from St Louis, 2000

Anti-seizure medication	Usual adverse effects	Severe idiosyncratic toxicities
Older ASMs		
Carbamazepine	Diplopia, dizziness, ataxia, hyponatremia	Yes
Ethosuximide	Nausea, sedation	Yes
Phenobarbital	Sedation, psychomotor slowing	Yes
Phenytoin	Sedation, dizziness, ataxia, gingival hyperplasia	Yes
Primidone	Sedation, psychomotor slowing	Yes
Valproate	Nausea, tremor, hair loss, weight gain	Yes
Newer ASMs		
Felbamate	Irritability, insomnia, weight loss	Yes
Gabapentin	Sedation, dizziness, weight gain	No
Lacosamide	Sedation, fatigue	Unknown
Lamotrigine	Dizziness, rash	Yes
Levetiracetam	Sedation, dizziness	No
Oxcarbazepine	Sedation, dizziness, hyponatremia	Yes
Rufinamide	Sedation, diarrhoea	Unknown
Tiagabine	Sedation, dizziness	No
Topiramate	Sedation, cognitive complaints, paresthesias, weight loss, rare nephrolithiasis	No
Zonisamide	Sedation, paresthesias, weight loss, rare nephrolithiasis	Yes

Unstructured interviews or spontaneous reporting identified adverse effects in 10-40% of individuals on stable ASM treatment (Beghi, Mascio and Sasanelli, 1986), which rose to 60-90% when standardised screening questionnaires or checklists were used (Perucca *et al.*, 2009; Perucca and Gilliam, 2012). This suggests the degree of adverse effects parents report during clinic appointments may not capture the extent of side effects experienced by their child. However, there is surprisingly little data available on the incidence of ASM related adverse effects in children.

A recent observational study of 200 children aged 2-17 years, with epilepsy treated with ASMs used the Paediatric Epilepsy Side Effect Questionnaire to identify adverse drug reactions (Kaushik *et al.*, 2019). Ninety-seven children experienced 139 adverse drug reactions identified via the questionnaire and 30 additional adverse effects were reported by their parents. Cognitive and neurological problems characterised by poor school results were the most common issues seen and authors concluded that polytherapy increased the likelihood of adverse effects. Children with drug resistant epilepsy referred for KD therapy are commonly treated with polytherapy having previously trialled and failed other ASMs and so are likely to experience adverse effects of ASMs.

1.5.2 Surgery and vagus nerve stimulation

Epilepsy surgery is the most effective way to achieve long term seizure freedom for children with drug resistant focal epilepsy, where the single region of the brain responsible for seizures can be defined and resection is deemed relatively safe, without compromise to cognitive function. The ultimate goal of surgery in catastrophic drug resistant epilepsies is to stop the seizures, interrupt the downhill course of the epileptic encephalopathy and improve the child's developmental capacity (Van Schooneveld and Braun, 2013). When asked about their decision to explore epilepsy surgery, interviewed parents and children described their concerns about long term wellbeing, the risks to safety and their hope for a 'normal life' as motivators (O'Brien, Gray and Woolfall, 2020). Post-surgery all participants experienced improvements in seizure control, psychological wellbeing, quality of life, social relationships and family functioning, demonstrating the positive impacts of surgery. However, longer term outcomes post-surgery may be related to the degree of seizure control

achieved (Puka and Smith, 2016). Epilepsy surgery is not without risk, however the incidence of neurological complications decreased substantially between the periods 1980-1995 and 1996-2012 (Tebo *et al.*, 2014). One estimate suggests that major neurological complications, not wholly resolved within three months post-surgery, have been experienced by 4.7% of patients with major visual field defects the most common complication (Hader *et al.*, 2013).

When resective surgery is not possible, vagus nerve stimulation (VNS) is considered as an adjuvant therapy to ASMs in drug resistant epilepsy (Orosz *et al.*, 2014). This involves electrical impulses being sent to the vagus nerve at regular intervals which are then carried by the vagus nerve to the brain. Typically, stimulation was achieved via an implantable electrical device (generator), sited under the skin in the chest with a lead connecting the generator to the vagus nerve. More recently non-invasive devices are becoming available where transcutaneous external stimulation of the vagus nerve occurs (Toffa *et al.*, 2020). In a large European cohort of 347 children aged 6 months to 18 years, adjuvant VNS therapy reduced seizure activity and was well tolerated (Orosz *et al.*, 2014). At 6, 12 and 24 months after implantation 32.5%, 37.6% and 43.8% respectively, of children experienced 50% or more reduction in baseline seizure frequency. Secondary outcome measures also improved including seizure duration, post ictal recovery and quality of life. Implantable devices are surgically placed and as such there is risk of vocal cord and facial paresis, however the incidence of these adverse effects have decreased significantly with advances in surgical techniques. The most commonly reported complications include hoarseness, sore throat and cough (Panebianco *et al.*, 2016). It is not uncommon for paediatric drug resistant epilepsy to be treated

with both VNS and KD therapy simultaneously. Two small retrospective studies (total N=63, 30 and 33 respectively) demonstrated that combining both therapies appeared synergistic and reduced seizure frequency further than one modality alone (Kossoff *et al.*, 2007a; Abdelmoity *et al.*, 2021). However, this has not yet been examined in larger prospective studies.

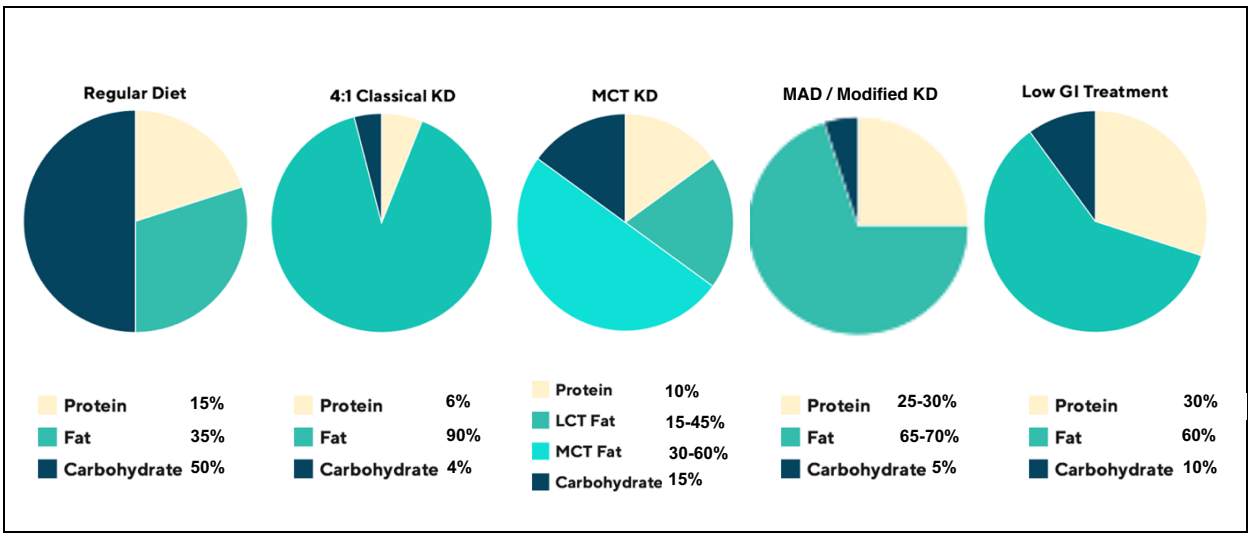
In summary, epilepsy surgery is only suitable for a very specific group of children with focal drug-resistant epilepsies, so alternative treatment modalities are needed for those with generalised or unknown onset epilepsies. Clinically, we routinely assist parents in identifying the potential advantages and disadvantages of both VNS and KD therapy to assist them in making an informed decision with regards to their child's treatment. In some cases, parents are concerned about the surgical nature of VNS and opt to try KD therapy first.

1.6 Ketogenic diet therapy as a treatment for epilepsy

A KD regimen is very high in fat, low in carbohydrate and provides adequate protein to sustain normal growth. There are five types of KD used to treat drug-resistant epilepsy today; classical KD, medium chain triglyceride (MCT) KD, modified Atkins diet (MAD), modified ketogenic diet (MKD) and low glycaemic index treatment (LGIT); all with varying degrees of dietary restriction. Figure 3 compares their macronutrient composition to a regular western diet as a percentage of total energy. Often referred to as medical KDs, these are calculated by a specialist ketogenic dietitian for each individual and are very different from the KDs described in the popular press and social media (Easter, 2019). In contrast, lifestyle 'keto' dietary approaches are predominately undertaken by adults for a variety of reasons including perceived general

health, weight loss, body building, blood glucose control and migraines. They tend to be lower in carbohydrate (50-100g/day) than a standard western diet (272g/day[1]) yet not as extremely low in carbohydrate or regimented as medical KDs (as low as 10g/day).

Figure 3. Macronutrient composition of ketogenic diets as a percentage of energy



MCT KD: medium chain triglyceride ketogenic diet, MAD: modified Atkins KD, Low GI: low glycaemic index, LCT fat: long chain triglyceride fat, MCT fat: medium chain triglyceride fat.

The classical KD is calculated as a ratio of fat to carbohydrate; usually 3:1 or 4:1 where 87% or 90% respectively of total dietary energy is derived from fat (Neal *et al.*, 2009). Long chain triglyceride fats like butter, double cream and oils are the predominant fat source, carbohydrates are very heavily restricted, and protein is limited to that required to maintain growth. Medium chain triglyceride fats are absorbed and transported more efficiently than long chain triglyceride fats with greater ketone production per unit of dietary energy (Schon von, Lippach and Gelpke, 1959), meaning less total dietary fat is needed to produce the same level of ketosis. A slight relaxation of dietary restrictions is therefore

[1] 50% (Department of Health, 1991) of the estimated average requirement for energy (2175kcals) for a 19-34 year old female

possible when MCT fat is incorporated into the KD prescription, resulting in an increase in carbohydrate and protein intake. The original MCT KD provided 60% of dietary energy from MCT fat (Huttenlocher, Wilbourn and Signore, 1971). However, it is not uncommon for patients to experience gastrointestinal side effects including abdominal pain and diarrhoea when consuming large doses of MCT fat (Huttenlocher, 1976). Therefore, a modified version (John Radcliffe MCT KD) was proposed which contained only 30% MCT, replacing the omitted 30% MCT with long chain triglycerides instead (Schwartz *et al.*, 1989). The classical and MCT KD are considered the strictest of the KDs as all macronutrients are prescribed in set quantities and all foods are weighed.

In the 2000s, two further KD protocols were developed, the modified Atkins (MAD) KD (Kossoff *et al.*, 2003, 2013) and the low glycaemic index treatment (LGIT) (Pfeifer and Thiele, 2005). Both aimed to achieve similar efficacy to the traditional classical and MCT KDs but in a simpler, more pragmatic and accessible way. On the modified Atkins protocol carbohydrate is limited to 10-20g per day, together with unlimited protein and liberal fat is encouraged rather than prescribed and measured. It allows visual, or household measurements as opposed to strict weighing of all macronutrients. The LGIT allows 10% of energy from carbohydrate sources with a glycaemic index of <50, a liberal protein allowance of 30% and approximately 60% of energy from fat. When established, the macronutrient intake is approximately equivalent to a 1:1 classical KD ratio. Although MAD and LGIT provide additional flexibility for individuals, anecdotally some parents are uncomfortable with the lack of specific macronutrient targets, particularly in MAD, and prefer more specific targets. Dietitians can also find it difficult to identify a patient's macronutrient

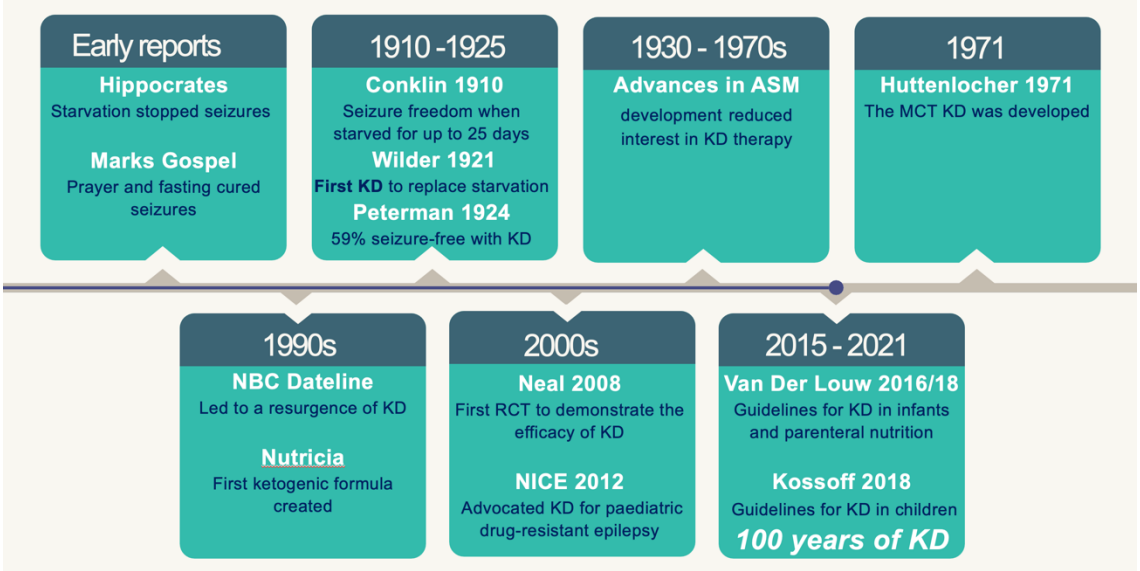
intake when foods are not weighed and measured. This issue is of particular concern for children, where a key goal is the maintenance of normal growth. Dietitians may also find it more difficult to fine tune the KD prescription in order to achieve optimal ketosis for their patients. Owing to these challenges, an adaptation or hybrid KD evolved among UK dietitians – the modified ketogenic diet (MKD) (Martin-McGill *et al.*, 2019). This sits firmly in the middle between the very strict traditional classical and MCT KD and the very flexible MAD and LGIT. With MKD, carbohydrate and fat are both prescribed and weighed, but protein is not. Guidance is provided on appropriate portions to ensure it is not consumed to excess, as this can negatively impact on ketosis. The macronutrient percentages outlined in Figure 3 are approximate and suggested targets. Ultimately, dietitians fine tune the starter KD prescription as needed to establish adequate ketosis and effect positive change in both seizure and non-seizure related outcomes. It is recommended that KD therapy be trialled for a minimum of three months in order to determine if there is an improvement in seizure control or other non-seizure related outcomes for the treated child (Kossoff et *al.,* 2008). If KD is effective in managing drug-resistant epilepsy, the treatment is usually continued for two years, although the length of treatment can vary depending on individual need and clinical assessment.

1.6.1 History of ketogenic diet therapy use

KD therapies have been used to treat epilepsy for just over 100 years (Figure 4). However, earlier references are found in Marks gospel and Hippocrates where starvation or fasting were associated with improved seizure control. Similarly in 1911, two Parisian physicians trialled starvation in 20 children and adults and reported seizure severity was reduced during fasting (Guelpa and

Marie, 1911), unsurprisingly though compliance was poor. Wilder (1921), some years later proposed that ketosis, the state achieved during starvation could also be induced via dietary manipulation. In essence, mimicking the starved state without the traditional prolonged fasting that understandably caused patients to previously fail and seizures to return. The first KD prescription followed consisting of 10-15g carbohydrate, 1g of protein/kg body weight and the remainder of energy from fat (Peterman, 1925), similar to the classical KD still used today. The MCT KD was first described in 1971, as an alternative less restrictive KD (Huttenlocher, Wilbourn and Signore, 1971). Despite this advance for patients, the development and use of first and second-generation ASMs in the 1930's resulted in KD falling out of favour.

Figure 4. Timeline and history of ketogenic diet therapy use



In 1997, a movie starring Meryl Streep, "First Do No Harm", was produced by NBC Dateline. It depicted the true story of Charlie, treated with KD and led to a resurgence in its use in America, which followed worldwide. Charlie's parents set up The Charlie Foundation to support families with KD therapy. Publication

of observational studies demonstrating efficacy in drug resistant epilepsy followed (Freeman *et al.*, 1998; Lefevre and Aronson, 2000; Keene, 2006) and the first RCT was published (Neal *et al.*, 2008a) and others followed (Raju *et al.*, 2011; El-Rashidy *et al.*, 2013; Sharma *et al.*, 2013, 2016; Kim *et al.*, 2016; Lambrechts *et al.*, 2017). These will be discussed further in section 1.7 when the impact of KD therapy on a range of outcomes is considered. Finally, optimal clinical recommendations and guidelines have been developed by international expert groups to inform the clinical management of KD for infants (van der Louw *et al.*, 2016) and children (Kossoff *et al.*, 2018; van der Louw *et al.*, 2020).

1.6.2 Mechanism of action of ketogenic diet therapy

KD therapy mimics a starvation state whereby the bodies main energy source switches from that of glucose to ketones produced through lipolysis of high levels of dietary fat. Consequently, circulating ketone bodies and fatty acids are elevated while glucose levels are reduced (Bough and Rho, 2007). The aim of KD therapy is to achieve ketosis and then fine tune the KD prescription to achieve optimal ketosis of 4-16mmol/l in urine (Ketostix) or 2-5mmol/l in blood (finger prick test). Despite ongoing research, the exact mechanisms by which KD therapy exerts its anticonvulsant effects remain unclear. It may be directly via the alternative brain fuel that ketones provide in place of circulating glucose, or it may be via indirect mechanisms including mitochondrial biogenesis, neurotransmitter metabolism, antioxidant status or epigenetic mechanisms (Murakami and Tognini, 2022). It is possible that there is no single mechanism, rather the cascade of metabolic shifts a KD induces may be responsible for its positive effect. Although some would question whether the answer matters

when it works as a treatment for many with epilepsy, a deeper understanding of the mechanisms may facilitate better targeting or delivery of the therapy.

1.6.3 Referral and use of ketogenic diet therapy

NICE (2012) originally recommended that children should be referred to a tertiary centre for consideration for treatment with KD when their epilepsy failed to respond to two or more appropriately prescribed and adequately trialled ASMs. A more recent update (NICE, 2022a) recommends that KD could be considered in a range of childhood-onset epilepsy syndromes and drug resistant epilepsy, if other treatment options have been unsuccessful or inappropriate. Although the specific criteria of two failed ASMs has been removed, the treatment pathway remains similar. The International Ketogenic Study Group in their consensus statements (Kossoff *et al.*, 2009, 2018) also recommend consideration of KD therapy after two failed ASMs.

Yet KD is often viewed as a 'last resort' treatment (Wang and Lin, 2013) and considered when multiple ASMs beyond the recommended two have failed to achieve seizure freedom. This was demonstrated in a survey of 88 child neurologists, 60% of whom report using KD only as a last resort (Mastriani *et al.*, 2008). Unfortunately, the survey has not been repeated since to explore if views have changed. By using KD in this way, children will likely have to wait longer than necessary to receive a treatment that may prove effective. This is potentially detrimental in light of the fact that on average, 40-50% of treated children achieve a reduction in seizures of at least 50% (Neal *et al.*, 2008a; Sharma *et al.*, 2013, 2016; Lambrechts *et al.*, 2017).

The number of children being treated with KD therapy in the UK has grown significantly over recent years, however, many still face long waiting times to access therapy. The use of KD therapy was examined in 2000 (Magrath, MacDonald and Whitehouse, 2000), 2010 (Lord and Magrath, 2010) and most recently 2017 (Whiteley *et al.*, 2020) via a national survey of paediatric ketogenic dietitians. The number of KD centres increased by 73% from 2010 to 2017 (22-38 centres). Equally, the number of patients treated with KD therapy increased by 647% (101 to 754 patients) in the same period. This growth may be attributed to several factors. Firstly, the growing body of evidence supporting the use of KD in childhood epilepsy (Martin *et al.*, 2016; Martin-Mcgill *et al.*, 2018) and secondly, NICE (2012) guidelines recommended referral to a tertiary centre when two ASMs failed to adequately control seizure activity. The surveys did not examine the point at which patients were referred in their epilepsy journey or how many ASMs had been trialled and failed. However, it is plausible that the increase in patients being treated with KD in the last decade, may demonstrate a slight shift in attitude away from it being a last resort therapy. Frustratingly for families, demand outstrips supply for this resource intensive treatment. In total, 276 patients were waiting to commence KD therapy and most UK KD centres (31 of 38 centres) were operating waiting lists (Whiteley *et al.*, 2020). Waiting times are not readily published, however parents report waiting times of over two years at some centres.

1.6.4 Parents expectations of KD therapy

KD therapy is expected to reduce seizure frequency by more than 50% in approximately half of treated children, while only 15% are expected to achieve complete seizure freedom (Kossoff *et al.*, 2018). As such it is critical that keto

teams explore parental expectation of KD therapy and support them to develop realistic goals for their child. There are a variety of approaches to help to achieve this, from a simple conversation to more formal documentation of hopes and expectations. These can then be revisited later in the treatment pathway. Before commencing KD therapy, parents in a KD centre in the US were asked to write a letter detailing their treatment expectations and what they hoped their child would attain with KD therapy. Letters for 100 children were evaluated (95 written by mothers and 75 by fathers) and demonstrated that the most common goals were seizure reduction, ASM reduction and cognitive improvement (Farasat *et al.*, 2006). There was a sense that parents generally set realistic goals, with only approximately one third of parents expecting complete seizure freedom and half expecting to stop ASMs completely. The authors expected that a higher proportion of parents would expect complete seizure freedom. In reality though, not all would achieve these goals, demonstrating the importance of counselling parents regarding this.

A smaller study of twelve parents expanded on this by asking parents to identify what it would mean for their child and family if their hopes and expectations of KD therapy were achieved (Bruce *et al.*, 2017). Parents were asked to complete a short one page unvalidated questionnaire, stating their hopes and expectations of KD therapy and to rate their quality of life (QoL) (0-10 poor to very good QoL) prior to their child commencing KD therapy. These were then discussed in the pre assessment clinic with a dietitian, neuropsychologist and neurology nurse, allowing for any misconceptions to be addressed. During KD therapy, responses were reviewed at 3, 6 and 12 months, facilitating constructive discussions about progress with outcomes. The authors found the

tool in itself was a valuable therapeutic intervention, facilitating discussion of individualised personalised goals and gains for children. If we consider the definition of expectation, it is described as *'your strong hopes or beliefs that something will happen or that you will get something you want'*. Arguably, then these two studies, (Farasat *et al.*, 2006; Bruce *et al.*, 2017) shed some light on what parents hope or expect their child can achieve by following a KD. To date, however, no direct research has been undertaken to examine parents' views on outcomes; what is important to them and why. Keeley *et al.* (2016) suggest a qualitative phase is particularly valuable in core outcome set development, when the existing literature doesn't adequately reflect service user views. This is a time and resource intensive process, yet essential in the CORE-KDT study, where so little is understood about parents' views on outcomes and in particular their priority outcomes. Including parents in the development of the core outcome set will help to ensure the outcomes measured and reported in research and practice are relevant to them and their children.

1.6.5 Practicalities of ketogenic diet therapy

To gain a better understanding of what KD therapy involves for families it is worth considering some of the practical aspects of the diet. In the weeks preceding the start of KD therapy, a specialist ketogenic dietitian will provide extensive education and support to the family. A broad range of topics are addressed, such as the macronutrient composition of foods, ketone testing, vitamin and mineral supplementation, food shopping and keto-friendly foods, calculating keto meals, keto meal preparation, and online support and resources. The dietitian undertakes a full nutritional assessment and calculates a bespoke KD prescription for each child based on the target daily portions

(grams) of the macronutrient's - fat, carbohydrate, and protein. An example of a 2.5:1 classical KD prescription for a 3-year-old boy is presented in Table 4a as an illustration of how this information is communicated to parents. It demonstrates the level of understanding they must possess in order to implement KD for their children. Carbohydrate-free vitamins and minerals are necessary to maintain adequate nutritional status during the KD. However, these nutritional supplements are often unpalatable and can therefore add to the burden of medication on families. The dietitian calculates individualised recipes to meet the KD prescription and parents must weigh all foods carefully. Food choice lists which provide the macronutrient contents of typical foods are provided to enable parents to exchange individual ingredients for alternatives. However, dairy products, nuts, seeds, and plant-based foods pose a particular challenge since they contain a combination of macronutrients that must be counted. Table 4b provides an example of a keto meal plan and illustrates how parents need to understand basic arithmetic to follow recipes and make food swaps. The dietitian helps families identify keto-friendly alternatives to typically carbohydrate-laden foods such as bread, potatoes, muffins, and biscuits. This has become easier due to the interest in lifestyle keto diets, with a growing range of keto friendly ingredients and products available in shops and online. However, these items are usually far more expensive, and it can be difficult for parents to determine which items they can trust and use safely for their child. Alternatively, they may bake their own, but this requires specialist ingredients and trial and error to produce a palatable bake that fits within the target macronutrients.

Eating out, holidays and special occasions require careful consideration and preparation as a break cannot be taken from KD. The resultant loss of ketosis would risk negatively impacting upon any positive gains in seizure control and non-seizure related outcomes. In light of these practical considerations, it is easy to see how KD therapy may present challenges to parents in an already very busy household. However, parents' proactive involvement in the preparation and management of KD therapy may provide a sense of control and active participation in the care of their children, in spite of the stress that may be associated with it.

Table 4. (a) Sample 2.5:1 classical KD prescription for a three-year-old boy

CLASSICAL KD PRESCRIPTION 2.5:1 RATIO			
Carbohydrate (CHO) 20g/day	**Fat 118g/day**	**Protein 27g**	**Kcals 1250/day**
Name: XXX		**Date:** XXX	
Additional information: Ketones currently 2.4-3.8mmol/l versus target of 2-5mmol/ **Aim:** To optimise ketosis **Action:** Increase from a 2:1 to a 2.5:1 classical KD			
MEAL	**Carbohydrate** Refer to 1g CHO choices lists	**Fat** Refer to 10g fat choices list	**Protein** Refer to 6g protein choices list
BREAKFAST Check ketones	**4g** 4 x 1g choices	**30g** 3 x fat choices	**6g** 1 x pro choice
LUNCH	**6g** 6 x 1g choices	**30g** 3 x fat choices	**9g** 1.5 x pro choice
DINNER	**6g** 6 x 1g choices	**30g** 3 x fat choices	**9g** 1.5 x pro choice
SNACK 1 (e.g. butter biscuit)	**2g**	**7g**	**-**
SNACK 2 (e.g. keto muffin)	**2g**	**10g**	**3g**
BEDTIME Check Ketones Almond milk as usual	**-**	**-**	-
DAILY TOTAL	**20g**	**107g added fat** (Excludes 11g fat in protein choices)	**27g**
Vitamins and minerals ½ sachet (3g) of FruitiVits daily			

CHO – carbohydrate, kcals - kilocalories

Table 4b. Sample 2.5:1 classical KD meal plan for a three-year-old boy

Breakfast – creamy porridge				
Ingredients	**Weight**	**Protein**	**CHO**	**Fat**
Alpro Almond no sugars or other CHO free milk	50ml or as needed	-	-	-
Quaker jumbo oats	2g	0.4g	1.2g	-
Ground almonds	30g	4g	2g	17g
MCT oil	5g	-	-	5g
Double cream	10g	-	-	6g
Whole earth peanut butter	5g	1.4	0.5g	2.5g
Meal total		**6g**	**4g**	**31g**
Snack – butter biscuits				
Ingredients	**Weight**	**Protein**	**CHO**	**Fat**
2 x butter biscuits as per recipe provided	2 biscuits	-	1g	7g
Strawberries	16g	-	1g	
Meal total		-	**2g**	**7g**
Lunch – beans on keto toast				
Ingredients	**Weight**	**Protein**	**CHO**	**Fat**
Keto Paleo bread	43g	6.5g	1.5g	15g
Heinz reduced sugar and salt baked beans	45g	2g	4.5g	-
Butter	18g	-	-	15g
Meal total		**9g**	**6g**	**30g**
Dinner – creamy carbonara				
Ingredients	**Weight**	**Protein**	**CHO**	**Fat**
55g raw or 39g fried bacon or 45g raw or 40g cooked salmon	-	9g	-	-
Double cream	42g	-	1g	20g
Butter	6g	-	-	5g
MCT oil	5g	-	-	5g
Mushrooms	Free	-	-	-
Onion	26g	-	2g	-
Frozen peas	27g		3g	
Pepper + pinch garlic powder	free	-	-	-
Carb free pasta/noodles	free	-	-	-
Meal total		**9g**	**6g**	**30g**
Snack – mini keto muffin				
1 x mini muffin as per recipe provided	1 muffin	3g	2g	10g
Alpro Almond no sugars or other CHO free milk	Free to taste			
Meal total		**3g**	**2g**	**10g**
Daily total		**27g**	**20g**	**108g**

CHO- carbohydrate

1.6.6 Parents experiences of ketogenic diet therapy

Earlier, the consequences of epilepsy for the child and wider family were discussed, many of which relate to the child's additional complex care needs. Family life is busy and many parents report feeling overwhelmed and daunted when introducing labour-intensive KD therapy. As early as the 1920s (Peterman, 1925; Talbot, Metcalf and Moriarty, 1927), parents were recognised as essential to KD therapy management, yet few existing studies have examined how KD therapy affects parents and families today. Only two papers were identified: a first-hand account of four parents' perspectives of KD therapy, and a sociological exploration of twelve parents' identities and food values when using KD therapy. In the first paper, Williams (2012), together with three other parents shared their child's story of epilepsy and KD therapy. They discussed the trauma and despair of witnessing their child seize uncontrollably, the difficulties of accessing KD therapy, and the fear and anxiety they felt when weaning their children from KD after years of successful treatment. Although the accounts provide helpful insights into some key themes for families, they lack depth because of their short narrative nature. The CORE-KDT study seeks to address this gap in knowledge by conducting interviews with parents to understand their experiences of the KD.

Webster and Gabe (2016) explored the meanings that twelve parents attached to foods during in-depth semi-structured interviews. Their strategies for overcoming some of the contradictions that KD presents to their identities as good parents included medicalising KD therapy, treating food as a symbol of inclusion, and using food as a symbol of love. Parents had to alter the meanings they had previously attached to food, instead food became functional;

a medicine and a treatment for illness. This was a well-designed study; however, the data analysis was from a sociological perspective and firmly grounded in that literature. Generally, sociology involves the study of society, how people live, how relationships develop, social change, and the consequences of human behaviour through an interdisciplinary lens that transcends individual viewpoints. We see this in Websters study where the focus is on the sociology of food, its intrinsic social functions, the meanings attached to it and how KD therapy challenged parenting identity. As a result, it failed to address in great depth the daily experiences of parents with the KD, in a manner that could help us gain a deeper understanding of the practical challenges families face, and the ways in which they could be supported to overcome these challenges.

The CORE-KDT study will build upon these early findings by exploring parents' experiences throughout their child's journey, from epilepsy diagnosis to commencing and managing KD therapy. Data analysis will focus on the parents' voices, minimising researcher interpretations and theorising. The results will be positioned within the epilepsy literature in order to enhance the relevance for neurology researchers, clinicians and the potential impact on families in the future.

1.7 Ketogenic diet therapy outcomes

To date there have been ten RCT or quasi RCTs of KD therapy, involving 711 children with epilepsy aged 4 months to 18 years (Bergqvist *et al.*, 2005; Kossoff, *et al.*, 2007b; Seo *et al.*, 2007; Neal *et al.*, 2008a; Raju *et al.*, 2011; El-Rashidy *et al.*, 2013; Sharma *et al.*, 2013, 2016; Kim *et al.*, 2016; Lambrechts *et*

al., 2017). The majority of these studies examined the effects of KD therapy on seizure control outcomes and the adverse effects of KD therapy, with the exception of one study (2 papers) that also considered cognition, behaviour and the health economics associated with the use of KD therapy (IJff *et al.*, 2016; Wijnen *et al.*, 2017). A recent Cochrane review (Martin McGill et al., 2020) examined the ten studies and their subsequent findings informed the development of Table 5. However, each publication was also reviewed by the author to ensure all possible outcomes were extracted and included in Table 5. It is necessary, however, to discuss additional prospective and retrospective studies in order to capture the breadth of our understanding of the impact of KD therapy, particularly with respect to non-seizure-related outcomes. This section will introduce some of the challenges associated with outcome selection, measurement, and reporting, and these issues will be explored in greater detail in sections 1.8 and 1.9, where the development of a core outcome set is presented as a possible solution.

Table 5. Outcome heterogeneity in 10 randomised or quasi randomised controlled trials of drug resistant epilepsy and KD therapy (14 publications)

Study	Partic-ipants	Interven-tion	Compar-ison	Follow up	Outcome	Definition or description	Results at final follow up	Method of measurement	Validated Yes/No
(Bergqvist *et al.*, 2005) **USA**	48 children 1-14 yrs	Fasted KD onset	Non fasted gradual KD onset	1, 2 & 3 months	>50% seizure reduction, seizure freedom	1) % of responders achieving > 50% seizure reduction 2) % seizure free	- 58% responders in fasted group vs 67% in non-fasted - 21% of both onset were seizure free	Seizure diary	No
					Level of ketosis	Whole blood BHB, Serum BHB, Urine acetoacetic acid, glucose. No target parameters.	- Ketosis reached more quickly with fasted onset	Serum or urine	N/A
					Adverse effects and tolerability	Weight, biochemistry, other	- Non fasted gradual protocol: less weight loss, fewer and less severe episodes of hypoglycaemia, fewer treatments for acidosis and dehydration. - No difference in vomiting between groups. - 1 withdrawal in each group unrelated to KD, 3 additional in fasted and 1 in non-fasted group	Anthropometry Serum or urine, Parent or clinician reported.	N/A
(El-Rashidy *et al.*, 2017) **Egypt**	40 children 1-3 yrs	MAD	4:1 CKD delivered via a liquid feed	3 & 6 months	Reduction in seizure frequency	Number of seizures	- MAD group: 61.5% had decreased seizure frequency (28.03+/- 21.39) - CKD group 100% had decreased seizure frequency (70.79 +/-19.26)	Seizure diary	No
					Seizure severity	As per Chalfont seizure scale	100% of both groups experienced reduction in seizure severity	Chalfont Seizure severity scale	Yes
					Adverse effects and tolerability	Weight, biochemistry, other	- Constipation, diarrhoea, and dysphagia in both groups, vomiting in MAD only. All managed conservatively - 2 withdrawals from each group	Anthropometry Serum, urine. Parent or clinician reported	N/A

Study	Partic-ipants	Interven-tion	Compar-ison	Follow up	Outcome	Definition or description	Results at final follow up	Method of measurement	Validated Yes/No
(Kim *et al.*, 2016) **Korea**	104 children 1-18 yrs	MAD	4:1 CKD	1, 3, 6 months	Seizure reduction	>50% reduction, >90% reduction. Minimum acceptable outcome difference was a 25% reduction in seizure activity	- 39% of CKD and 36% of MAD group achieved >50% seizure reduction - 37% of CKD and 30% of MAD group achieved >90% seizure reduction. - MAD group reduced to 47.9% and CKD 38.6% of baseline seizure freq	Seizure diary	No
					Seizure freedom	Absence of seizures	- 31% of CKD group and 23% of MAD group seizure free	Seizure diary	No
					Adverse effects	Biochemistry, radiological and other	- Less adverse effects with MAD - Hyperuricaemia, dyslipidaemia, metabolic acidosis occurred with similar frequency in both groups. - Hypercalcuria, renal calculi and osteopenia more common in 4:1 CKD	Serum, DeXA scan, Ultrasound	N/A
					Attrition	Reasons for discontinuation	- 38% of CKD and 41% of MAD group withdrew before 6mths. - Vomiting, diarrhoea, constipation, severe infection and lack of energy	Parent or clinician reported	No
(Kossoff *et al.*, 2007a) **USA**	20 children 3-18 yrs	MAD 10g CHO per day. (Cross over to 20g/day at 3 mths)	MAD 20g CHO per day. (Cross over to 10g/day at 3 mths)	1, 3 & 6 months	Seizure reduction	<50% improvement, 50-90% improvement, >90% improvement and seizure free	- Significantly higher likelihood of >50% seizure reduction at 3 mths when started on 10g CHO/day - At 6 mths 50% had >50% seizure reduction, 15% had >90% seizure reduction, 10% were seizure free	Seizure diary	No
					Level of urinary ketosis	Small to moderate (20-40mg/dL), High (80-160mg/dL	- 67% in both high and low ketone groups experienced >50% seizure reduction. High ketones did not correlate with improved efficacy	Urine	N/A
					Tolerability	Weight, biochemistry	Low incidence of side effects. No difference in weight changes in 10g vs 20g CHO groups. 40% experienced raised Ca:creat ratio but nil renal stones, 20% experienced constipation	Anthropometry Serum, urine	N/A

Study	Partic-ipants	Interven-tion	Compar-ison	Follow up	Outcome	Definition or description	Results at final follow up	Method of measurement	Validated Yes/No
***(Lambrechts *et al.*, 2017)** ***(de Kinderen *et al.*, 2016)** ***(IJff *et al.*, 2016)** ***(Wijnen *et al.*, 2017)** **The Netherlands**	57 children 1-18 yrs	Classical or MCT KD	Care as usual (CAU)	1.5 & 4 months + 16 months	Seizure reduction	1) proportion with at least 50% seizure reduction. 2) mean number of seizures as % of baseline. > 50% seizure reduction, >90% seizure reduction and seizure freedom	At 4 mths - 50% classified as responders >50% seizure reduction (18.2% CAU) - 27% had >50% seizure reduction (4.5% CAU) - 11.5% had >90% seizure reduction (4.5% CAU) - 11.5% were seizure free (9.2% CAU) - Mean % of baseline seizures: 56% in KD group versus 99% CAU group	Seizure diary	No
					Seizure severity	Clinician assigns a score to seizure severity based on interference with patient function	- 65.2% improved in KD group, 36.8% in CAU group	National Hospital Seizure Severity Scale	Yes
					Level of ketosis	Urine predominately No target values	- Correlation between raised ketosis and % seizure reduction at 6wks but not 4 mths	Urine	NA
					Adverse effects	Weight, height, biochemistry, other	- KD group had higher score on SIDAED for GI symptoms, peaked at 6 weeks, improving at 4 mths - clinically relevant height decrease (N=1) and weight decrease (N=1) in KD group - at 6 wks clinically significant raised total cholesterol in KD group but not 4 months	Adapted Side-Effects of Anti-Epileptic Drugs (SIDAED) Usually, adult self-reported Anthropometry Serum/urine Parent/clinician reported	In adults N/A
					Attrition	Reasons for KD discontinuation	- compliance (N=1), ineffective (N=1), ineffective and GI side effects (N=1), GI side effects (N=2), change in seizures (N=1), withdrew consent (N=1)	Parent or clinician reported	No

Study	Partici-pants	Interven-tion	Compar-ison	Follow up	Outcome	Definition or description	Results at final follow up	Method of measurement	Validated Yes/No
Contin Ued…. ***(Lamb rechts *et al.*, 2017)** ***(de Kinder en *et al.*, 2016)** ***(IJff *et al.*, 2016)** ***(Wijne n *et al.*, 2017)** **The Netherl ands**					ASM use	Reduction in dose or number	- No change in ASM at 4 mths	Clinician reported	No
					Mood	Fluctuating affective mood states: tension/anxiety, depression/dejection, anger/hostility, vigor/activity, fatigue/inertia, and confusion/ bewilderment	At 4 mths - KD group scored higher for energy than CAU group, correlated with seizure reduction - Less tension, anxiety, hostility and confusion in KD group	The Profile of Mood States (POMS)	Yes
					Impairment in daily functioning	Restrictions imposed by seizures.	- Severity of seizures reported to be lower in KD versus CAU group Negative correlation with seizure reduction – more severe the seizures were perceived the less the reduction	The Hague Restrictions in Childhood Epilepsy Scale (HARCES)	Yes
					Cognition	1) Neuropsychological ability – vocabulary 2) Neuropsychological ability - visual and motor abilities	1) KD group scored higher for word comprehension than CAU group (at baseline and 4mths though) 2) Improved reaction time activation in KD group	1) Peabody Picture Test (PPVT-III) 2) The Beery Developmental Test of VMI 2) FePsy Neuropsychological Computerised Test Battery	Yes Yes Yes
					Behaviour	1) Psychosocial adjustment in children with chronic physical illness, assessing peer relations, dependency, hostility, productivity, anxiety, depression, and withdrawal	1) KD group higher score on productivity subscale than CAU group, no correlation with seizure reduction.	1) The Personal Adjustment and Role Skills Scale - Third Edition (PARS-III)	Yes

Study	Partici-pants	Interven-tion	Compar-ison	Follow up	Outcome	Definition or description	Results at final follow up	Method of measurement	Validated Yes/No
Continued…. ***(Lambrechts *et al.*, 2017)** ***(de Kinderen *et al.*, 2016)** ***(IJff *et al.*, 2016)** ***(Wijnen *et al.*, 2017)** **The Netherlands**					Behaviour cont.	2) children and young people's behaviours, emotions, and relationships, assessing emotional symptoms, conduct problems, hyperactivity, peer relations, and social behaviour 3) four domains of behavioural and social emotional dysfunction assessed: attention-deficit and hyperactivity disorders, oppositional defiant behaviour and conduct disorders, anxiety and depression	2) Parents report no significant difference in groups on SDQ domains 3) Parents report KD group less anxious and less mood disturbed behaviour versus CAU group, no correlation with seizure reduction	2) The Strengths and Difficulties Questionnaire (SDQ) 3) The Social Emotional Questionnaire (SEV)	Yes Yes
					Child QoL	1) Quality adjusted life years for children aged 1-5 years 2) Quality adjusted life years for children aged 8+ years 3) Quality adjusted life years for children aged 6-16 years with chronic disease	- The total QALYs for the 16 mths follow-up in the two groups were 0.996 and 0.998. ie no difference between KD and CAU	1) TAPQOL (TNO-AZL Preschool Childrens Quality of Life) 2) EuroQol-Youth. 3) TACQOL (TNO-AZL Childrens Quality of Life)	Yes Yes Yes
					Parent QOL	Quality adjusted life yrs	No difference in QoL	The EQ-5D	Yes
					Cost effectiveness	All associated costs of KD for 4 months versus costs of usual care	- The benefits of KD failed to outweigh the cost of therapy. Intervention costs were E6571 for the KD group and E1548 for the control group.	Statistical analysis	N/A

Study	Partic-ipants	Interven-tion	Compar-ison	Follow up	Outcome	Definition or description	Results at final follow up	Method of measurement	Validated Yes/No
**(Neal *et al.*, 2008a) **(Neal *et al.*, 2009) **(Neal *et al.*, 2008b) UK	145 children 2-16 yrs	Classical (CKD) or MCT KD	Usual care - ASMs	1.5 & 3 months + 6, 12 months	Seizure reduction	>50% reduction in seizures, >90% reduction in seizures. Mean % of baseline seizures	At 3 mths - 38% KD group had >50% seizure reduction (6% CAU) - 7% KD group had >90% seizure reduction (0% CAU) of which N=1 seizure free - mean % of baseline seizures (62% KD group versus 136.9% CAU)	Seizure diary	No
					ASM use	Chang in dose or number of ASMs	- At 3 mths, 55% CKD and 60% of MCT KD groups could reduce ASM dose	Clinician reported	No
					Attrition	Reasons for KD discontinuation	-Parental unhappiness with KD restrictions (N=3), behavioural food refusal (N=2), increased seizures (N=1), extreme drowsiness (N=1), constipation (N=1), vomiting (N=1) and diarrhoea (N=1)	Parent reported questionnaire	No
					Adverse effects	Weight, height, biochemistry, other	- Constipation (33%), vomiting (24%), lack of energy (24%), hunger (22%), diarrhoea (13%) or Abdo pain (9%). - renal stone (N=1), treated and remained on KD - At 12 mths weight and height z scores decreased with KD treatment.	Anthropometry Serum or urine Parent or clinician reported	N/A
					Level of ketosis	Serum at follow up Daily urinalysis, target parameters not stated	- Higher ketones in CKD group which correlated with seizure control at 3 months only	Serum or urine	N/A
(Raju *et al.*, 2011) India	38 children 0.5-5 yrs	4:1 classical KD	2.5:1 classical KD	3 months	Seizure frequency	Proportion achieving <50% seizure reduction, >50% reduction or seizure freedom	- 58% of 4:1 CKD group and 63% of 2.5:1 CKD group had >50% seizure reduction - 26% in 4:1 and 21% in 2.5:1 CKD group were seizure free	Seizure diary	No

Study	Partic-ipants	Interven-tion	Compar-ison	Follow up	Outcome	Definition or description	Results at final follow up	Method of measurement	Validated Yes/No
Continued… **(Raju *et al.*, 2011)** **India**					Adverse effects	Weight, biochemistry, other	- Constipation (N=9: 5 on 4:1 and 4 on 2.5:1 CKD). - Weight loss (N=3 on 4:1 and 1 on 2.5:1 CKD) - Lower respiratory tract infection (N=2 on 4:1 and 1 on 2.5:1 CKD) - No biochemical abnormalities	Anthropometry Serum or urine Parent or clinician reported	N/A
					Attrition	Reasons for discontinuation	- 4:1 CKD group: poor seizure control (N=1), food refusal (N=1) and parents not accepting of KD (N=1). - 2.5:1 CKD group: poor seizure control (N=2) and food refusal (N=1).	Parent or clinician reported	No
					Level of urinary ketosis	Moderate; 40mg/dl Large; 80-160mg/dl	- No significant difference between 4:1 or 2.5:1 CKD. - 4:1 CKD large ketosis in all -2.5:1 CKD large ketosis in all but 1 who had moderate ketosis	Urine	N/A
(Seo *et al.*, 2007) **Korea**	76 children 0.3-16 yrs	3:1 classical KD	4:1 classical KD	3 months	Seizure reduction rate	<50%, 50-75%, 75-90%, >90% seizure reduction or seizure freedom.	- Seizure frequency was better improved on 4:1 CKD versus 3:1 CKD - 55% of 4:1 CKD and 30.5% of 3:1 CKD were seizure free - 5% of 4:1 CKD and 5% of 3:1 CKD had >90% seizure reduction - 5% of 4:1 CKD and 11.1% of 3:1 CKD had 75-90% seizure reduction - 20% of 4:1 CKD and 25% of 3:1 CKD had 50-75% seizure reduction - 15% of 4:1 CKD and 27.8% of 3:1 CKD had <50% seizure reduction	Seizure diary	No

Study	Partic-ipants	Interven-tion	Compar-ison	Follow up	Outcome	Definition or description	Results at final follow up	Method of measurement	Validated Yes/No
Cont… **(Seo *et al.*, 2007)** **Korea**					Adverse effects	Biochemical, radiological, other	- GI symptoms (nausea, vomiting diarrhoea and poor feeding) experienced by 13.9% of 3:1 CKD and 35% of 4:1 CKD group - Hypercholesterolaemia in 30.6% of 3:1 CKD and 40% of 4:1 CKD. - Bone density decreased in 13.9% of those on 3:1 CKD and 17.5% on 4:1 CKD - 5% experienced gallbladder stones (4:1 CKD), 5.6% fatty liver (3:1 CKD) and 2.8% renal calculi (4:1 CKD and 2% in 3:1 CKD)	Serum, radiological	N/A
(Sharma *et al.*, 2013) **India**	102 children 2-14 yrs	MAD	Care as usual (CAU)	1, 2 & 3 months	Seizure reduction	>50% seizure reduction, >90% reduction or seizure freedom. Mean % of baseline seizures	- 52% KD group had >50% seizure reduction (11.5% CAU) - 30% KD group had >90% seizure reduction (7.7% CAU) -10% seizure free in KD group versus 0 in CAU group - mean % of baseline seizures: 37.3% in KD group versus 100% CAU	Seizure diary	No
					Adverse effects	Biochemical, other	Constipation (46%), anorexia (18%), lethargy (6%), vomiting (10%)	Serum or urine Parent or clinician reported	N/A
					Alertness	Assessed for subjective improvement	46% of parents reported improved alertness and interaction	Parent reported	No
					Attrition	Reasons for KD discontinuation	Hyperamneomic encephalopathy (N=1), frequent chest infections (N=2), KD too restrictive (N=2)	Parent or clinician reported	No

Study	Partic-ipants	Interven-tion	Compar-ison	Follow up	Outcome	Definition or description	Results at final follow up	Method of measurement	Validated Yes/No
(Sharma *et al.*, 2016) **India**	81 children 2-14 yrs	Simplified MAD	Care as usual (CAU)	15 days, 1, 2 & 3 months	Seizure reduction	>50% seizure reduction, >90% reduction or seizure freedom. Mean % of baseline seizures.	- 56.1% KD group had >50% seizure reduction (7.5% CAU) - 19.5% KD group had >90% seizure reduction (5% CAU) -14.6% KD group seizure free (5% CAU). Mean % of baseline seizures: 47.5% KD group versus 118.9% CAU	Seizure diary	No
					Level of urinary ketosis	Trace, small, moderate, large	- All in KD group had moderate to large ketosis	Urine	N/A
					Adverse effects	Weight, biochemistry, other	- Constipation (16.6%), anorexia (12.5%), lethargy (8.3%), weight loss (5%), intercurrent infections (2.7%)	Anthropometry Serum or urine Parent or clin-ician reported	N/A
					Compliance	Difficulties parents and children faced with KD	- Reported to be very restrictive especially for vegetarians, co-habiting grandparents struggled to accept the KD for their grandchild, travelling outside of the home difficult	Parent reported	No
					Attrition	Reasons for KD discontinuation	- Food refusal (N=1) and anorexia and lethargy (N=1)	Parent or clin-ician reported	No
					Non-seizure outcome domains: alertness, activity, speech and communication, comprehension, sleep, motor skills, social interaction and behaviour.	Rate characteristics on a Likert scale ranging from much worse (1), somewhat worse (2), same (3), some- what better (4), or much better (5)	- Parents reported improved alertness (66.6%), activity level (58.3%), sleep (72.2%), social interaction (52.7%) and behaviour (52.7). - No change in motor skills, speech and communication	Parental Questionnaire	No

* All 4 publications used the same dataset (IJff *et al.,* 2016; de Kinderen *et al.,* 2016; Lambrechts *et al.,* 2017; Wijnen *et al.,* 2017) ** All 3 publications used the same dataset (Neal *et al.,* 2008a; Neal *et al.,* 2008b; Neal *et al.,* 2009). KD – ketogenic diet, mth – month, CKD – classical ketogenic diet, MCT – medium chain triglyceride ketogenic diet, MAD – modified Atkins diet, sMAD- simplified modified Atkins diet, BHB- beta hydroxybutyrate, CHO – carbohydrate, CAU – care as usual. QoL – quality of life, QALY – quality adjusted life years.

1.7.1 Seizure control

Early retrospective and prospective studies found that 50% of children treated with KD therapy saw a reduction in seizure frequency of 50% or more, with some children becoming seizure-free after just three months (Freeman *et al.*, 1998; Vining *et al.*, 1998; Coppola *et al.*, 2002). Table 5 summarises the findings of ten RCTs, all demonstrating the efficacy of KD therapy in reducing seizure frequency in childhood drug resistant epilepsy. Six of these studies compared the efficacy of different types of KDs, while the remaining four compared KD therapy to care as usual (Neal *et al.*, 2008a; Sharma *et al.*, 2013, 2016; Lambrechts *et al.*, 2017). These four studies are of particular relevance, since meta-analysis indicated that treated children are up to six times more likely to experience a 50% or more reduction in seizure activity and up to three times more likely to achieve seizure freedom (Martin-McGill *et al.*, 2020).

Focussing first on the four RCTs which compared KD to care as usual, Neal *et al's.* (2008a) RCT was the first to demonstrate that KD therapy can reduce seizure frequency among children with drug-resistant epilepsy. In total, 145 children aged 2-16 years were included; 54 of whom were randomised to treatment with classical or MCT KD. After three months of treatment, the mean percentage of baseline seizures decreased by 75% in the intervention group (62% versus 136.9% in the control group). In total, 38% of children experienced a reduction in seizure frequency of greater than 50% and 7% experienced a reduction of greater than 90%, including one child who was seizure free. In the second RCT (N=54), 29 children aged 1-18 years were randomised to the KD group and treated with either MCT or classical KD (Lambrechts *et al.*, 2017). Contrary to Neal *et al.* (2008a), response rates were higher at the four month

follow up with 50% of children experiencing greater than a 50% reduction in seizures, 11.5% experiencing greater than a 90% reduction in seizures, and 11.5% experiencing full seizure freedom. The difference in response rates may be explained by the fact that Neal's study was the first trial of KD therapy in the UK and participants may have been more drug-resistant, with KD therapy being introduced later in their clinical course. Lambrechts *et al.* (2017) suggest their higher responder rate is also attributable to their study design, where the protocol allowed replacement of participants who did not attend the first visit at six weeks.

Sharma *et al*. (2013) undertook an RCT involving 102 children aged 2-14 years, 50 of whom were randomised to the MAD KD group. After 3 months of treatment, 52% experienced greater than 50% reduction in seizure frequency, 30% greater than 90% reduction and 10% of treated children were seizure free. Later, they conducted a study with a very similar design, but instead utilised a simplified version of MAD, in which household measures were used in place of weighing (Sharma *et al.*, 2016). This study was designed to enhance access to KD therapy among families with low literacy levels and assess whether a simplified approach could be effective in treating drug-resistant epilepsy. Interestingly, similar proportions of children achieved seizure reduction despite the simplified approach, with 56.1%, 19.5% and 14.6% achieving greater than 50% reduction in seizure frequency, greater than 90% reduction or seizure freedom, respectively. However, further studies have not explored the efficacy of this simplified MAD approach, so it has not been implemented in KD treatment centres beyond this trial in India. Among these four studies, several types of KD were used (classical KD, MCT KD and MAD) and each was

successful in controlling seizures, suggesting that KD selection can be driven by an individual's needs and then fine-tuned to success.

The meta-analysis by Martin McGill *et al.* (2020) was undertaken as part of the most recent Cochrane review and the findings were graded as very low certainty evidence owing to the small sample sizes and heterogeneity within the data The issue with small sample sizes is not surprising in light of the earlier discussion identifying that only 101 patients in the UK were receiving KD therapy in 2010. While this number increased to over 700 patients in 2017, the number of patients receiving this therapy remained relatively low. Although there are no international estimates available, the number of patients treated with KD therapy is likely to be of a similar scale in each country that utilises it. It is therefore realistic to assume that sample sizes will remain small and will be unable to reach levels seen in other clinical settings. There is however room for improvement in the heterogeneity observed within trials of KD therapy, particularly with the variety seen in outcome selection and reporting. Seizure frequency outcomes were assessed in the meta-analysis as all four studies classified and reported seizure reduction in the same way. There are, however, differences in the classification used in other trials listed in Table 5, which makes comparisons difficult. For example some; omit greater than 90% seizure reduction (Bergqvist *et al.*, 2005), report only the total number who experienced any level of seizure reduction (El-Rashidy *et al.*, 2013) and introduce extra classifications of 50-75% and 75-90% seizure reduction (Seo *et al.*, 2007). In addition, seizure severity was assessed in only two studies, both of which employed different tools that are not comparable (El-Rashidy *et al.*, 2013; Lambrechts *et al.*, 2017). Similarly, only two studies considered the possibility of

changing the dose or number of ASMs used (Neal *et al.*, 2008a; Lambrechts *et al.*, 2017). There is clearly a need for a core outcome set to help reduce the inconsistency in the reporting of these seizure-related outcomes. Successful implementation would subsequently enable meta-analysis of a larger number of studies with higher quality outputs.

In light of the evidence presented in table 5, it is widely accepted that at least 50% of children will experience a reduction of 50% or more in seizure frequency, while up to 15% of children can achieve full seizure freedom (Kossoff *et al.*, 2018) There are, however, certain epilepsy syndromes and conditions that respond particularly well to KD therapy (Table 6), with higher responder rates, where 60-70% of those treated achieve at least a 50% reduction in seizures. This is evident in Kim *et al's.* (2016) RCT where a large proportion of the participants were younger and had a diagnosis of infantile spasms – a condition that responds favourably to KD therapy. In total 37% of those treated with classical KD and 30% treated with MAD KD achieved greater than 90% reduction in seizure frequency. KD therapy is therefore recommended early in the course of treatment for patients presenting with infantile spasms and the range of other conditions listed in Table 6 (Kossoff *et al.*, 2018).

For many years now, it has been widely accepted that two years is the recommended duration of KD therapy (Kossoff *et al.*, 2009, 2018). Yet few studies have evaluated the long-term efficacy of KD therapy (Dressler *et al.*, 2010; Kang *et al.*, 2011; Khoo *et al.*, 2016). These studies were mostly conducted in the early 2000's prior to the more recent RCTs. However,

Lambrechts research group did report the findings of a follow up analysis undertaken at 16 months within their RCT cohort (Wijnen *et al.*, 2017). In total, 58% of the KD group completed the 16 month follow up and 35% achieved ≥ 50% seizure reduction compared to 18% of the care as usual control group. Interestingly, the difference in seizure control between the intervention and control group was no longer significant (p=0.171) at 16 months. However, seizure severity improved further between 4 and 16 months, for both the worst seizure type and overall seizures.

Table 6. Indications for ketogenic diet therapy.
Adapted from Kossoff *et al.,* 2018.

Epilepsy syndromes and conditions for which KD therapy has been consistently reported as more beneficial (>70%) than the average 50% KD therapy response*	**Conditions in which KDT has been reported as moderately beneficial †**
• Angelman syndrome • Complex 1 mitochondrial disorders • Dravet syndrome • Epilepsy with myoclonic–atonic seizures (Doose syndrome) • Glucose transporter protein 1 deficiency syndrome (Glut1DS) • Febrile infection–related epilepsy syndrome (FIRES) • Formula-fed (solely) children or infants • Infantile spasms • Ohtahara syndrome • Pyruvate dehydrogenase deficiency • Super-refractory status epilepticus • Tuberous sclerosis complex	• Adenylosuccinate lyase deficiency • CDKL5 encephalopathy • Childhood absence epilepsy • Cortical malformations • Epilepsy of infancy with migrating focal seizures • Epileptic encephalopathy with continuous spike-and-wave • during sleep • Glycogenosis type V • Juvenile myoclonic epilepsy • Lafora body disease • Landau-Kleffner syndrome • Lennox-Gastaut syndrome • Phosphofructokinase deficiency • Rett syndrome • Subacute sclerosing panencephalitis

** Defined as >50% seizure reduction. † Not better than the average dietary therapy response, or in limited single-centre case reports.*

A further consideration is whether the positive effects achieved on KD can be sustained after the diet is weaned and a normal diet is reintroduced. This was investigated by following up (via a questionnaire) with 101 patients or their parents from a single centre, 0.8 to 14 years after they discontinued KD (Patel *et al.*, 2010). At the time of diet discontinuation, 52% were classified as responders achieving greater than 50% seizure reduction. Upon follow up 79% were similarly improved suggesting that for the majority, the seizure control gained on KD can be sustained when weaned. Ninety six percent of parents would recommend KD to others suggesting they were satisfied their child had tried the diet. However, there is a risk of recall bias given this is a retrospective questionnaire especially for those who discontinued KD many years previously. Nevertheless, the results add to our understanding of the long-term outcomes for children treated with KD, which may be helpful to share with families, together with clinical experience and local outcomes data.

1.7.2 Choice of ketogenic diet and impact on efficacy

Parents often ask which KD their child should follow to achieve the best seizure control outcomes. All versions of the KD (Figure 3) have been used to treat childhood epilepsy. However, in practice LGIT is rarely used for children as it produces very low levels of ketosis (Martin-McGill *et al.*, 2019). Instead, it is predominately used by adults who favour the flexibility it provides. The evidence to date suggests all KDs are effective at improving seizure control, why this is the case is unclear and was discussed earlier in the mechanism of KD (section 1.6.2). However, it does appear that achieving and sustaining ketosis is key regardless of the means of doing so (Neal *et al.*, 2009). The classical KD was regularly used in older studies examining the efficacy of KD

(Freeman, Freeman, & Kelly, 2000) possibly because it is the oldest and most well-known KD or perhaps its rigidity and extremely low carbohydrate levels suggested better ketosis may be achieved. The clinical and metabolic effects of three KDs; 30% MCT KD, 60% MCT KD and a 4:1 ratio classical KD were investigated in 55 children and 4 adults (Schwartz *et al.*, 1989) and demonstrated that all three diets were equally efficacious in controlling seizures for children aged 15 years and under. However, the study was not randomised, and results were obtained following only three weeks of KD treatment, which was an unusually short treatment period, as most trials last from three to six months.

More recently, six trials (Table 5) have assessed the efficacy of different versions of KD therapy (Bergqvist *et al.*, 2005; Kossoff *et al.*, 2007; Seo *et al.*, 2007; Raju *et al.*, 2011; El-Rashidy *et al.*, 2013; Kim *et al.*, 2016). Generally, it appears that a lower ratio classical KD (2.5:1 and 3:1) and modified Atkins KD are less efficacious with lower proportions of children achieving reduced seizure frequency of greater than 50%, 90% and seizure freedom. However, we need to be cautious in our interpretation of these results as the difference in responder rates may equate to just 1-2 participants. In reality, in clinical practice, a child would not be restricted to remain on a lower ratio classical KD or MAD protocol for 3 months if their clinical outcomes were suboptimal. Instead, the KD would be introduced at a low ratio and the KD prescription would be fine-tuned as needed to increase the ratio or percentage total fat in order to optimise ketosis and the potential for optimal improvement in seizure control. Neal et *al.* (2008a; 2008b;2009) utilised this approach in their cohort, each participants KD prescription was individually tailored and fine-tuned, as opposed to a protocol

limiting the prescription to a specific ratio or maximum carbohydrate intake. In total, 145 children with drug resistant epilepsy were randomised to classical or MCT KD and 94 completed the trial (N=45 classical KD, N=49 MCT KD). There was no significant difference between the number of children achieving greater than 50% or 90% seizure reduction suggesting both MCT and classical KD can be used effectively.

The efficacy of classical KD has also been compared with the modified Akins diet in a randomised trial of 103 children (N=51 classical KD, N=53 MAD) with follow up at three and six months (Kim *et al.*, 2016). Interestingly, the rate of seizure freedom was demonstrated to be significancy higher in infants aged one to two years treated with classical KD (53% versus 20% for MAD), suggesting the classical KD is in fact more efficacious among younger infants. As a result, clinical guidelines suggest that classical KD therapy should be considered as a first line approach in those under the age of two years (van der Louw *et al.*, 2016). However, for children, the classical KD, MAD or MCT KD can be used and fine-tuned to support optimal efficacy (Kossoff *et al.*, 2018).

1.7.3 Adverse effects of ketogenic diet therapy

In table 5, all ten trials discuss the adverse effects associated with KD therapy for children. These are typically classified as short and longer-term side effects. During the introductory phase of KD therapy, patients may experience shorter term gastrointestinal symptoms such as vomiting, diarrhoea, constipation, and abdominal pain, as well as lethargy. The incidence is often higher in the classical KD (Seo *et al.*, 2007; Neal *et al.*, 2009) as a higher percentage of total fat is consumed. In contrast a low incidence of side effects was reported using a

more relaxed MAD protocol (Kossoff *et al.*, 2007a). In most cases, these short-term effects can be resolved by dietary changes (Neal *et al.*, 2008a) and rarely require a child to discontinue treatment for KD. This was demonstrated among 41 children treated with MAD KD; where 47.5% complained of lethargy and 40% of constipation on day 15. However, this decreased to 8.3% and 16.6% respectively after 3 months of treatment (Sharma *et al.*, 2016).

Longer term side effects of KD therapy include dyslipidaemia (Seo *et al.*, 2007; Kim *et al.*, 2016; Lambrechts *et al.*, 2017), metabolic acidosis (Bergqvist *et al.*, 2005; Kim *et al.*, 2016), renal calculi formation (Seo *et al.*, 2007; Neal *et al.*, 2008; Kim *et al.*, 2016) and reduced bone mineral density (Seo *et al.*, 2007; Kim *et al.*, 2016). Clinical guidelines recommend that children on KD therapy are very closely monitored in order to reduce the risk of these issues occurring and to initiate appropriate treatments quickly if there is evidence of deranged biochemical or radiological investigations (Kossoff *et al.*, 2018). The benefit of regular close monitoring was highlighted when 40% of children treated with MAD KD presented with an elevated urinary calcium:creatinine ratio on follow up (Kossoff *et al.*, 2007). This was an early indication of increased risk of renal calculi formation, and subsequent treatment with potassium citrate prevented further complications. Lambrechts *et al.* (2017) reported a trend often seen in clinical practice where blood lipids are initially deranged at the 6-12 week follow up, but then normalise again at the 6-12 month follow up as the body adjusts to fat energy utilisation.

On KD therapy, growth parameters are closely monitored in order to prevent weight loss or weight gain if the energy provision is not adequate. The dietitian

can recalculate and adjust the KD prescription as needed to support adequate weight gain. Neal *et al.* (2008b) demonstrated at 12 mth follow up at that weight and height z-scores had decreased in treated children but there was no difference between those treated with classical KD or MCT KD. Anorexia is reported in both of Sharma *et al's* trials (2013; 2016), however the characteristics of this diagnosis or degree of weight loss or malnutrition is not shared. While weight z-scores tend to normalise when KD therapy is discontinued, height trajectories do not. A survey found that 40% of 101 children treated with KD in the past, were still below the 10^{th} percentile of height for age (Patel *et al.*, 2010). High levels of ketosis and metabolic acidosis are thought to negatively influence growth in this population.

Although there are many similarities between studies and commonly reported issues, there are also outliers which may not be directly related to KD therapy. For example lower respiratory tract or intercurrent infections are reported in three studies (Raju *et al.*, 2011; Sharma *et al.*, 2013, 2016), however this has not been replicated elsewhere. As there is no physiological reason why KD therapy could cause infections, it is likely that all 'out of the ordinary' issues encountered while receiving KD therapy were recorded and reported as adverse events in these trials.

Although adverse effects are similar across trials, it is not possible to reliably compare the incidence across trials, and meta-analyses cannot be performed due to the variety of methods used to measure and report outcomes. In the case of biochemical investigations, reference ranges may not always be available and may vary from centre to centre and country to country. There is a

considerable variation in the frequency of renal ultrasonography (to monitor kidney stones) and Dexa scanning (to monitor bone mineral density). In many cases, identification of adverse effects relies on clinician or parent reports, which are subject to recall bias. Furthermore, the data presented here are somewhat open to interpretation as the included trials describe the adverse effects of KD therapy under categories of "tolerance", "adverse effects", and "attrition." The tolerability issues as well as some of the reasons why participants withdraw from a study may also be considered as adverse effects of KD therapy. This inconsistency in nomenclature of outcomes is challenging for researchers and clinicians to interpret, reinforcing the need for a core outcome set to improve consistency.

1.7.4 Cognition and behaviour

For parents, cognitive improvement is one of the main motivators to start and continue a KD (Farasat *et al.*, 2006), yet few studies explore the potential for KD therapy to improve cognition. In existing studies, cognitive abilities have primarily been assessed by subjective reports from parents, which assess attention, alertness, adaptability to environments, concentration, learning, language, and general development. A systematic review identified 33 studies which assessed cognition however these included both paediatric and adult studies (van Berkel, IJff and Verkuyl, 2018). In total, 29 studies reported on subjective cognitive outcomes derived from clinician, parent or patient reports and only 13 studies used objective standardised neuropsychological tests. However, there was a broad range of tests used which limits the ability to easily compare results. The authors concluded that subjective assessment of cognition identified improvements in alertness, global cognition and attention,

however only improvements in alertness were confirmed by objective neuropsychological testing. Arguably parents may be biased and subconsciously over report the impact for their child. However, it is possible that the neuropsychological tests used are not sensitive enough to pick up the subtle improvements for children with complex neurological deficits.

One RCT evaluated the effect of KD on cognition and behaviour among 50 children, where 28 were randomised to the KD group (IJff *et al.*, 2016). A broad range of mood, behaviour and neuropsychological tests were used including The Profile of Mood States (POMS), The Personal Adjustment and Role Skills Scale (PARS), The Strengths and Difficulties Questionnaire (SDQ), The Hague Restrictions in Childhood Epilepsy Scale (HARCEs), The Social Emotional Questionnaire (SEV) Peabody Picture Test (PPVT-III) (Dutch version), The Beery Developmental Test and finally subset tests from the FePSY 'The Iron Psyche'. At the four month follow up, those in the KD group were reported to be more active (FePsy), more productive (PARS), less anxious (SEV and POMS), less tense, hostile and confused (POMS). Improvements in mood, anxiety and productivity were all independent of improved seizure control. Notably though this study excluded participants with severe behavioural difficulties despite the study assessing the impact of KD on these outcomes. Differences were noted in baseline mood and behaviour scores, but significance values were not presented to fully assess these.

Sharma *et al.* (2016) evaluated alertness, behaviour, and social interactions in an RCT where 41 children were randomised to treatment with a simplified modified Atkins protocol. All factors were reported as improved in the treatment

group; however, the findings are limited by the fact that parental ratings were based on a 5-point Likert scale ranging from much worse to much better and not based on validated assessment tools. Similarly, Nordli *et al.* (2001) used a parent completed Likert type scale to assess infants (N=39) cognition when treated with classical KD. Authors report the majority of parents reported improvements in attention, alertness, activity levels and social interactions, however the specific percentage of improved patients was not reported. In contrast, cognition was assessed in a prospective study of 52 children with drug resistant epilepsy treated with classical KD using the Gesell Developmental Scale (Wu *et al.*, 2018). Improvements in cognition including language were reported in 23 children, but the gains experienced were too small to be of statistical significance.

In summary, KD generally appears to improve cognition and behaviour, although perhaps less so when objective validated tests are used compared with parental reports. At present it is challenging to establish if the observed cognitive benefits are as a direct result of KD therapy or an indirect consequence of other improvements for the child such as seizure reduction or ASM reduction.

1.7.5 Sleep

As discussed earlier, epilepsy negatively impacts sleep, yet this outcome has not been appropriately examined in any of the RCTs in Table 5. Only Sharma *et al.* (2016) attempted to examine this and reported improved sleep among 72% of children treated with a simplified MAD KD. However, sleep was assessed using a parent reported five-point Likert scale ranging from much worse to much

better, at one time point and not compared to baseline pre-KD results, so the results are open to bias and questionable. Only two other studies have formally examined the impact of KD on sleep. Firstly, sleep patterns were evaluated in 18 children with drug resistant epilepsy using ambulatory polysomnographic recordings at baseline pre-KD and then after 3 and 12 months of treatment (Halböök, Lundgren and Rosen, 2007). This direct method of measurement reduced the risk of bias, often inherent in parental reporting or observations. Daytime sleep significantly decreased and night-time sleep quality improved at 3 months (N=18) and 12 months (N=11). Increased rapid eye movement sleep was significantly correlated with improvement in quality of life (QoL) at 3 months on KD. However, QoL was assessed using a visual analogue scale and not a validated tool. A further study assessed sleep quality in 14 children with epilepsy using the Pittsburgh Sleep Quality Index and the Child Sleep Habits Questionnaire, both completed by their mothers (Ünalp *et al.*, 2021). Small improvements in sleep quality were reported in 50% of children after 3 months of KD treatment. However, 35.7% experienced deterioration in their sleep but the reasoning why is unclear. Anecdotally parents often report that their child's sleep is improved on KD therapy, so it is surprising that this outcome is not assessed more often. A robust approach such as Halböök *et al*. would not be feasible in a clinical setting and would prove to be time-consuming and labour-intensive to replicate in clinical trials testing multiple outcomes of KD therapy. However, the Child Sleep Habits Questionnaire may be a useful, feasible measure to use.

1.7.6 Quality of life

Just one systematic review has been undertaken assessing the impact of KD therapy on QoL for families (Poelzer *et al.*, 2019), however, it is of poor quality. The authors lacked experience with KD therapy, as evidenced by their misinterpretation of the clinical management. This then cast doubt on the trustworthiness of the interpretation of extracted data and recommendations that followed. Studies were included which did not directly measure QoL so improvement could only be inferred when other factors improved such as seizure control, cognition, sleep and behaviour. In addition, there was an unexplained four-year delay between the literature searches and publication. The authors were constrained by the inconsistent measurement of QoL outcomes, a challenge which has prevented further attempts at a systematic review. Only one RCT (Wijnen *et al.*, 2017) has attempted to assess QoL in children treated with KD therapy by means of a utilities assessment using the TNO-AZL Preschool Childrens Quality of Life (TAPQOL) and Childrens Quality of life measures (TACQOL). They concluded that there was no significant difference in quality-adjusted life years (QALYs) between the group treated with KD therapy and the usual care group at 4 or 16 months. However, the study was underpowered, and unfortunately, the authors did not investigate a relationship between the level of functioning and QoL. A significant change in QoL is needed to see a subsequent improvement in QALYs. However, it is possible that more discrete changes in QoL may have been experienced by those treated with KD which may have been impactful for the child and family. This was apparent in Bruce *et al.* study (2017) where twelve parents rated their QoL (0-10 poor to very good QoL) prior to their child commencing KD therapy and at 3 ,6 and 12 months follow up. QoL improved on KD for the majority of

families with only one family remaining static. Parents described this improvement as; their child smiling and being happier, gaining developmental progress, seizure reduction and increased alertness.

Clearly, few attempts have been made to directly assess QoL for children treated with KD therapy and further research is needed. In the interim, quality of life is assumed to improve as a result of positive improvements in both seizure and non-seizure related outcomes including seizure freedom, seizure reduction, cognition, behaviour or sleep. Several factors may account for the limited QoL data available, including the fact that many QoL assessment tools are long, complex, and require repeated completion. As such compliance among parents can be challenging. Assessment tools including the Paediatric quality of life Inventory (Varni, Seid and Rode, 1999) and Quality of Life of Childhood Epilepsy (Sabaz *et al.*, 2000) assess heath related quality of life and are used in research and clinical settings. However, anecdotally parents report that that these often reinforce what their child cannot do rather than what they can. This may be due to the fact that these tools are developed for a wider range of childhood epilepsies than the more complex epilepsies and encephalopathies that frequently require adjuvant KD therapy. Therefore, they may not capture the often small gains that children with complex needs achieve as a result of KD therapy. This was one of the motivating factors for Bruce *et al.* (2017) to develop a shorter bespoke tool for children with epilepsy treated with KD therapy. Despite its unvalidated nature, it does contribute to a better understanding of parents' perceptions of factors that influence quality of life for their children. Some are so specific and individual that they would not likely be noted as improvements in existing validated tools, yet they have a profound

impact on both the child and parents QoL. According to one parent, getting their child out of nappies would allow them to go out as a family, thus improving their quality of life. Another parent wanted to see their child react when blood was drawn, as this would indicate that they were aware of what was happening to and around them, which would mean a great deal to their parents. It is interesting to note that a parent-reported health-related quality of life measure was developed for children receiving KD therapy called the KetoQoL (Barwick *et al.*, 2017). There is no evidence, however, that it has been used in any subsequent studies and the authors have not shared any further work. This is surprising as it underwent a robust development process which included interviews with parents to inform the development of the tool, pilot testing with parents followed by exploratory factor analysis and updates to the tool. However, a sample size of 90 participants was estimated to be necessary for the validation of the tool, significantly greater than the 18 parents who piloted the study.

This section has highlighted that clinical trials of KD therapy for childhood drug resistant epilepsy primarily assess seizure reduction and freedom, with adverse effects of KD and the reasons for KD discontinuation as secondary outcomes. Functioning outcomes such as cognition, behaviour, sleep and quality of life are less frequently evaluated. In keto clinics, parents often list these non-seizure related outcomes as important, yet their views on outcomes have not yet been formally assessed. The CORE-KDT study seeks to address this issue by conducting interviews with parents to inform the development of the core outcome set.

1.8 Challenges with outcomes in existing trials of drug resistant epilepsy and ketogenic diet therapy

Health outcomes refer to the changes that occur as a result of interventions. In clinical trials, interventions are evaluated based on the effects they have on pre-defined outcomes, so ensuring the right outcomes are measured is crucial. The primary outcome is an integral component of the research question, and many trials will also measure secondary outcomes to evaluate other beneficial or harmful effects of the treatment under investigation (Skivington *et al.*, 2021). Both primary and secondary outcomes should be clearly stated in the study protocol and subsequent reports to enhance transparency. When treating childhood epilepsy, NICE guidance (2012) recommended seizure freedom as the primary outcome and seizure reduction, cognitive function and quality of life as secondary outcomes. Yet as has been demonstrated in section 1.7, published clinical effectiveness trials typically assess seizure reduction and freedom as the primary outcomes with the adverse effects of KD treatment and attrition assessed as secondary outcomes. To date, few studies have assessed cognitive function and QoL (Table 5).

When designing a clinical trial, the chosen outcomes will have a direct impact on how the results can be translated into clinical practice and policy for the benefit of patients. Three critical issues hamper the translation of research findings into benefit for patients;

(i) failure to include outcomes which are meaningful to patients or relevant to clinicians

(ii) using a wide range of outcomes and definitions limits comparison of results and meta-analysis

(iii) selective reporting of outcomes increases the risk of outcome reporting bias.

Although the ten trials included in Table 5 represent the best available evidence, they are still constrained by methodological issues. The evidence presented in section 1.7 indicated that (i) and (ii) are critical issues in this clinical area. Firstly, trials almost exclusively assessed seizure control, adverse effects of KD therapy, and attrition, with only one study assessing quality of life, cognitive and behavioural functioning. Possibly, this focus on seizure-related outcomes and adverse effects may not capture the breadth of outcomes that are meaningful to parents. As no trial reported Patient and Public Involvement and Engagement (PPIE) as part of its study design, parents' views were likely not considered or recorded. Secondly, due to the wide range of definitions, classifications, and ways of measuring outcomes, it is difficult to perform meta-analyses and compare the results of different studies. Instead, it is necessary to describe the results through narrative synthesis and descriptions of the outcomes which limits the quality and generalisability of the evidence.

To date, Martin-McGill *et al.* (2020) have conducted five updates of their Cochrane systematic review of KD therapy, but the meta-analysis of four studies comparing KD therapy to usual care, described in section 1.7 was the first they have been able to undertake. They intended to conduct three additional meta-analyses examining KD in comparison with; other dietary interventions, other non-dietary interventions and finally one type of KD compared with another. However, these were not feasible due to methodological and clinical heterogeneity. Since there are no RCTs comparing

KD therapy with non-dietary interventions, it is not surprising that this meta-analysis was not possible. There are, however, six trials that compare at least one KD with another, so while the data is available, variations in measurement and reporting of outcomes prevented a meta-analysis of the results. Among the main issues were differences in intervention (type of KD used), outcomes assessed, instruments used to measure outcomes, and missing data, all of which led to the evidence quality being downgraded to low or very low in the Cochrane review. The NICE evidence committee review for the most recent update to the guidance for epilepsies (NG217) concluded similar (NICE, 2022b).

A narrative synthesis was required for cognitive, behavioural, and quality of life assessment due to the variety of approaches used to assess these outcomes, and subsequently they were also downgraded for imprecision. This Cochrane review reinforces the issue of heterogeneity in outcome measurement and reporting and how it limits meta-analysis and synthesis of evidence. There was less concern about selection bias as five trials were assessed to be of low risk, and five held uncertain risk because the protocols were not available. Martin McGill *et al.* (2020) concluded that a core outcome set would help to improve consistency in outcome selection and associated definitions. The CORE-KDT study aimed to address this need.

1.9 A core outcome set as a solution

A core outcome set defines the minimum outcomes that should be consistently measured and reported in future clinical trials in a specific area of healthcare for individuals with a particular health condition and or type of intervention (Kirkham *et al.*, 2016; Williamson *et al.*, 2017). Researchers and clinicians are not limited

to measuring just these core outcomes. They are also free to measure others that are relevant to their study or setting, in addition to the priority outcomes defined in the core outcome set. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative was founded in 2010 to facilitate and promote the development and use of core outcome sets across all health areas. COMET maintains a public registry of all core outcome development studies (COMET Initiative, no date) and works to ensure that core outcome sets are endorsed for use by trial funders, trial registries, regulatory authorities, systematic review groups and guideline developers. The development of core outcome sets has increased rapidly in recent years, with the majority being developed for use in research settings (Gargon *et al.*, 2018).

Core outcome sets can reduce the heterogeneity of outcomes in clinical trials and enable more effective comparisons of results, facilitating meta-analysis and the development of clinical guidelines (Tugwell *et al.*, 2007). Furthermore, publication bias and duplication of research are minimised (Williamson *et al.*, 2012a; Williamson *et al.,* 2012b). In addition to guiding outcome selection in research, a core outcome set can inform routine data collection, audit and service evaluation in clinical practice. Yet only 12% of existing core outcome sets are used both for research and clinical care (Gargon *et al.*, 2018). Core outcome sets are developed using consensus methods in partnership with major stakeholders, including experts in the clinical area, patients and parents where appropriate (Williamson *et al.*, 2017). A core outcome set developed in conjunction with parents, health professionals and researchers would identify the most important clinically relevant outcomes to measure for childhood drug resistant epilepsy treated with KD therapy and ensure outcomes relevant to all

are considered. It is likely that seeking the views of a broader range of stakeholders would address the imbalance we see in the predominant focus on seizure versus non-seizure related outcomes.

Successful examples of core outcome sets in other clinical areas include Outcome Measures in Rheumatology (OMERACT) (Boers *et al.*, 2014), The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) (Turk *et al.*, 2003) and Harmonising Outcome Measures in Eczema (HOME) (Schmitt *et al.*, 2015). OMERACT is perhaps one of the most notable examples of successful core outcome set development, where work first started in 1992 and today it is a large global organisation focussed on improving outcomes for patients with autoimmune and musculoskeletal disease. A key learning point from their success is the inclusion of patient research partners in core outcome set development.

A core set of outcomes has not yet been developed for drug resistant childhood epilepsy treated with KD therapy, so it is timely to address this. Crudginton *et al.* (2019) recently developed the CHOICE (core health outcomes in childhood epilepsy) core outcome set for Rolandic childhood epilepsy. This is often described as benign Rolandic epilepsy as most children outgrow the condition by puberty. In contrast to complex drug resistant epilepsy, Rolandic epilepsy can be well managed with ASMs. Outcome criteria have also been established to measure the effectiveness of ASMs in childhood epilepsy (Murugupillai *et al.*, 2018). Similar to the CHOICE study, this study is not specific to children with drug-resistant epilepsy and does not address KD therapy. Whilst there are likely to be some shared outcomes, it is expected that our proposed set will capture

additional outcomes relevant to the complexity of drug resistant epilepsy, the severity of associated co-morbidities and monitoring of KD therapy use. These might include; hospital related admissions, financial burden of KD therapy, ketosis, adverse side effects and growth.

1.10 The CORE-KDT project

1.10.1 Aims and objectives

The overall aim of this project is to develop a core outcome set for drug resistant childhood epilepsy treated with KD therapy. The findings will also support the selection and reporting of outcomes in clinical practice via routine data collection, audit or service evaluation. It is advantageous for routine clinical data and trial data to be consistent, particularly in this clinical area where one unique treatment (KD) is under investigation. Figure 5, maps the aims and objectives against the phases of the CORE-KDT study and associated research questions.

Research Question

What outcomes should be included in a core outcome set for drug resistant childhood epilepsy treated with ketogenic diet therapy?

The key objectives are:

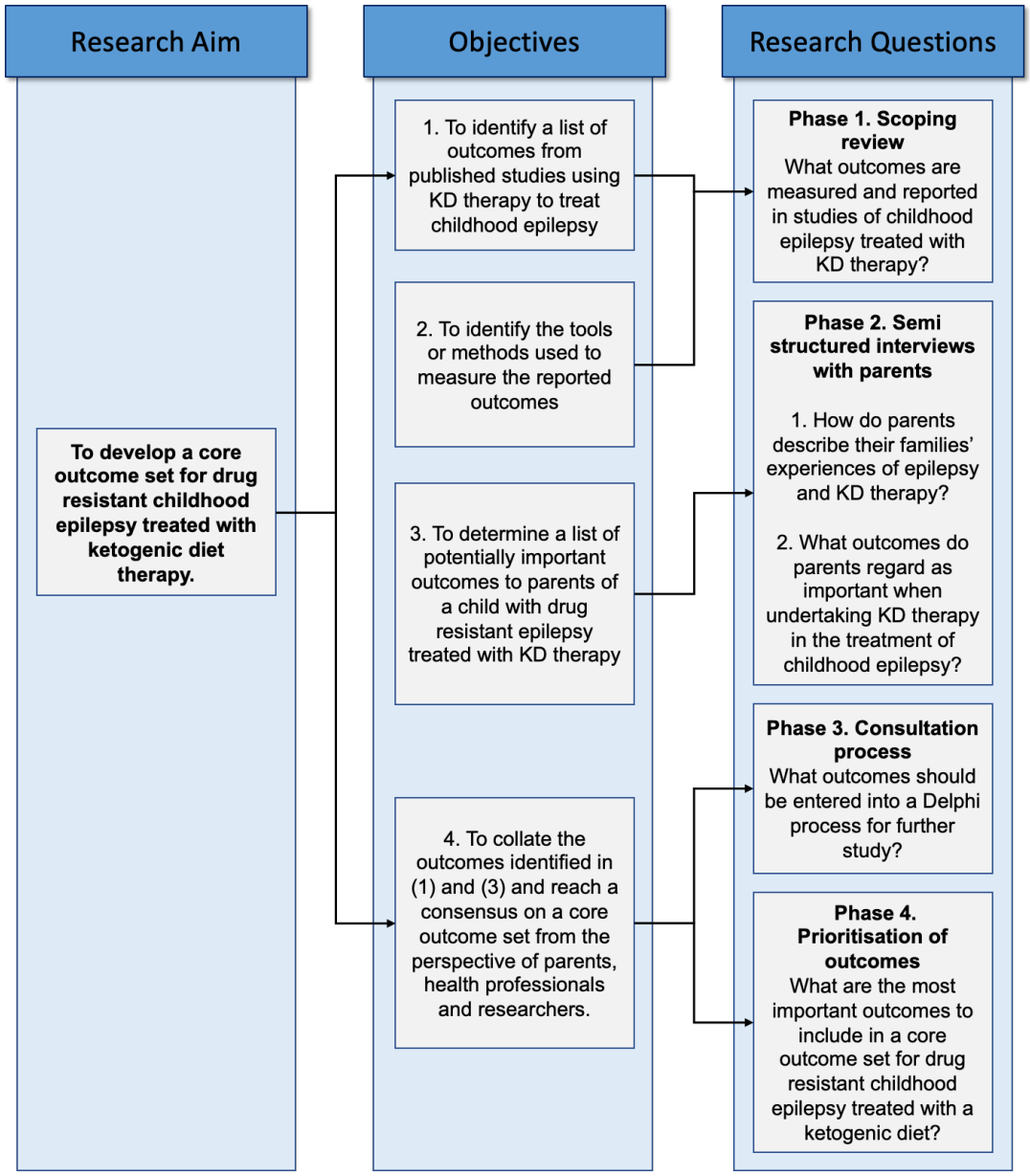
(1) to identify a list of outcomes from published studies using KD therapy to treat childhood epilepsy

(2) to identify the tools or methods used to measure the reported outcomes

(3) to determine a list of potentially important outcomes to parents of a child with drug resistant epilepsy treated with KD therapy

(4) to collate the outcomes identified in (1) and (3) and reach consensus on a core outcome set from the perspective of parents, health professionals and researchers.

Figure 5. Outline of the CORE-KDT study aims and objectives



1.11 Thesis outline

This thesis examines the challenge of outcome selection for children with epilepsy treated with KD therapy and offers a core outcome set to guide outcome selection in both research and clinical practice, encompassing the views of parents, health professionals and researchers. The development of the CORE-KDT core outcome set is presented in seven chapters. The purpose of this chapter has been to provide an overview of childhood epilepsy and KD therapy, setting out the challenges associated with the outcomes in this clinical area and how a core outcome set may assist in addressing these. The protocol for this mixed methods study is presented in chapter two, which details the methodological decisions taken and the justification for these. A scoping review is described in chapter three, which identified all outcomes reported in previous studies and the methods used to measure them, both validated and unvalidated.

Chapter four is the first of two qualitative chapters arising from semi structured interviews with parents. Here the focus is on exploring and understanding parents' experiences of their child's epilepsy diagnosis, the day-to-day management of KD therapy and the impact this has on the wider family. These discussions provided valuable insights into the reasoning underpinning parents views on outcomes in chapter five. Here the aim was to explore if the outcomes identified in the scoping review adequately reflected the outcomes parents considered important for their children. If new outcomes were identified they were added to the list of scoping review outcomes, ready to undergo a consultation process with the study advisory group and research team, described in chapter six. The list of outcomes was consolidated, and lay

descriptors agreed in order to populate a two-round online international Delphi survey. The Delphi survey and stakeholder consensus meeting results are shared, illustrating the prioritisation of outcomes for inclusion in the finalised CORE-KDT core outcome set. The study findings are discussed in chapter seven in terms of their implications for future research and clinical practice. Dissemination and implementation of the core outcome set will be considered, and finally the planned future work outlined. In order to address the challenge of measuring the agreed outcomes, an international expert group has been convened to identify the most appropriate outcome measurement instruments.

Chapter 2: Methodology

Preface

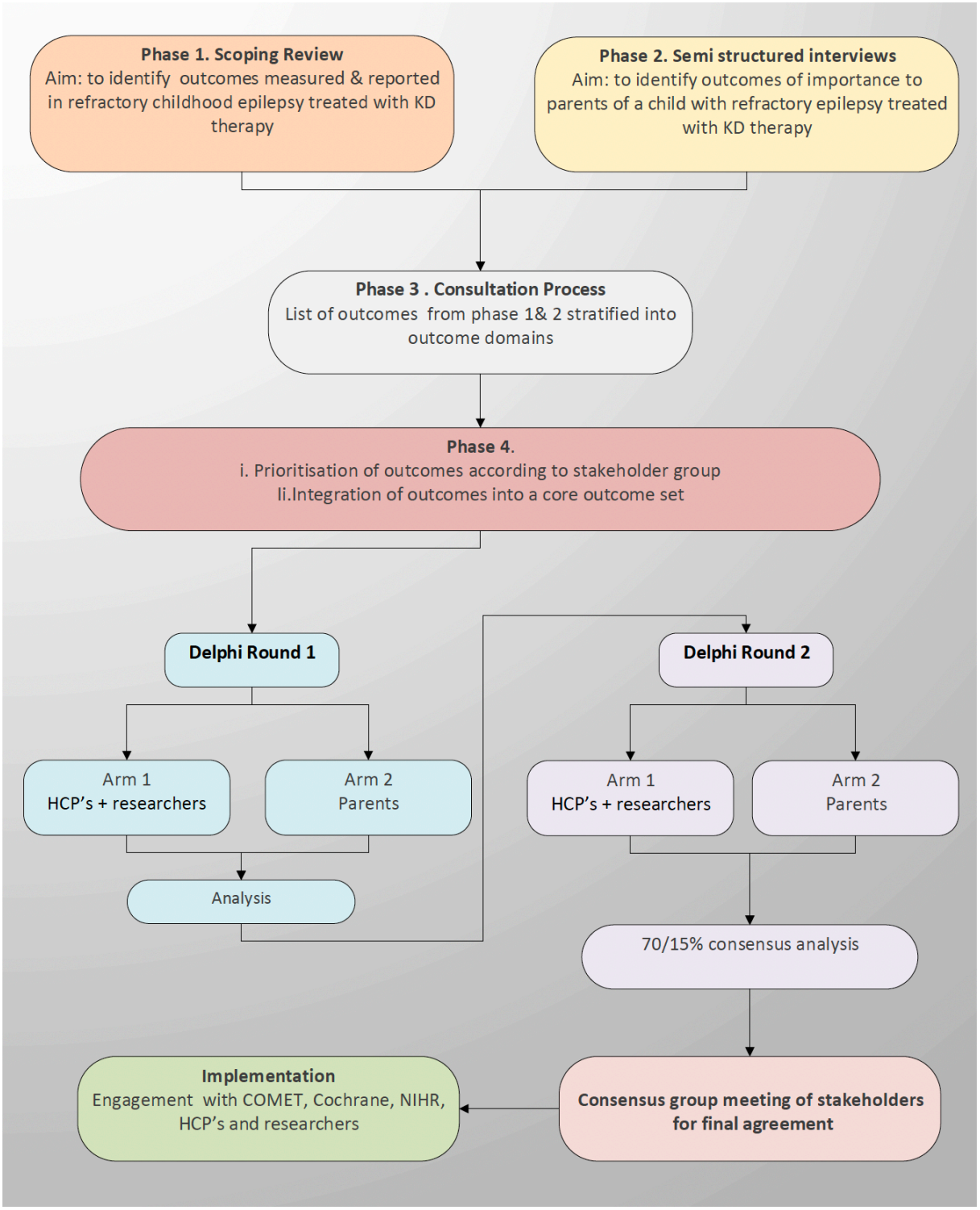
Chapter 2 describes the methodological approaches and decisions taken when planning this mixed-methods study. The scoping review protocol was published *a priori* in The Joanna Briggs Institute (JBI) Database of Systematic Review and Implementation Reports (Carroll *et al.*, 2019). The CORE-KDT study protocol was written *a priori* and published (open access) in BMC Trials (Carroll *et al.*, 2022a). Both published manuscripts are available in Appendix A and B. Sections of this chapter have been taken directly from the edited manuscripts. The researcher prepared the original draft of both protocol manuscripts, which were edited by the supervisory team and then subject to peer review.

2.1 Overview of the study design

Mixed-methods research combines qualitative and quantitative research approaches in order to enhance the breadth and depth of understanding and corroboration (Johnson and Onwuegbuzie, 2007). CORE-KDT, a mixed-methods study, is underpinned by sequential explanatory design where qualitative data helped to explain or build upon quantitative results (Creswell and Plano Clark, 2007). The four phases of the study are outlined in Figure 6. In phase one, quantitative data was collated via a systematic scoping review which identified a list of all possible relevant outcomes and tools used to measure these. In phase two, qualitative data collected via semi-structured interviews with parents helped to enrich and elaborate on the quantitative results collected in phase one. Participants in the qualitative phase are purposely selected to best address the qualitative research question. In the

CORE-KDT study, this was parents or carers to a child with epilepsy treated with KD therapy. The two phases are connected in the intermediate phase three of the study, where the outcomes from phases one and two were combined and grouped according to the COMET taxonomy (Dodd *et al.*, 2018). The rationale for this approach is that the scoping review provided a general understanding of the outcomes measured and reported in the literature. In light of the fact that this research was conducted by researchers and health professionals, it is reasonable to assume that these are outcomes that they consider valuable. Qualitative data added depth by identifying new outcomes and exploring parents' views on the outcomes that were important to them. Phase 4 prioritised the most important outcomes from two stakeholder groups via a two-arm anonymous remote international Delphi survey. Stakeholder group 1 included health professionals, researchers, charity and industry representatives and group 2 included parents. The findings were integrated into a core outcome set at a consensus group meeting with representation from both stakeholder groups. The CORE-KDT core outcome set will be implemented via engagement with triallists, clinicians and organisations like COMET, Cochrane and the National Institute of Health Research.

Figure 6. Overview of the CORE-KDT study



2.2 Theoretical framework

Collins and Stockton (2018, pg 2), describe a theoretical framework as being at the intersection of (i) our existing knowledge and previously formed ideas about the phenomena of interest, (ii) the researchers' epistemological dispositions and finally (iii) a lens and a methodically analytic approach. Essentially, it is a dynamic state with potentially differing ideas, views, and concepts. Review of the literature in Chapter 1 helped to deepen understanding of existing knowledge in this clinical area and inform the assumptions made in the CORE-KDT study. It is essential that researchers maintain reflexivity in their work, but especially in qualitative research, where they must consider their own epistemological and ontological perspectives (Macbeth, 2001). Through this process, researchers are encouraged to reflect on their conclusions from the research in order to enhance transparency and quality. It could be argued that a pragmatism paradigm would suit the mixed methods nature of this study. It emphasizes a flexible approach and worldview, allowing the researcher to use whatever works in the study to answer the research questions without worrying about the positivism versus interpretivism dichotomy (Alise and Teddlie, 2010). Pragmatism recognises that the reality is constructed by individuals (interpretivist view) but these are a reconstruction of something relatively stable that exists (positivist view). Choosing to follow a pragmatist approach would, however, be driven solely by the mixed methods nature of the study rather than my epistemological beliefs.

The researcher believes that the world is a dynamic, flexible and constantly changing reality (interpretivist paradigm), so to understand it we have to speak with people to understand their subjective perspectives (Guba and Lincoln, 1989). Overlap exists with the constructivist paradigm where knowledge is

socially constructed, and everyone participates in the construction of that knowledge, including the researcher (Kivunja and Kuyini, 2017). The researcher has worked in this clinical speciality for 12 years and supported many families with KD therapy. As the idea developed for the study, it was evident that this pre-existing knowledge would be valuable, as it would provide insight into the challenges faced with outcomes and enable the researcher to influence change with the study findings. However, there was concern that the same experiences might bias the work; it was challenging to identify how one could be unbiased and impartial when interviewing parents and completely remove themself from past experiences. The lack of experience in qualitative methods largely led to these concerns. As time and reading progressed, it became apparent that this pre-existing knowledge could be used positively and transparently by co-creating with the respondents. This has been described as mission orientated research, where the co-creators (parents, researchers and health professionals in the CORE-KDT study) work together to solve a problem (Mazzucato, 2018).

The final element of Collins and Stockton's definition of a theoretical framework is the lens and analytic methodology. The CORE-KDT study employs mixed methods, using deductive and subjective inductive analysis approaches to achieve the aim of developing a core outcome set. Axiology considers the philosophical approach to making ethical decisions in research (Finnis, 1980) and the values that will guide the project and the researcher. Principally, my values aligned with a value-laden axiology where the research findings benefits children with epilepsy treated with KD therapy and their parents. Furthermore, health professionals and researchers benefit from guidance on outcome selection and reporting (Kivunja and Kuyini, 2017). The remainder of this

chapter describes and justifies the methodological decisions taken within the study. Section 2.6.4-2.6.6 addresses the theory and philosophical underpinnings of the qualitative phase of the study.

2.3 Patient and Public Involvement and Engagement (PPIE)

Patient and public involvement is defined as research which is carried out with or by members of the public rather than to, about or for them (National institute of Health Research NIHR, 2021). The aim being to work collaboratively and involve the public in shared decision making. Patient and public engagement focuses on helping to raise awareness and share research knowledge and findings so it can be particularly impactful in the dissemination phase of a study. Patient and public involvement in clinical trials was examined via a systematic review of 27 reviews and the benefits of public involvement were reported following a thematic analysis of 20 of the included reviews (Price *et al.,* 2018). It was reported that PPI partners brought lived experience and knowledge of conditions and interventions. They helped to expand the perspectives of the research team, influenced protocol development, set patient focussed research questions and objectives, supported user testing, enhanced interview schedules and the dissemination of the study findings. Interestingly, PPI contributions were found to increase recruitment and retention to studies and improve the relevance and value of research outputs and material.

The motivations for including meaningful public involvement and engagement in this study were to gain deeper insights from the lived experiences of lay research partners and parents in order to positively influence the development and dissemination of the core outcome set. This was achieved in three ways; (i) by collaborating with two lay research partners from a large charity, (ii)

undertaking a PPI consultation with parents to inform the design of the study and (iii) via the establishment of a Study Advisory Group (SAG) with parent, charity, and health professional representation. In addition, parents were actively recruited to participate in the interviews (Phase 2), Delphi study and consensus meeting (Phase 4) to ensure parents views as key stakeholders were incorporated into the development of the core outcome set. Ultimately, PPIE would help to improve the quality of the research and ensure the CORE-KDT study and core outcome set was relevant to the end users of parents and their children with epilepsy treated with KD therapy.

Two lay research partners (Emma Williams and Val Aldridge) were recruited from Matthew's Friends, a UK based charity supporting families with KD therapies. Both had sons with drug resistant epilepsy who had been treated with KD therapy in the past. Emma set up and leads the charity as CEO and Val is a Trustee and dietetic assistant. They both brought their expertise as parents to the research team but also their experience of supporting families with epilepsy and KD therapy. A patient and public involvement consultation was undertaken with recruitment supported by Young Epilepsy, a charity for children and young people with epilepsy and Matthew's Friends. Two parents of children with epilepsy on KD therapy were interviewed. They felt this study of outcomes was worthwhile research in order to explore the breadth of outcomes and the impact of KD therapy for their children. Interestingly, they both spoke about the many functional outcomes their child experienced beyond seizure control. In both cases, they supported the inclusion of parents in each phase of the CORE-KDT study, as it would ensure the voice of parents would be heard and incorporated into the core set of outcomes. The findings informed the

design of the semi-structured interview schedule for use in phase 2 (see section 2.6.4, Table 10). They highlighted that the primary considerations when undertaking interviews with parents were likely to be time and competing demands within their busy households. It was felt parents were more likely to choose a telephone or video call for ease and convenience rather than a face-to-face meeting.

A study advisory group was convened involving health professional, parent and charity representation. This group provided oversight for the study and reviewed the documentation listed in Table 7. Valuable feedback relating to readability and design were incorporated into the finalised versions of study documents. In addition, the study advisory group participated in the phase 3 consultation process to ratify the list of outcomes arising from phases 1 and 2 and associated lay descriptors in preparation for the 2-round Delphi study. Finally, members joined the consensus meeting and ratification of the core outcome set.

A reporting checklist is a useful way of transparently and consistently mapping and reflecting upon the PPI activities within a research project. Staniszewska et al. (2017) improved upon the original Guidance for Reporting Involvement of Patients and the Public (GRIPP) in research (2011) by undertaking a three round Delphi process to achieve international consensus among the PPI community on the items that should be included in a PPI reporting checklist. This resulted in the development of GRIPP2 both in long and short form. The GRIPP2-short form is used throughout this thesis to map and reflect upon the PPI activities within the CORE-KDT study. Table 8 provides an overview of PPI

within the design and planning stages and the checklist will be revisited for Phases 2, 3 and 4 of the study which follow in Chapters 4, 5 and 6.

Table 7. Study documentation reviewed by the study advisory group

Document	Implemented feedback
1. Semi-structured qualitative interview schedule (see section 2.6.4 Table 10)	*'Very clear and logical', include the number of anti-seizure medications pre-KD in demographics as this starting point may influence parent's later views on outcomes'*
2. Participant information sheet for parents (Appendix C)	*'Shorten and explain the core outcome set and what an outcome is in more detail'. 'Simplify the potential benefits'.*
3. Participant information sheet for professionals (Appendix D)	*'Elaborate on the use of a core outcome set to guide routine monitoring in clinical practice'.*
4. Consent form (Appendix E)	*'precise and quick to complete'*
5. Study Logo (Appendix F)	Nil
6. Advertising leaflet (Appendix G)	The SAG and researcher deliberated at length regarding the correct terminology to use in the advertising leaflet that would be eye-catching yet accessible and informative for potential participants.
7.Social media posts (Appendix H)	Nil

SAG – study advisory group

Table 8. PPI in the design and planning of the CORE-KDT study
Reported in accordance with the GRIPP2-SF (Staniszewska *et al.,* 2017)

Section and topic	Item
1. Aim Report the aim of the study	- To collaboratively involve parents as research partners and stakeholders in the design and planning phase of the CORE-KDT study which ultimately aims to develop a core outcome set for childhood drug resistant epilepsy treated with KD Therapy.
2. Methods Provide a clear description of the methods used for PPI in the study	- Two lay research partners were recruited to the research team to assist the design and delivery of the CORE-KDT study. - Both had implemented KD therapy for their sons so had lived experience of the treatment but also supported other families to implement KD therapy in their roles at Matthew's Friends charity (CEO and Trustee/dietetic assistant). - Their views on the proposed study idea were sought and they contributed to the design of the study - They supported advertisement and recruitment to a PPI consultation to seek parental views on the proposed research and the factors to consider during the interview phase. - The research manager at Young Epilepsy was consulted on the proposed study and agreed to support advertisement and recruitment to the PPI consultation - A PPI consultation was undertaken with two parents of children with drug resistant epilepsy treated with KD therapy, both of whom later agreed to join the study advisory group - A study advisory group was convened, and the membership included: • two parent representatives • one senior specialist ketogenic dietitian as a healthcare representative • Both lay research partners as parent and charity representatives - The study advisory group supported the preparation of study documents - Lay research partners were consulted in the preparation of the documentation for HRA ethical approval.
3. Results Outcomes – report the results of PPI in the study, including both positive and negative outcomes	PPI contributed to this phase of the study in many ways. - Validating that this was worthwhile and necessary research and supporting the overall design of the CORE-KDT study -Lay research partners were responsible for recruiting two parents to the PPI consultation - This consultation highlighted that time and competing demands would be the likely challenges for participating parents. - This influenced the decision to offer interviews 7 days a week early to late to optimise parents' ability to participate. - Feedback from the study advisory group informed the demographic information collected from parents in the interviews relating to ASM use and improved the accessibility of the language used in all materials

Section and topic	Item
4. Discussion Outcomes – comment on the extent to which PPI influenced the study overall. Describe the positive and negative effects.	- PPI in this early stage of the study was critical as it influenced decision making and supported design of study materials and successful application for HRA ethical approval.
5. Reflections Critical perspective – Comment critically on the study, reflecting on the things that went well and those that did not so others can learn from the experience	- The ethos of core outcome set development is to involve key stakeholders from the outset, so it was critical that this was undertaken in a meaningful and not tokenistic manner. The lay research partners from Matthew's Friends charity had expertise beyond their role as parents, having previously been involved in research studies. As such it was important to include additional parent representatives in the SAG without charity and research expertise. Collectively, they brought additional expertise into the research team and study advisory group. However, there were some limitations. - A larger PPI consultation with up to 5 families may have provided deeper insights, however resource and time pressures limited extended recruitment. - The lay research partners and members did not receive formal study advisory group training to support their involvement in study design, planning and delivery. Instead, the lead researcher set expectations and provided support and guidance when needed. While no member raised this as an issue, the lack of formal training could have caused anxiety regarding their ability to contribute effectively. However, formal training may have also increased the burden on them commanding more of their time. - This study was largely unfunded, so representatives did not receive remuneration for their time owing to resource constraints.

2.4 Core outcome set methodology guidance

The scope of a core outcome set defines the specific area of health which the core outcome set will apply to in terms of the setting, population, health condition and types of intervention (Kirkham *et al.*, 2017). A clearly defined scope will help to ensure the outcomes included in the core outcome set are relevant for the intended use and users. The health condition under investigation was drug resistant (refractory) epilepsy in a paediatric population (<18 years old) treated with the intervention of KD therapy. The core outcome set 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. A gold standard methodology for developing core outcome sets does not exist. However, the COMET Initiative have produced a range of guidance and standards for core outcome set development and reporting. The design of the CORE-KDT study was informed by The COMET Handbook (Williamson *et al.*, 2017) which provides guidance on the methodological considerations when planning and developing a core outcome set. The study conformed to standards established for the development of core outcome sets outlined in COS-STAD (Core Outcome Set-STAndards for Development) (Kirkham *et al.*, 2017) and the standards for core outcome set protocol items by COS-STAP (Core Outcome Set- STAndardised Protocol items) (Kirkham *et al.*, 2019). The results will be reported in line with COS-STAR (Core Outcome Set- STAndards for Reporting) (Kirkham *et al.*, 2016).

2.5 Phase 1: A scoping review of outcomes measured and reported in studies of childhood epilepsy treated with KD therapy

2.5.1 Overview

The scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (Tricco *et al.*, 2018). It was registered on the Joanna Briggs Institute (JBI) systematic review register and the COMET Initiative online database (COMET Initiative, n.d.). The full inclusion and exclusion criteria, search strategy, approaches to study screening, data extraction and synthesis were stipulated *a priori* in a published protocol (Carroll *et al.*, 2019). The protocol followed the criteria recommended by the JBI. This study focused on

reporting the frequency of outcomes and how these were measured 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 developing and using a standardised data extraction proforma instead of JBI SUMARI® (Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information) as this necessitated quality assessment of included studies.

2.5.2 Research question and objectives

What outcomes are measured and reported in studies of childhood epilepsy treated with KD therapy?

Objectives

(1) to identify a list of outcomes from published studies using KD therapy to treat childhood epilepsy

(2) to identify the tools or methods used to measure the reported outcomes

2.5.3 Study participants

Table 9 lists the inclusion criteria applied to the search strategy. Participants could be treated with other medical therapies, such as but not limited to ASMs, VNS or surgery in conjunction with KD therapy. However, all adult studies and those in children treated with KD therapy for diagnoses other than childhood epilepsy were excluded. For example, neuro-oncology and metabolic disorders.

Table 9. Inclusion criteria for the scoping review

Inclusion criteria
Human studies
English language
Ten or more patients
Published between 1st January 2008 and 19th October 2018
Children aged ≤18 years
Diagnosis of epilepsy, treated with ketogenic diet therapy for at least one month

2.5.4 Concept

The intervention under investigation was KD therapy. The scoping review considered all outcomes measured and reported in studies that assessed the use of KD therapy in the treatment of childhood epilepsy. The following components were investigated; intervention (type of KD therapy), outcomes, definition (if used) of the outcome, the tool or indicators used to measure the outcome, the validity of tool used, the time to measurement of the outcome after the intervention commenced and the reporting of the outcome.

2.5.5 Context

The context of the review was settings with paediatric patients undertaking KD therapy for refractory drug resistant epilepsy.

2.5.6 Search Strategy

An initial limited search was undertaken in PubMed and CINAHL, which identified relevant keywords and index terms. These informed the development of a detailed and comprehensive search strategy, reviewed by an information specialist before finalising (Appendix I). Electronic databases were searched, including; PubMed, CINAHL, Scopus, Embase, AMED, Cochrane Database of Systematic Reviews, Cochrane Central, PROSPERO and JBI Database of Systematic Reviews and Implementation Reports. The ISRCTN (*International*

Standard Randomized Controlled Trials Number) and ClinicalTrials.gov registers were searched for ongoing or completed studies. Where possible, authors of potentially relevant studies were contacted to ascertain the outcomes assessed and if the study was ongoing or concluded. Grey unpublished literature was searched through the British Library e-theses online services (EThOS) database, OAIster and OpenGrey (System for Information on Grey Literature in Europe; SIGLE). A wide range of study designs were included to capture the breadth of assessed outcomes with significant repetition in outcomes expected. At the time this review was conducted, there were only seven randomised or quasi randomised controlled trials *(*Martin *et al.,* 2016), so non-randomised controlled trials, prospective and retrospective cohort studies, case-control studies and case note reviews were considered for inclusion. Reference lists of systematic reviews were hand searched to ensure all eligible primary studies were identified and screened. Reference lists of all included full texts were screened for additional studies.

Studies published from 1 January 2008 to 19 October 2018 were included in this review. The search was limited to post 2007 because the first RCT assessing the effectiveness of KD therapy for childhood epilepsy (Neal *et al.*, 2008a) and the first internationally agreed guidelines on the management of children treated with KD therapy (online first) (Kossoff *et al.*, 2009) were both published in 2008. These two key publications have guided subsequent research and clinical management of children treated with KD therapy. ENDNOTE V8 (Clarivate Analytics, PA, USA) reference management software was used to collate citations and remove duplicates.

2.5.7 Study selection

Kirsty Martin McGill (KMMG), an experienced Cochrane review author, undertook the role of a second reviewer. Both authors independently screened titles and abstracts using Rayann QCR, then critically reviewed the full text of selected studies to assess eligibility. Cases of disagreement were discussed until consensus was reached.

2.5.8 Data extraction

A data extraction form was piloted by both reviewers. It collected data on study design and location, journal of publication, patient demographics, attrition, type of KD used, *a priori* identification of outcomes, measured and reported outcomes, definition of outcome, assessment tool or method used, responder and time points at which measured. Relevant data was extracted from all included studies. KMMG independently extracted data from 10% of included studies, chosen randomly, to check for consistency. Agreement was reached for all, so further extraction by another reviewer was unwarranted.

2.5.9 Data presentation

The extracted data was presented in diagrammatic and tabular form. Tables and charts reported the outcomes measured and reported by researchers, the definitions used to describe these outcomes, and the measurement method. A narrative summary accompanied the tabulated and charted results to explain how the results related to the reviews research question and objectives.

2.6 Phase 2: Qualitative descriptive study

2.6.1 Overview

A qualitative descriptive study is a pragmatic approach that comprehensively summarises an event in the everyday terms of those events. There are elements of interpretation and researcher influences per se, however the data is minimally theorised (Sandelowski, 2000) with the researcher staying true to the data and the surface of the words and events used and described by participants. In the context of this proposed study, it is an account of what happened to the parents and or their child, what it meant and what the participants think and believe. It is recommended that patients and the public are consulted when developing a core outcome set, preserving the perspective of these stakeholders and improving the accessibility of the later consensus process for participants (Young and Bagley, 2016; Williamson *et al.*, 2017). Parent proxy reporting is an accepted approach when the child is unable to respond independently; for example, due to age, cognitive impairment or illness (Ronen, Streiner and Rosenbaum, 2003). Few children would have the understanding or capacity to participate in this study, so it was decided to interview parents only. Data generated through qualitative research is accepted to be contextually rich and meaningful, enabling an in-depth exploration of issues that cannot be achieved through quantitative methods alone (Mack *et al.*, 2005). Core outcome set studies that did seek patient or public opinion highlighted further outcomes of importance that were not previously identified through systematic review of published studies (Arnold *et al.*, 2008; Rosenbaum *et al.*, 2010; Boers *et al.*, 2014). These findings reinforced the critical role of parent participation in the CORE-KDT study.

2.6.2 Research question and objectives

1) How do parents describe their families' experiences of epilepsy and KD therapy?

2) Which outcomes do parents regard as important when undertaking KD therapy to treat refractory childhood epilepsy?

Objectives

1) Explore the impact of drug resistant epilepsy on the child and wider family

2) Identify parents' expectations of KD therapy and the extent to which these were met

3) Identify the effects of KD therapy

4) Explore the day-to-day management of KD therapy

5) Identify strategies which have supported families with KD therapy

6) Make recommendations for clinical practice

7) Explore outcomes of importance to families

8) Assess whether the scoping review outcomes list adequately reflects parents' perspectives or if there are any additional important outcomes that have not yet been identified.

2.6.3 Sampling

International participation was welcomed from stakeholders with lived experience of childhood epilepsy and KD therapy. Participants were eligible if they were a parent or carer to a child aged 0-18 years with drug resistant epilepsy being treated with KD therapy or had weaned from KD in the past year, were English speaking and were 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 (e.g. neuro-oncology or metabolic disease) or weaned from KD over one year ago were excluded. Children with neuro-oncology related conditions or metabolic disease may also experience seizures; however, both present other complicating factors that would likely influence outcomes. KD therapy has occasionally been used as an adjunct in the palliative management of paediatric brain tumours, yet this has not been explored in human trials. While some overlap might be expected in outcomes across both clinical conditions, it is plausible to suggest that neuro-oncology would require additional specific, bespoke outcomes. With that in mind, I elected to focus solely on paediatric epilepsy as a starting point with the potential for future expansion of the core outcome set into other related clinical conditions informed by experienced stakeholders.

A sampling frame was developed, and a maximum variation sampling strategy employed to ensure optimal diversity in terms of the following characteristics: child's age (classified according to World Health Organisation paediatric age categories (WHO, 2007), epilepsy diagnosis and length of time since diagnosis, home country, type and duration of KD therapy and response to treatment with KD. Duration of therapy was broadly defined as recently commenced KD (less than or equal to three months of treatment) and established on KD therapy (four months or longer). Parental experiences of a recently diagnosed infant who has just commenced KD therapy will likely differ from those whose adolescent child is diagnosed many years and stable on KD therapy. It is plausible that these different factors may influence the families' experiences of epilepsy treated with KD therapy and identification and perceived importance of associated outcomes.

2.6.3.1 Recruitment

Participants were recruited from across the UK and internationally via gatekeepers at three primary sources:

1) Nine KD centres operated as Participant Identification Centres. An information sheet was shared with prospective families by their direct 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 (UK and international participants)

A CORE-KDT Facebook page was developed, and advertising materials and posts shared there and on Twitter. Charities placed adverts provided by the researcher on their website, social media pages, online forums and newsletters (Appendix G and H). These directed interested participants to the study webpage (Carroll, 2019), where the participant information sheet was available and an online contact form to register interest. Initially, the potential participants who made contact were parents to children who had experienced a very positive response to treatment with KD therapy and predominantly children aged 12 years or older, despite the advertising materials not explicitly requesting this. Given the importance of gaining insight into parent's views and experiences across the spectrum of responses to treatment, subsequent social media posts were targeted to welcome parents whose children had a mixed response to KD and were aged 12 years or younger.

2.6.4 Data collection

Semi-structured interviews were undertaken to gain an in-depth description of families' experiences of epilepsy and KD therapy and their views on essential outcomes. Written consent was taken prior to the interviews and participants were reminded that they could stop the interview or withdraw from the study at any point. An interview schedule with a range of open questions facilitated parent-led discussion (Table 10). During the interview, each participant was invited to share 'the story' of their child's epilepsy. Naturally, this often began with the epilepsy diagnosis, followed by the subsequent impact on the child and wider family. Parents' hopes and expectations of KD therapy, day-to-day experiences, outcomes of treatment, and helpful strategies to manage the KD were explored. The researcher conducted all in-depth, semi-structured interviews, a female doctoral student and experienced ketogenic dietitian working as an academic and not clinically at the time. They have a strong foundation of knowledge relating to epilepsy, KD therapy, and supporting families. Furthermore, established communication and listening skills facilitated good rapport with participants and fostered a sense of trust and engagement. As a result of existing knowledge and communication skills, it was possible to probe for richer detail within each interview and obtain a depth of data relevant to this qualitative study.

Table 10. Semi structured interview schedule

	Questions
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?

Participants were not known; however, they were aware of the professional background of the interviewer and that the research was undertaken in pursuit of a PhD in epilepsy and KD therapy. Participants were informed that the study's objective was first to explore and understand their experiences of epilepsy and KD therapy and second to identify the important outcomes or results when treating childhood epilepsy with KD therapy. A conversational approach was used to encourage parents to articulate their stories with little tension (Cohen, Kahn and Steeves, 2000). Field notes were documented during the interview to identify the significant themes that emerged from the discussions. Furthermore, a reflective research diary was used to record thoughts and reactions to the interview, which supported later analysis (Meloy, 1994).

Participants were offered the choice of an in-person meeting (UK only), audio telephone call, or video call using Zoom or Skype. It could be argued that telephone or video calling may reduce rapport and recognition of non-verbal cues (Lo Lacono, Symonds and Brown, 2016) however others argue it is comparable to in person face to face interviews (Deakin and Wakefield, 2014). Despite these potential challenges, video conferencing technology enabled the inclusion of otherwise inaccessible international participants to this study.

The first two interviews were transcribed and analysed to enable reflection and iterative changes to the interview schedule. Interestingly, participants struggled to understand the word outcome. Following discussion with an expert qualitative researcher, the word 'result' was added to enhance understanding of the word 'outcome' and used thereafter. When asked 'what might make KD easier?' both participants identified 'peer support via a mentor or buddy', suggesting that this might be a supportive strategy for starting KD therapy. The feasibility of implementing a peer mentoring system has been explored at past professional meetings but not progressed. Therefore, a question was added to subsequent interviews to explore parents' views on peer mentoring in more depth.

Outcomes were identified directly by asking participants to describe the important results or outcomes for children with epilepsy treated with KD therapy. Participants who listed multiple outcomes were asked to prioritise, to help us 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 in the transcripts using content analysis, when exploring

families' experiences of epilepsy and KD therapy. Together, this enabled the identification of all possible outcomes.

2.6.5 Analysis

Participants were assigned a numerical identifier prefixed with FP for a female participant and MP for a male participant to maintain anonymity. All interviews were audio-recorded, professionally transcribed (intelligent verbatim transcription), and stored in accordance with the University of Plymouth Research Data Policy for ten years (Information and Data Management Advisory Group, 2019). Electronic data (including audio recording files) were stored in Microsoft One-Drive on a password-protected University laptop and files encrypted. All hard copies of any associated study materials (including audio file transcription) were anonymised using participant numbers except written consent and stored in a locked filing cabinet until they were scanned and uploaded to One-Drive.

The transcripts were uploaded to NVivo for anaylsis and read several times, as well as listening back to the audio recordings to become more immersed in the data (Burnard, 1991; Polit and Beck, 2004), gaining understanding and insight into the context of the discussion. Data analysis occurred in two stages, with each requiring a different analysis approach. The first stage aimed to explore and understand families' experiences of childhood epilepsy and KD therapy. The second stage aimed to identify outcomes of importance to parents and any new outcomes not previously identified in the scoping review.

2.6.5.1 Stage 1 thematic analysis to explore families' experiences of epilepsy and KD therapy

It is a widely held belief that reporting frequency counts in qualitative research is not helpful (Pyett, 2003; Braun and Clarke, 2006; Buetow, 2010). For example, Pyett (2003 p.1174) states that *'counting responses misses the point of qualitative research'* as frequency does not determine value. Instead, we should consider the importance of the code in answering the research question. Buetow (2010) expands on this by describing an enhancement of thematic analysis; he termed 'saliency analysis', whereby a code should be included if it can enhance understanding or insight to a real-world problem, regardless of how frequently it recurred in the data. A code may be 1) highly important and recurrent, 2) highly important but not recurrent, 3) not highly important but recurrent, and 4) not highly important and not recurrent. Yardley (2000) argues that findings are considered highly important when they are new and advance our understanding and or help to address a real-world problem. Until now, little is known regarding parental experiences of KD, so Buetow (2010) and Yardleys (2000) findings guided the analysis approach. The interviews set out to explore the broad area of parent's experiences of epilepsy and KD to gain insight into this poorly understood area. The core open questions asked of parents were consistent, however, the interactive conversation evolved depending on their answers, as is typical in an interview. Hence importance cannot be assumed from the number of responses for or against or those who did or did not mention something.

In contrast, the number of respondents are reported in the content analysis of outcomes described in section 2.6.5.3. Questions relating to the identification

and prioritisation of outcomes were more directed and often elicited list like responses from participants. Frequency counts are more typical in content analysis (Hsieh and Shannon, 2005), However, caution is required in interpretation as the data participants chose to share was possibly shaped and influenced by the narratives and stories they shared earlier in their interview.

Thematic analysis was undertaken to investigate the detailed contextual descriptions of families' experiences (Braun and Clarke, 2006). The data was minimally theorised, instead, it is an account of the experiences of the families, what it meant to them, what they think and believe. An inductive approach to coding was adopted, deriving codes that reflected concepts emerging from the data. Interpretive description departs from other typical qualitative descriptive approaches as it assumes the researcher wants to interpret the data rather than simply describe it, understanding the participants views and experiences and most importantly the implications for practice. Sandelowski and Barroso (2003) describe this as "interpretive explanation". The outcome would be a tentative truth rather than an entirely new truth within a clinical phenomenon. This tentative truth would inform or make sense of clinical reasoning, provide insight for practice decisions and make sense of some of the eccentricities that might occur in the real-world application (Thorne, Kirkham, and O'Flynn-Magee, 2004). In this case, giving clinicians insight into how parents experience epilepsy and KD therapy. It should help to make sense of something that clinicians ought to understand. Interpretive description is often used in nursing research and the facets that make it attractive to nurses also appeal here. In Interpretive description the researcher's technical knowledge and clinical experiences are described as a major source of insight, to be used as a

valuable instrument in the research rather than a bias as is often thought to be the case (Mills, 2000). In fact, it would be impossible to completely remove one-self from those experiences from those experiences, instead transparency and openness are key to ensure rigour.

2.6.5.2 Philosophical underpinnings of the thematic analysis

The philosophical underpinnings of this phase of data collection and analysis are informed by the work of Thorne (2008);

- there are multiple constructed realities that can be studied holistically but ultimately reality is subjective
- the participant and the inquirer are described as the knower and the known, they interact to influence each other and are inseparable
- there is no existing theory that could address the multiple realities so instead theory must emerge from the data
- data collection takes account of what is already known about the phenomena and embraces the researchers influence.

The interviews explored parents' experiences of epilepsy and KD therapy in the context of; life with epilepsy since diagnosis, considering KD therapy as a treatment option, expectations of KD therapy, implementation and daily routine with the diet. Parents often gave very rich answers using stories or anecdotes to illustrate their points. Consequently, this gave insight to the challenges of KD therapy and the strategies they used to overcome some or all of these. If the participants did not raise these topics, they were probed in line with the interview schedule.

2.6.5.3 Stage 2 Content analysis to identify outcomes

The theory underpinning the second stage of analysis was aligned with directed content analysis, described by Hseih and Shannon (2005). This deductive approach is particularly relevant when there is some existing knowledge about a phenomenon. In this case; outcomes, but further context, description, and understanding are desired (Elo and Kyngäs, 2008). The long list of outcomes identified in the scoping review (Table 13, chapter 3) became the template for the categorisation matrix. Any newly identified outcomes that did not fit within the matrix were coded inductively and categorised according to the same COMET taxonomy (Dodd *et al.*, 2018). Content analysis can be undertaken on any unit of analysis; an extract, a portion of pages, or a select number of participants' transcripts (Polit and Beck 2004). In this study, the manifest content of the full transcript for all 20 interviews were analysed to ensure all possible outcomes were identified (Lundman and Graneheim, 2004).

2.6.6 Trustworthiness

Lincoln and Guba (1985) outline the importance of *truth value* and *consistency* in order to demonstrate rigour in qualitative research. *Truth value* commands the researcher to outline their personal experiences and viewpoints that may have resulted in methodological bias. Interviews were conducted by a female, registered dietitian and academic with 12 years of expertise in the area of KD therapy. This may have increased the risk of observer basis, however this was mitigated by ensuring the wider research team and study advisory group were consulted in the planning of the interview schedule. The semi-structured interview schedule was used for all participants ensuring consistency in the core questions asked. Participants were aware that the interviewer had worked as a

ketogenic dietitian but was speaking to them in a research capacity, in pursuit of a PhD and no participant was or had been treated in the past by the interviewer. These factors may have increased participants trust in the integrity of the research. It is possible that participants modified their responses (social desirability bias) owing to their knowledge of the background of the interviewer, however many were frank and open about their disappointing experiences with health care professionals, suggesting they were comfortable to be honest and share this with the interviewer.

Truth and value are also demonstrated by clearly and accurately presenting participants perspectives. Coding and identification of themes was performed by the researcher in collaboration with a senior researcher experienced in qualitative research methods, who independently reviewed 10% of the coded transcripts. Interpretive description, outlined earlier ensured minimal interpretation of the interview data, ensuring the analysis stayed true to participants views. The final themes and newly identified outcomes were agreed through discussion.

The second of Lincoln and Guba's principles (1985) is *consistency* where trustworthiness is demonstrated by the maintenance of a decision log which demonstrates clear and transparent decisions. This was sustained throughout the study including the reasoning guiding the decisions. This was particularly important when mapping iterations of the outcomes list and associated descriptors. Content validation of the newly identified outcomes were undertaken by the research team and the study advisory group, which included; consultant paediatric neurologist, parents of a child with epilepsy treated with

KD therapy, KD charity representatives and a ketogenic dietitian. Representative anonymised citations from the transcripts were used to demonstrate the context and naming of the outcome. Discussion ensued and agreement on the final list of seven new outcomes was reached.

2.7 Phase 3: Pre-Delphi consultation process

Overview

A consultation process was undertaken with the study advisory group and research team to agree the outcomes that should be entered into a Delphi process.

2.7.1 Research question, aims and objectives

Research question: What outcomes should be entered into a Delphi process for further study?

Aim

To seek final agreement within the CORE-KDT Study Advisory Group and research team regarding the list of outcomes and descriptors to go forward to the Delphi survey of parents, health professionals and researchers, who will rate the critical importance of each outcome.

Objectives

1) ensure there is limited overlap in the list of outcomes

2) ensure language used is accessible

2.7.2 Outcome long list generation

The outcomes identified in the scoping review (chapter 3) and qualitative interviews (chapter 5) were combined to create a comprehensive list of

outcomes classified according to an outcome taxonomy (Table 11) (Dodd *et al.*, 2018). This is an updated version of Williamson and Clarks original taxonomy (Williamson *et al.*, 2017) which was developed following review of two cohorts of Cochrane systematic reviews (Davey *et al.*, 2011; Smith *et al.*, 2015) and the outcomes recommended in 198 core outcome sets (Gargon *et al.*, 2014). Plain language outcome descriptors were informed by the definitions of outcomes in the scoping review and parents' terminology or descriptions in the interviews. The long-list was reviewed by the research team and the study advisory group. For each outcome the group considered (i) face validity, understanding and acceptability (ii) merging with closely related items, (iii) exclusion if felt to be a factor or descriptor rather than a true outcome and (iv) addition of related outcomes. The outcomes list was modified according to feedback, ready to populate the Delphi survey.

Table 11. COMET outcome taxonomy
adapted from Dodd et al., 2018

Outcome Taxonomy
1. Mortality
2. 2-24: **Physiological/clinical**
2: Blood and lymphatic system outcomes
3: Cardiac outcomes
4: Congenital, familial and genetic outcomes
5: Endocrine outcomes
6: Ear and labyrinth outcomes
7: Eye outcomes
8: Gastrointestinal outcomes
9: General outcomes
10: Hepatobiliary outcomes
11: Immune system outcomes
12: Infection and infestation outcomes
13: Injury and poisoning outcomes
14: Metabolism and nutrition outcomes
15: Musculoskeletal and connective tissue outcomes
16: Outcomes relating to neoplasms: benign, malignant and unspecified
17: Nervous system outcomes
18: Pregnancy, puerperium and perinatal outcomes
19: Renal and urinary outcomes
20: Reproductive system and breast outcomes
21: Psychiatric outcomes
22: Respiratory, thoracic and mediastinal outcomes
23: Skin and subcutaneous tissue outcomes
24: Vascular outcomes
Functioning
25: Physical functioning
26: Social functioning
27: Role functioning
28: Emotional functioning/well-being
29: Cognitive functioning
31: Perceived health status
32: Delivery of care, including;
- Satisfaction/patient preference
- Acceptability and availability
- Adherence/compliance
- Withdrawal from treatment
- Appropriateness of treatment
- Process, implementation, and service outcomes
33: Personal circumstances
Resource use
34: Economic
35: Hospital
36: Need for further intervention
37: Societal/carer burden
38: Adverse events/effects

2.8 Phase 4: Prioritisation of outcomes according to stakeholder group and integration of outcomes into a core outcome set

2.8.1 Overview

A survey of key stakeholders; parents, healthcare professionals and researchers was undertaken using Delphi survey methodology following recommendations in the development of core outcome sets (Williamson *et al.*, 2017). A two round remote anonymous online Delphi survey asked participants to rate the importance of the list of outcomes agreed in phase three. The survey was designed and administered using the DelphiManager software package. Representatives from both stakeholder groups piloted the survey prior to dissemination to all participants to assess acceptability. Participants were invited to rate each outcome in two Delphi rounds, with high scores indicating the importance of inclusion in the final core outcome set.

2.8.2 Research question, aim and objectives

Research question

What are the most important outcomes to include in a core outcome set for refractory childhood epilepsy treated with ketogenic diet?

Aim

To reach consensus on a core outcome set for drug resistant childhood epilepsy treated with KD therapy, from the perspective of key stakeholders including parents, health professionals and researchers.

Objectives

1. To undertake a two-round Delphi survey where stakeholders are invited to rate the list of outcomes

2. To identify three sets of outcomes from the Delphi survey;

    i) with a consensus for inclusion in the core outcome set

    ii) with a consensus for exclusion from the core outcome set

    iii) without a consensus – undecided outcomes

3. To convene a stakeholder consensus meeting to discuss and vote upon the undecided outcomes and agree the core outcome set.

2.8.3 Stakeholders

2.8.3.1 Sample identification and eligibility

The CORE-KDT study aimed to consider the views of key stakeholders throughout the development of the core outcome set. 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 were likely to be from a professional or researcher background and in small numbers so these were allocated to the health professional and researcher group. Participation was open internationally to all interested stakeholders who had lived experience with providing KD therapy for their child or experience supporting families to undertake KD therapy. The Delphi study was conducted in English so participants were proficient with written English. Parent participants were recruited by the same processes outlined in 2.6.4. Health and neurology professionals were invited to participate through specialist interest groups and professional societies (Ketogenic Professional Advisory

Group, Ketogenic Dietitians Research Network, Matthew's Friends Professionals mailing list and the Epilepsy Nurses Association) and social media. Charity and industry representatives with relevant experience with ketogenic diet therapy were invited.

2.8.3.2 Sampling technique

Non-probability convenience sampling techniques were employed to assess the views of all participants who registered their interest in the Delphi survey and who meet the inclusion criteria.

2.8.3.3 Size of sample

There are no recommendations for appropriate sample sizes for Delphi surveys. The protocol was therefore guided by other relevant Delphi surveys (Sinha *et al.*, 2012; Wylde *et al.*, 2015; Crudgington *et al.*, 2019) and aimed to recruit between 20-50 participants in each stakeholder group within the available timeframe. Whilst the use of KD therapy has grown exponentially over the past decade; there were estimated to be 750 patients in the UK on KD therapy in 2017, with 250 waiting to commence therapy (Whiteley *et al.*, 2020). With international recruitment 20-50 stakeholders was deemed to be feasible. I aimed for representation from across a range of age groups (children), epilepsy diagnosis, duration of treatment with KD therapy and type of KD therapy. Informed consent was assumed if participants registered online for the Delphi survey and submitted their answers. The following demographic details were collected: age of the child undertaking KD therapy, type of KD and duration of treatment, diagnosis and country of residence.

There were approximately 100 paediatric neurologists nationally in the UK (Morris *et al.*, 2017) not all of whom will have experience with KD therapy, approximately 90 ketogenic dietitians (personal correspondence with the Ketogenic Dietitians Research Network) and 202 paediatric epilepsy specialist nurses (personal correspondence with a representative from Epilepsy Action). The small size of the UK healthcare professional group meant that international recruitment was essential. The inclusion of international healthcare professionals and researchers should help to ensure that the core outcome set is acceptable worldwide. To achieve optimal diversity, it was important to include as many of the above healthcare professionals as possible. Data relating to their profession, experience with KD therapy and the country in which they practiced was collected. Informed consent was assumed if participants registered online for the Delphi survey and submitted their answers. Each participant was assigned a unique identifier to ensure anonymity yet enable the research team to monitor their participation and send invitation and reminder emails.

2.8.4 Data collection

The COMET initiative DelphiManager software was used to administer the survey. Two Delphi rounds were undertaken in line with other core outcome set studies (Sinha *et al.*, 2012; Harman *et al.*, 2015; Crudgington *et al.*, 2019) as three rounds would likely be overly burdensome on participants. Equally, two rounds were expected to be sufficient given the focussed nature of the single intervention (KD therapy) under investigation. The list of outcomes agreed in phase 3 (results of the scoping review and qualitative interviews combined) were inputted to DelphiManager software to create an online survey. Screen

captures of the design, layout and content of the Delphi survey are included in Appendix J. Participants were asked to identify which stakeholder group they belonged to using a dropdown menu and to complete additional demographic questions. Healthcare professionals and researchers identified their profession, country of work, and experience with KD therapy. Parents identified their child's diagnosis, age, duration of treatment with KD therapy and type of KD. They then proceeded to the Delphi survey which was identical for both groups, to rate the importance of each outcome identified in phase three. A 9-point Likert scoring system was used in line with other core outcome set studies (Harman *et al.*, 2015; Maclennan *et al.*, 2017; Crudgington *et al.*, 2019) where 1-3 signifies an outcome is of limited importance, 4-6 important but not critical and 7-9 is of critical importance. An 'unable to score' option was included for stakeholders who felt they did not have the expertise to score all outcomes. A free text section encouraged participants to list any other outcomes they felt were not represented in the survey but are of importance. These were reviewed by the research team and added to round two if they were not already represented. Regular reminder emails were sent encouraging participation or completion of incomplete submissions.

2.8.5 Delphi survey round one analysis

The scores for each stakeholder group, (i) parents and (ii) health professionals or researchers, were analysed separately to ensure both groups were equally represented. Scores from participants who partially completed the survey were included to ensure their views were represented. Descriptive statistics were used to summarise the results of each round, including the percentage of

participants scoring 1-9 for each outcome. The results of both groups were analysed and presented separately in round two.

2.8.6 Delphi survey round two

All outcomes were carried forward from round one and new additional outcomes proposed by participants. Those who participate in round one were invited to participate again in round two, where their individual round one score and the group scores of each stakeholder group were presented on histograms. They were asked to reflect on the scores of others, rescore each outcome again and share their reasoning for any changed scores. Presenting the aggregate scores for each stakeholder group has been shown to improve consensus between groups in what is important to retain in the final core outcome set (Brookes *et al.*, 2016). A final question asked respondents if they would be willing to attend the stakeholder consensus group meeting.

2.8.7 Delphi survey round two analysis and defining consensus

Descriptive statistics summarised the aggregate results of round two for each stakeholder group. Consensus criteria for inclusion or exclusion from the core outcome set were defined *a priori*. A 70/15% consensus definition is proposed (Williamson *et al.*, 2012b; Wylde *et al.*, 2015; Williamson *et al.*, 2017) whereby an outcome is *included* in the core outcome set if 70% or more of each stakeholder group rated it 7-9 (critically important) and 15% or less considered it of little importance by scoring it 1-3. Conversely, outcomes scored not important (1-3) by 70%, or more and critically important by 15% or less in both stakeholder groups were *excluded* from the core outcome set. Outcomes that failed to reach a consensus for inclusion or exclusion were categorised as *undecided*. Following

round two, no outcomes met the criteria for exclusion from the core outcome set. Fish *et al.* (2018) encountered a similar problem in their core outcome set for anal cancer and proposed revised criteria, whereby an outcome was excluded if 50% or less of participants in both stakeholder groups scored the outcome as critically important. This criteria was applied to reduce the number of undecided outcomes going forward into the consensus meeting.

2.8.8 Stakeholder consensus group meeting

There are no recommendations for target number of participants at consensus meetings, however other highly regarded core outcome set studies recruited between 3-14 patient representatives and 13-33 professionals (Al Wattar *et al.*, 2017; Maclennan *et al.*, 2017; Crudgington *et al.*, 2019; Sahnan *et al.*, 2019). The aim therefore was to recruit at least 10 parents and up to 20 health professionals or researchers purposely sampled to ensure representation of key stakeholders, including parents, health professionals, charities, and industry. In a deviation from the protocol, the consensus meeting was convened virtually online using Zoom. Initially, this was due to the potential of ongoing Coronavirus restrictions and to minimize risk for participants in terms of travel and mixing. However, as the pandemic progressed, it became apparent that people were becoming more comfortable with online meetings and meeting this way had the added benefits of reducing upheaval for busy parents and professionals while facilitating international participation. COMET guidance for online consensus meetings and personal experiences of online teaching and learning supported the fact that the meeting would need to be limited to half a day with appropriate breaks. The aim of the meeting was to present the Delphi survey results and

review and score the undecided outcomes (using Zoom polling) to identify if they should be included in the core outcome set.

Preparation for the consensus meeting

All participants were sent a participant information sheet (Appendix K) and consent form upon invitation (Appendix E). Many outcomes remained undecided after the Delphi survey. Typically, all 'undecided' outcomes are discussed and voted upon at consensus meetings. However, it would not be feasible to discuss and score all outcomes in the online meeting format where participants struggle to sustain the same level of focus as an in-person format (Shoshan and Wehrt, 2022). Therefore, the decision was taken to prioritise discussion and 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 a consensus meeting information pack (Appendix L) which contained;

(i) an agenda

(ii) a copy of their Delphi scores

(iii) A list of the outcomes which had reached consensus for *inclusion* and *exclusion* from the core outcome set.

(iv) instructions to review the remaining *undecided* outcomes and propose (via an online form) any additional outcomes they felt should be discussed and voted upon at the consensus meeting

(v) parent participants were invited to an individual online pre-meeting to answer any questions they might have, discuss the purpose of the

consensus meeting and trial the online zoom polling to ensure they were comfortable with its use.

The consensus meeting was chaired and facilitated by a female academic and dietitian, independent of the CORE-KDT study with no prior experience in epilepsy and KD therapy. The researcher outlined the agenda, the objectives of the meeting and provided an overview of the study methodology and findings to date. The chair then presented each outcome for discussion together with its lay descriptor, Delphi scores from each stakeholder group and similar outcomes (if any) already included in the core outcome set. Discussion and contrasting views were invited from all participants, and opinions welcomed in the chat pane followed by voting. The same Likert type scale (1-9, not important to critically important) was used as that in the Delphi survey. Scores were calculated separately for both stakeholder groups to mitigate the imbalance in numbers. Typically, voting results are shared immediately with participants. However, the researcher had observed a virtual consensus meeting where doing so, led to disgruntlement and frustration among patient participants. They felt their views were not being heard when the outcomes they perceived to be significant failed to reach consensus as health professionals scored them less important. This risked introducing bias to the discussion and scoring. Therefore, the decision was taken to analyse the scores after the meeting and share the results and core outcome set with participants within one week following the meeting. This approach also optimised the time available within the meeting for more in-depth discussion among participants. Feedback was sought from participants (JISC online survey) at two time points. Firstly, following the consensus meeting to assess their satisfaction with the process and secondly,

following review of the proposed core outcome set to evaluate their views and gather any final feedback.

2.9 Consent

The procedures for obtaining consent were informed by the HRA Guidance for Researchers and Ethics Committees on Consent (The NHS Health Research Authority, no date). Capacity to consent was assessed by the researcher and considered if the potential participant; understood the purpose of the research, its potential benefits, risk and burdens, the alternative to taking part and they demonstrated the ability to choose to take part. Potential participants who registered their interest via the contact form on the study website, via email or telephone did so expecting contact to be made from the researcher. They were then contacted via their preferred mode of contact to share the participant information sheet and consent form, and a discussion with the researcher offered to outline the study and answer any questions. Participants were free to withdraw from the study at any time. Written consent was gathered from participants in phase 2, prior to the semi-structured interviews and again in phase 4 from participants attending the consensus meeting. The first page of the online Delphi survey welcomed participants, reminded them of the aims of the research and that completing the registration questions and survey would be regarded as them consenting to take part in the study.

2.10 Ethical and regulatory considerations

2.10.1 Ethical approval

Ethical approval was granted for the patient and public consultation by the Faculty Research Ethics and Integrity Committee, Faculty of Health & Human

Sciences and Faculty of Medicine and Dentistry, University of Plymouth (Ref: 18/19-1022) (Appendix M).

Ethical approval was sought from the National Health Service (NHS) Health Research Authority and granted on 14.11.19 (London-Surrey Research Ethics Committee, reference 19/LO/1680) (Appendix N). The University of Plymouth Faculty Research Ethics and Integrity Committee were in agreement (FREIC ref 19/20-1197) (Appendix O).

2.10.2 Assessment and management of risk

There was a possibility that participants may become distressed or upset when discussing their experiences with epilepsy. Procedures were in place to offer to stop the interview if preferred and information for support groups or helplines at hand to offer which included:

Matthew's Friends Keto Support Line

(t) 0788 4054811

(e) enq@matthewsfriends.org

Available 365 days of the year via telephone

Young Epilepsy

(t) 01342 831342

(e) helpline@youngepilepsy.org.uk

Open between 9am - 3pm, Monday to Friday.

Epilepsy Action

(t) 0808 800 5050 (free)

(e) helpline@epilepsy.org.uk

Open Monday to Thursday 8:30am - 8pm, Friday 8:30am - 4:30pm, Saturday 10am - 4pm.

The researcher worked clinically in the NHS with this patient group as a senior specialist ketogenic dietitian and hence is very experienced in communicating with and supporting parents and carers. However, no patient they treated was included in the study. In addition, a qualitative interviewing techniques training course (delivered by the Social Research Association) was undertaken to further develop qualitative interviewing skills. Parents and carers may get a sense of satisfaction from being involved in the research, knowing their opinions were valued however, no direct therapeutic benefit was experienced by participants or their children.

2.10.3 Regulatory review and compliance

The researcher ensured the appropriate approvals were in place (via R&D office and local research teams) before any of the PIC sites advertised the CORE-KDT study.

2.10.4 Amendments

There were no substantial amendments put forward to the REC for consideration during the study.

2.10.5 Peer review

The study protocol was peer reviewed internally by our sponsor; The University of Plymouth. An independent expert (Professor Paula Williamson, The

University of Liverpool) was consulted to review the outline protocol for the proposed core outcome set. Minimal changes were suggested and implemented. The COMET Initiative also reviewed the proposed study proposal before agreeing to register it on its online database of core outcome set studies. http://www.comet-initiative.org/studies/details/1116

2.10.6 Data protection and patient confidentiality

A data management plan was compiled which adhered with the requirements of the Data Protection Act 2018 and GDPR regulations with regards to the collection, storage, processing and disclosure of personal information and upheld the Act's core principles. The upmost care was taken to handle personal data appropriately.

1. Where personal data was transferred electronically, data was encrypted during transfer.
2. Parents or carers who wished to conduct the interview in their own homes shared their residential address. The details of which were destroyed following the interview and only the email address and telephone number held securely (with their permission). The email address was used to invite participation to the Delphi survey (phase 4), consensus group meeting and sharing of results. Each participant was given a unique identifier number that was used across all related documentation.
3. Direct quotes were published but only those which did not risk identification of the participant.
4. Audio recordings commenced with the unique participant identifier number being stated and then only first name being used thereafter. Recordings were stored on the recording device for a maximum of 24 hours after which they were

transferred to a password protected computer and the audio files password protected. The original recordings were deleted from the recording device.

5. Data was stored on a personal password protected University laptop which is connected to OneDrive. This is accessible only via password.

6. The transcripts of interviews were stored electronically, and password protected.

7. Only two members of the research team had access to personal data. Personal data may also be seen by authorised third parties such as monitors from the University Quality Assurance department. Consent was sought from participants for this access.

8. All datasets will be stored securely for 10 years in line with The University of Plymouth's Research Data Policy (2019). Data will be managed in accordance with this policy when preparing for dissemination via poster, conference presentation and publication in peer-reviewed journals. The researcher is the named data custodian.

2.10.7 Indemnity

Indemnity is provided by sponsor; the University of Plymouth.

2.10.8 Access to final dataset

All named co-investigators (AC, MH, HC, EM, VA) will have access to the final dataset.

2.11 Funding

Funding was received from the University of Plymouth, The British Dietetic Association General Education Trust Fund and Nutricia Danone. The funders were not involved in the study design, conduct, analysis or write up.

2.12 Protocol deviations

The original study protocol (Carroll *et al.*, 2022a) was prepared prior to the covid pandemic and included an in-person consensus meeting. A virtual online meeting was convened instead to reduce the potential risk for parents or other participants who may be shielding. It also enabled international participation and was a more efficient and cost-effective use of time for all, particularly health professionals who were under significant clinical pressures at the time. The criteria for consensus exclusion from the core outcome set was modified as previously discussed. Finally, the protocol stated that all undecided outcomes would be addressed in the consensus meeting and voting results shared with participants immediately after voting. The reasoning for these amendments was outlined earlier. It was intended for participants to identify their five priority outcomes before entering the Delphi survey and reviewing the provided outcomes. This may have helped provide some early insights into their knowledge or views on outcomes. Unfortunately though, the DelphiManger software used to administer the Delphi survey was unable to offer this functionality.

2.13 Dissemination policy

Ultimately the goal was to develop a core set of outcomes that will aid consistency in outcome selection and reporting in future trials and clinical practice. However, its use will likely be limited if too many outcomes are included. A working group including members of the research team and expert stakeholders will be formed to explore ways to measure the agreed outcomes and support dissemination. If the resultant core outcome set is too large, the working group will aim to refine it further. Ensuring it is practical for use, while

still preserving the views and insights of the wider stakeholders identified during the interviews, Delphi study and consensus meeting. The final core outcome set will be reported following the Core Outcome Set - Standards for Reporting (COS-STAR) statement and checklist (Kirkham *et al.*, 2016). Dissemination will occur via engagement with trialists, Cochrane, COMET and publication in relevant journals. Study participants who opted to receive study updates will be sent a newsletter and links to relevant publications. The results will be shared at appropriate conferences, professional network meetings and parent forums.

2.14 Discussion

Summarised here is the protocol of a mixed methods study to develop a core outcome set. This will guide outcome selection and reporting in future trials of drug resistant childhood epilepsy treated with KD therapy. Professional networks regularly highlight the lack of consensus in outcome collection as an area for development. The findings will therefore inform and support clinicians undertaking audit and service evaluation. It might be argued that KD therapy as a treatment for drug resistant epilepsy is a niche area affecting a relatively small group of patients and the need for a core outcome set questioned. However, a core outcome set is indicated when considering the complexity of drug resistant epilepsy, the difficulties in achieving seizure control, the unique and intensive nature of KD therapy and the challenges families face when caring for a child with significant health needs. A core outcome set for rolandic childhood epilepsy was recently published (Crudgington *et al.*, 2019) and whilst there are likely to be some shared outcomes when both are compared, it is expected that our proposed set may capture different or additional outcomes relevant to the complexity of drug resistant epilepsy and severity of associated co-morbidities.

These might include; epilepsy related hospital admissions, anti-seizure medication reduction, financial burden and adverse effects of KD therapy. The collaborative and patient centred approach, with parent involvement throughout will ensure the agreed core outcomes reflect the views of all major stakeholders. Two key challenges for core outcome set developers include; achieving global consensus and implementation of the finalised core outcome set in future clinical trials (Williamson *et al.*, 2012b). To address these, the researchers will engage with international partners early in the study to foster participation and engagement. Expert panels at key conferences and engagement in professional networks will support this. Finally, the researchers will actively engage with trialists, regulators and funding bodies to ensure the finalised core outcome set is recognised and used.

Chapter 3: Outcome measurement and reporting in childhood epilepsy treated with ketogenic diet therapy: a scoping review to inform core outcome set development.

Preface

This chapter describes the results of the scoping review undertaken as the preliminary phase in the development of the core outcome set. Outcomes measured and reported in studies of childhood epilepsy treated with KD therapy are summarised and consolidated to generate a list of outcomes. The scoping review protocol was published *a priori* in The Joanna Briggs Institute (JBI) Database of Systematic Review and Implementation Reports (Carroll *et al.*, 2019) and registered on the JBI systematic review database. Work arising from this chapter has been published (open access) in Seizure – European Journal of Epilepsy (Carroll *et al.*, 2022a). Sections of this chapter have been taken directly from the edited manuscripts. The researcher prepared the protocol, performed all searches, data collection and analysis. Kirsty Martin-McGill an experienced Cochrane reviewer, assisted with data extraction as a second reviewer. Finally, the researcher wrote the original draft of the manuscripts, which were edited by the supervisory team and then subject to peer review. The published manuscripts are available in Appendix A and P.

3.1 Introduction

Epilepsy is a neurological disorder characterised by recurrent epileptic seizures. Up to 35% of children will be to resistant to standard ASMs (Kwan, Schachter and Brodie, 2011) and continue to experience regular debilitating seizures. KD therapy is a well-established treatment for paediatric drug resistant epilepsy,

with an increasing number of randomised controlled trials (RCT's) demonstrating efficacy (Neal *et al.*, 2008a; Raju *et al.*, 2011; El-Rashidy *et al.*, 2013; Sharma *et al.*, 2013, 2016; Kim *et al.*, 2016; Lambrechts *et al.*, 2017). Meta-analysis suggest that children treated with KD are six (Martin-McGill *et al.*, 2020) times more likely to achieve at least 50% seizure reduction in comparison to those treated with usual care. Yet, the mechanisms underlying the clinical effects of KD therapy are not yet fully understood (Murakami and Tognini, 2022).

The National Institute for Health and Care Excellence (NICE) guidance (CG137) recommended seizure freedom as the primary outcome and seizure reduction, cognitive function and quality of life (QoL) as secondary outcomes when treating epilepsy (National Institute for Health and Care Excellence (NICE), 2012). van Berkel *et al.* (2018) in a systematic overview, identified 33 studies that considered cognitive outcomes. Over half of which were retrospective and parent reports. Subjective reporting of cognitive improvement dominated with fewer studies using objective measures. Similarly, a recent Cochrane review (Martin-McGill *et al.*, 2020) identified only one RCT (IJff *et al.*, 2016; Wijnen *et al.*, 2017) which assessed the effect of KD therapy on QoL, cognition and behaviour, highlighting the need to assess these outcomes objectively in future clinical trials. The development of a core outcome set is suggested as a solution to the heterogeneity that exists in existing outcome reporting (Martin-McGill *et al.*, 2020). This systematic scoping review is the first phase of the development of a core outcome set for childhood epilepsy treated with KD therapy.

3.2 Aims and objectives

This scoping review aimed to identify a list of outcomes measured and reported in past studies of epilepsy childhood epilepsy treated with KD therapy.

Research question

What outcomes are measured and reported in studies of childhood epilepsy treated with KD therapy?

Objectives

i) to systematically identify a comprehensive list of outcomes reported in published studies of childhood epilepsy treated with KD therapy
ii) identify the range of tools or methods used to measure the reported outcomes.

3.3 Summary of methods

Chapter 2 outlined the detailed methodology. In summary, the review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (Tricco *et al.*, 2018). It was registered on the JBI systematic review register and the COMET online database (COMET Initiative, n.d.). The full inclusion and exclusion criteria, search strategy, approaches to study screening, data extraction and synthesis were stipulated *a priori* in a published protocol (Carroll *et al.*, 2019). The protocol followed the criteria recommended by the JBI. 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

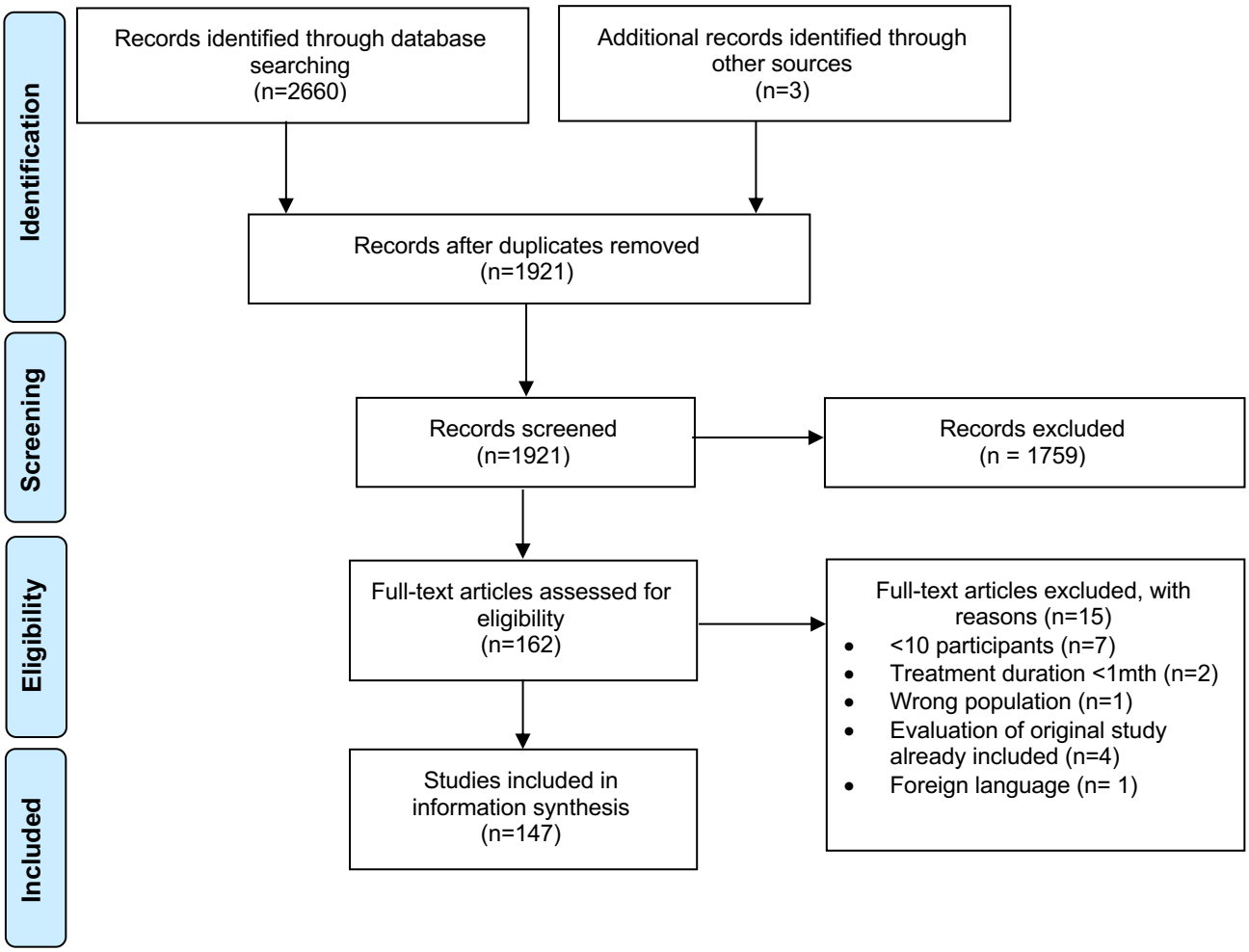
agreement. This study focussed on the reporting of the frequency of outcomes rather than the incidence or value of these outcomes, hence study quality nor risk of bias were relevant or assessed. The only deviation from protocol was to develop and use a standardised data extraction proforma instead of JBI SUMARI® (Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information) as this necessitates quality assessment of included studies.

3.4 Results

3.4.1 Studies identified

The search identified a total of 2663 articles (Figure 7); 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 OAIster returned relevant articles, though all were duplicates of those already identified in database searches. After duplicates were removed, 1921 articles remained. 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. Fifteen articles were excluded for reasons including: number of participants (<10), short treatment duration (<1 month), evaluation of an original study already included in full texts and foreign language.

Figure 7. PRISMA flowchart of scoping review
(Preferred Reporting Items for Systematic Reviews and Meta-Analyses)



Characteristics and demographics of the included studies are detailed in Table 12. There was almost an equal number of articles arising from prospective (n=73) and retrospective study designs (n=74). Recently there seems 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 the majority of 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.

Table 12. Characteristics and demographics of included studies

Study design (n = 147 studies)	
RCT	7 (plus 4 additional articles)
Prospective	62
Retrospective	74
Location (n = 147 studies)	
Europe	47
North America	32
South America	5
Asia	59
Australia	4
Year of publication (n = 147 studies)	
2008-2010	36
2011-2013	33
2014-2018	78
Study duration (n = 111 studies with stated duration)	
Mean	10 mths
Range	0.25-24 mths
Follow up (n = 147 studies)	
Range	0.25 mth – 10 years 7mths
Number of patients (n = 147 studies)	
Median	40
Range	10-317
Type of KD (n = 147 studies)	
Classical KD	95
MCT KD	3
MAD	12
LGIT	4
Classical KD or MAD	8
Classical KD or MCT KD	15
Classical KD or MCT KD or MAD	4
Classical or MAD or LGIT	1
Outcomes identified *a priori* (n = 147 studies)	
Primary and secondary outcomes	20
Primary outcomes only	21
Nil	106

3.4.2 Outcome classification

A total of 921 verbatim outcomes were measured and reported in 147 articles. Considerable repetition and overlap existed in outcomes and the terminology used to describe these so these were stratified into 90 unique outcome categories. For example, the outcome category ‘seizure frequency’ encompassed *seizure frequency, seizure reduction, seizure control and seizure freedom*. The 90 unique outcome categories were classified into 21 relevant domains of the COMET taxonomy (Dodd *et al.*, 2018). 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. Adverse effects on body systems were classified accordingly and the domain ‘adverse effects’ encompassed outcomes such as predictors and severity of adverse effects. The 90 unique outcome categories listed in table 13 were taken forward into the pre-Delphi consultation process (Chapter 6).

Table 13. 90 0utcomes in order of decreasing reporting frequency, classified according to the COMET taxonomy

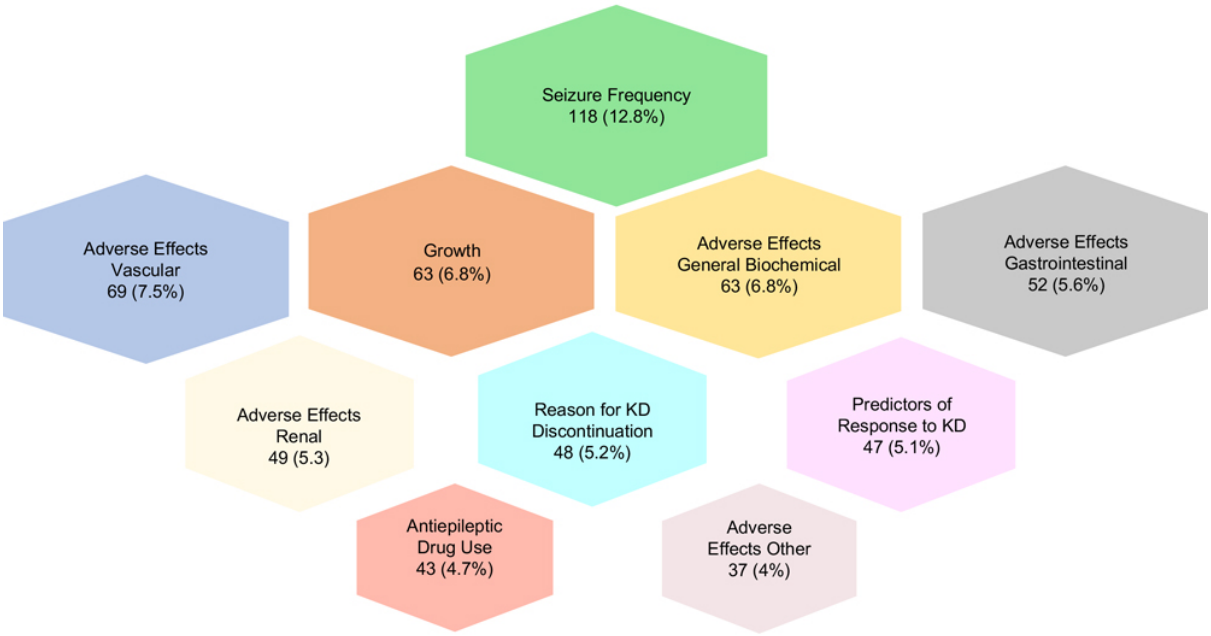
COMET Taxonomy core area and outcome domain	Outcome	Outcome N	Articles N
Physiological/Clinical *Nervous System outcomes*	Seizure frequency	118	107
	Anti-seizure medication use (ASM)	43	43
	Change in electroencephalogram (EEG)	34	34
	Spasm frequency	10	8
	Comparison of treatments	7	7
	Long-term seizure outcomes	7	7
	Seizure severity	6	6
	Anti-seizure medication drug levels	4	4
	Cholecystokinin-8	1	1
	Concentration of norepinephrine dopamine and serotonin	1	1
	Cerebrospinal fluid (CSF) serum levels	1	1
	Efficacy in different epilepsy syndromes	1	1
	Neurological improvement	1	1
	Seizure cluster	1	1
	Seizure intensity	1	1
	Seizure recurrence	1	1
	Seizure remission	1	1
	Status epilepticus incidence	1	1
Physiological/Clinical *General outcomes*	Growth	63	63
	Adverse effects general biochemical	63	59
	Adverse effects other	37	37
	Medication use other	1	1
	Predictors of growth on KD	1	1
	Sleep	1	1
Physiological/Clinical *Vascular outcomes*	Adverse effects vascular	69	69
	Level of ketosis	22	21
	Predisposing factors for dyslipidaemia	1	1
Physiological/Clinical Gastrointestinal outcomes	Adverse effects gastrointestinal	52	52
	Gut microbiota	3	3
	Predictors of gastrointestinal abnormality	1	1
Physiological/Clinical *Renal and urinary outcomes*	Adverse effects renal	49	48
	Effect of empiric potassium citrate use	1	1
Physiological/Clinical *Metabolism and Nutrition outcomes*	Dietary intake	11	7
	Adverse effects nutrition (incl. Parenteral nutrition)	3	3
	Tolerability	3	3
	Food preference	3	3
	KD adjustment	3	2
	Resting energy expenditure (REE)	2	2
	Change in substrate oxidation	1	1
	Efficacy of ketogenic parenteral nutrition	1	1
	Palatability of KD formula/supplements	1	1
	Impact of dietary changes and supplementary interventions on dyslipidaemia	1	1
	Appetite	1	1
Physiological/Clinical *Hepatic outcomes*	Adverse effects hepatic	28	27
Physiological/Clinical *Cardiac outcomes*	Adverse effects cardiac	26	19
Physiological/Clinical *Musculoskeletal outcomes*	Adverse effects bone health	16	16

COMET Taxonomy Outcome Domain	Outcome	Outcome N	Articles N
Physiological/Clinical *Respiratory outcomes*	Adverse effects respiratory	7	7
Physiological/Clinical *Endocrine outcomes*	Adverse effects endocrine	1	1
	Leptin	1	1
	Risk factors for development of hypothyroidism	1	1
	Thyroid hormonal status	1	1
	Physiological/Clinical Outcomes	**714**	
Functioning *Delivery of care outcomes* - withdrawal from treatment	Reasons for KD discontinuation	48	48
	Predictors of worsening during discontinuation	2	1
	Predictors of discontinuation rate	1	1
	Reasons for not commencing KD	1	1
	KD discontinuation approach	1	1
- Appropriateness of treatment	Predictors of response to KD	47	45
	Compliance	7	7
- Adherence/compliance	KD duration	3	3
	Retention	4	4
- Process and implementation	Onset of ketosis	2	2
	Time to KD response	1	1
	Recollection of KD	1	1
- Acceptability and availability	Reason for KD continuation	1	1
- satisfaction/patient preference	Recommend KD to other families	1	1
Functioning *Social functioning outcomes*	Behaviour	11	9
	Alertness and or interactivity	8	8
	Socialization	3	3
	Hyperactivity	1	1
	Psychosocial adjustment	1	1
Functioning *Cognitive functioning outcomes*	Cognition	16	11
	Neuropsychological ability	2	2
Functioning *Physical functioning outcomes*	Developmental progress	10	10
	Activities of daily living	2	2
	Motor function	1	1
Functioning *Emotional/well-being outcomes*	Mood	3	3
	Emotional dysfunction	1	1
Functioning *Global quality of life outcomes*	Quality adjusted life years children (1-16yrs)	6	2
	Quality of life	4	4
	Life Impact - Functioning Outcomes	**189**	
Resource Use *Hospital outcomes*	Cost effectiveness of KD	4	3
	Number of hospital admissions	3	3
	Length of hospital stay	2	2
	Cost of emergency department visit and hospitalisations	1	1
	Number of emergency department visits	1	1
Resource Use *Economic outcomes*	Quality adjusted life years parents	2	2
Resource Use *Societal/carer burden*	Mothers quality of life	1	1
	Resource Use Outcomes	**14**	
Adverse events/effects	Anti-seizure medication side effects	1	1
	Interventions for adverse effects	1	1
	Predictors of severity of adverse events	1	1
	Severity of adverse effects	1	1
	Adverse Effects Outcomes	**4**	

3.4.3 Outcome reporting

Table 13 shows that the most common core area was Physiological/Clinical (N=714 outcomes), followed by Functioning (N=189), Resource Use (N=14) and Adverse Effects (N=4). The most often reported outcome domains were nervous system (26%), general (18%), delivery of care (13%), vascular (10%) and gastrointestinal (6%). Aside from delivery of care, other functioning outcome domains were infrequently considered including; cognitive functioning (2%), physical functioning (2%), global quality of life (1%), emotional and well-being (1%). The ten most commonly reported outcomes are mapped in Figure 8 from seizure frequency to adverse effects – other. Together, adverse effects for all physiological/clinical outcome domains accounted for 351 (38%) verbatim outcomes. Only 47 of 90 outcome categories were reported more than once.

Figure 8. Map of the 10 most commonly reported outcomes



3.4.4 Outcome measurement

Objective or validated measures were undertaken for 376 (41%) verbatim outcomes. The most commonly used measures included; biochemical investigations; serum and urinalysis, anthropometry and clinical investigations; ultrasonography, DEXA, electroencephalogram, and electrocardiogram. In contrast, the remaining 545 (59%) outcomes were assessed using subjective measures including; review of clinical records, parent or clinician reported, seizure diaries and unvalidated questionnaires. Only 13 articles (9%) used validated outcome measurement instruments, 23 in total (Table 14) to assess a range of 40 verbatim outcomes. Parent by proxy completion was most common (44%), followed by clinician respondents (17%), child respondent (17%), parent and/or clinician respondents (9%), parent and/or teacher respondents (9%) and finally mother respondent (4%).

Table 14. Validated Outcome measurement instruments

Questionnaire	Assessed Outcome	Respondent	Articles used
Chalfont Seizure severity scale (Duncan and Sander, 1991)	Seizure severity	Clinician/ parent	(El-Rashidy *et al.*, 2013) (El-Rashidy *et al.*, 2017)
National Hospital Seizure Severity Scale (NHS3) (O'Donoghue, Duncan and Sander, 1996)	Seizure Severity	Clinician	(Lambrechts *et al.*, 2017) (Lambrechts *et al.*, 2015) (Wijnen *et al.*, 2017)
Bayley scales of Infant Development- II (Bayley, 1993)	Developmental progress	Clinician	(Kang *et al.*, 2011)
Gross Motor Function Measure-88 (GMFM) (Palisano *et al.*, 1997)	Motor function	Clinician	(Cubukcu, Guzel and Arslan, 2018)
Denver Developmental Screening Test (Frankenburg and Dodds, 1967)	Gross/fine motor, language, adaptive personal-social skills	Parent/clinician	(Pires *et al.*, 2013)
Functional Independence Measure for Children (Msall *et al.*, 1994)	Activities of daily living	Clinician	(Cubukcu, Guzel, and Arslan, 2018)
The Hague Restrictions in Childhood Epilepsy Scale (HARCES) (Carpay *et al.*, 1997)	Activities of daily living	Parent	(IJff *et al.*, 2016)
Peabody Picture Vocabulary Test (PPVT-III) (Dunn and Dunn, 1997) **Dutch version** (Schlichting, 2005)	Cognition	Child	(IJff *et al.*, 2016) (Lambrechts *et al.*, 2013)
The Beery Developmental Test of Visual Motor Integration (Beery and Beery, 2006)	Cognition	Child	(IJff *et al.*, 2016) (Lambrechts *et al.*, 2013)
FePsy neuropsychological computerized test battery (Alpherts and Aldenkamp, 1990)	Cognition	Child	(IJff *et al.*, 2016) (Lambrechts *et al.*, 2013)
Pediatric Quality of Life Inventory (PedsQLTM) (Portuguese translation) (Ferreira *et al.*, 2014)	Cognition, behaviour, socialisation	Parent	(Ferraria *et al.*, 2013)
The Personal Adjustment and Role Skills Scale, third edition (PARS-III) (Hendriksen *et al.*, 2009)	Behaviour	Parent	(IJff *et al.*, 2016) (Lambrechts *et al.*, 2013)

Questionnaire	Assessed Outcome	Respondent	Articles used
The Strengths and Difficulties Questionnaire (SDQ) (Van Berkel et al., 2006)	Behaviour	Parent	(IJff *et al.*, 2016)
Child Behaviour Checklist (CBCL) (Achenbach and Ruffle, 2000)	Behaviour	Parent & teacher	(Nabbout *et al.*, 2011)
The Social Emotional Questionnaire (SEV) (Scholte and Van der Ploeg, 2007)	Emotional & behavioural Dysfunction	Parent	(IJff *et al.*, 2016)
The Profile of Mood States (POMS) (McNair, Lorr and Droppleman, 1992)	Mood	Parent	(IJff *et al.*, 2016) (Lambrechts *et al.*, 2013)
EuroQol Five Dimensions Youth (EQ-5D-Y) (Wille *et al.*, 2010)	**QALYs children	Child	(de Kinderen *et al.*, 2016) (Wijnen *et al.*, 2017)
EuroQol 5 Dimensions (EQ-5D) (Shaw, Johnson and Coons, 2005)	QALYs parents	Parent	(de Kinderen *et al.*, 2016) (Wijnen *et al.*, 2017)
TNO-AZL Preschool Children's Quality of Life (TAPQOL) (Fekkes *et al.*, 2000)	QALYs preschool children	Parent	(de Kinderen *et al.*, 2016) (Wijnen *et al.*, 2017)
TNO-AZL Children's Quality of Life (TACQOL) (Verrips *et al.*, 1997)	QALYs preschool children	Parent	(de Kinderen *et al.*, 2016) (Wijnen *et al.*, 2017)
WHOQOL-BREF (Arabic translation) (WHO, 1998)	Mothers quality of life	Mother	(El-Rashidy *et al.*, 2017)
Conner's Scale (Conners, 1969)	Hyperactivity	Parent & teacher	(Nabbout *et al.*, 2011)
***Side effects of Anti-Epileptic Drugs (SIDAED)** (Uijl *et al.*, 2006)	Side effects of KD	Parent	(Lambrechts *et al.*, 2017) (Wijnen *et al.*, 2017)

**SIDAED adapted with permission from authors to assess the side effects of treatment with KD as reported by parents. QALYs – quality adjusted life years*
Same dataset (4 articles): (IJff et al., 2016; de Kinderen et al., 2016; Lambrechts et al., 2017; Wijnen et al., 2017)
Same research group (7 articles):(Lambrechts et al., 2013, 2015, 2017; IJff et al., 2016; de Kinderen et al., 2016; Wijnen et al., 2017)

3.5 Discussion

3.5.1 Main findings

This review sought to identify the range of outcomes reported in research involving children with epilepsy treated with KD therapy and the associated methods used to measure these. To my knowledge this is the first review to do so; presenting a comprehensive and representative breadth of outcomes use in this field of research. The review confirmed that there is significant heterogeneity in the range of outcomes assessed and wide variability in the terminology used to describe outcomes. Nine hundred and twenty-one verbatim outcomes were stratified to 90 unique outcome categories, of which only 47 were reported more than once. Only 20 studies stated their intended primary and secondary outcomes *a priori* and these were predominantly seizure frequency and adverse effects. In contrary to NICE guidance (2012) which suggests cognitive function and QoL as secondary outcomes, yet few studies used these outcomes. Physiological and clinical domain outcomes were most often reported, suggesting prioritisation of these outcomes over other domains that relate to functioning, resource use and QoL. This focus on physiological and clinical outcomes risks overlooking outcomes that may have a profound effect on day-to-day functioning and QoL for the child and wider family.

3.5.2 Context of existing literature

An important issue emerging from the findings is the lack of consistency in outcome selection and reporting, with only 52% of identified outcomes (N=47) 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.* (2020) 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.

Drug resistant epilepsy is complex in nature, increasing the likelihood of additional comorbidities, including impairments in cognitive and social functioning (Hamiwka and Wirrell, 2009) and developmental delay (Russ, Larson and Halfon, 2012). Together, affecting the child's potential for learning and physical development. Yet, infrequent reporting of cognition, social and physical functioning outcomes occurred. Perhaps, owing to difficulty in choosing a suitable validated instrument and its application in trials and clinical practice. Twenty-three individual validated instruments were identified and utilised in 13 published articles, a very small proportion (9%) of the 147 articles included in the search. To compound this further, the majority of instruments (14) identified in the review were utilised by one research group in the Netherlands who clearly value validated measures (Lambrechts *et al.*, 2013, 2015, 2017; IJff *et al.*, 2016; de Kinderen *et al.*, 2016; Wijnen *et al.*, 2017). Only 12 of the instruments were used more than once and always by the same researcher or research group. This lack of uniformity in instrument use and the variety of scales, questionnaires and scoring systems used can lead to difficulty in synthesizing results for meaningful meta-analysis. Of the scales used, 18 assessed functioning, cognition or QoL. The Pediatric Quality of Life Inventory 4.0 (Peds QL™) (Varni, Seid and Rode, 1999) is widely used to assess health related quality of life in children and adolescents including those with epilepsy, yet featured only once, as a Portuguese translation, in this review (Ferraria *et al.*, 2013). An epilepsy specific version; Peds QL™ Epilepsy Module developed in 2016 (Follansbee-Junger *et al.*, 2016) has not yet been used for those with complex epilepsies treated with KD therapy. Shortcomings and challenges exist when applying validated tools like Peds

QL to populations with disability. Anecdotally, parents report it highlights what their child is not able to do rather than what they have achieved, in spite of their comorbidities. In clinical practice, ketogenic teams try to address these shortcomings by developing alternative questionnaires tailored for parents or caregivers of children with chronic epilepsy (Bruce *et al.*, 2017). Whilst focussed and brief, these are rarely validated which raises concerns regarding the reliability of the findings. One exception; the KetoQoL (Barwick *et al.*, 2017) should be considered for use given it is a parent reported health related quality of life assessment tool which evaluates physical, cognitive, social, intrapersonal, effect on family and overall QoL domains.

Seizure frequency was the most commonly reported outcome; an unsurprising finding given a common goal of KD therapy is to improve seizure control. Similarly, growth and adverse effects dominate possibly due to the long-held concern that KD may affect growth velocity (Vining *et al.*, 2002; Neal *et al.*, 2008b; Armeno *et al.*, 2019; Ferraris *et al.*, 2019) and the potential for such drastic change in dietary intake to cause short (Neal *et al.*, 2008a; Lambrechts *et al.*, 2017; Sondhi *et al.*, 2020) and longer term adverse effects (Dressler *et al.*, 2010; Caraballo *et al.*, 2011; Chen and Kossoff, 2012; Youn *et al.*, 2020). This review does not address the actual incidence of adverse effects; instead, the adverse effects considered by researchers and the reporting; null or otherwise was the topic of interest.

Subjective parent reported seizure diaries were most often used to assess seizure frequency. A relatively crude measure that demands a moderate degree of intellectual capability and literacy to complete. The challenge of accurate seizure reporting is increased by children often have multiple daily caregivers at home, school and in respite centres. Seizure diaries are open to non-compliance, recall

bias, inaccurate awareness or nomenclature of seizure types and under-reporting (Akman *et al.*, 2009; Fisher *et al.*, 2012). Yet despite these challenges, it is a low cost and easily accessible measurement for caregivers. Online seizure diaries may be more flexible, graphing date and time stamped data that may be shared with clinicians. Future studies should state whether a paper based, or electronic seizure diary was used in data collection.

Almost half (43) of the 90 unique outcome categories were reported only once in the 10-year period assessed, suggesting these outcomes may be considered of less importance. Sleep was among these, which is somewhat surprising given the interest in the relationship between sleep and epilepsy (Mendez and Radtke, 2001; Kotagal and Yardi, 2008; Reilly *et al.*, 2018) and earlier work by Hallbook *et al*. (2007) which suggested a significant decrease in daytime sleep and improved sleep quality in children with drug resistant epilepsy treated with KD therapy. Further to this, a recently developed core outcome set for benign Rolandic childhood epilepsy included five sleep related outcomes in the final list of 39 core outcomes, suggesting that sleep may in fact be a key outcome to consider (Crudgington *et al.*, 2019).

The importance of involving families in research is well documented (INVOVLE, 2012.; Rosenbaum, 2011), yet, it was not reported in the design of any study in this review. Previous studies have examined parental expectations (Farasat *et al.*, 2006; Bruce *et al.*, 2017) and attitudes (Schoeler *et al.*, 2014) towards KD therapy via questionnaires, but no attempt has been made to establish parental opinion on healthcare outcomes of importance. The importance of which should not be underestimated given core outcome set studies that sought patient opinion, highlighted further new outcomes not previously identified through systematic review

of published studies (Kirwan *et al.*, 2003; Arnold *et al.*, 2008; Rosenbaum *et al.*, 2010).

3.6 Strengths and limitations

Our rigorous approach to identifying a range of reported outcomes in childhood epilepsy treated with KD therapy has produced a representative breadth of outcomes used in this field of research. Strengths of this work include the *a priori* registered and published protocol (Carroll *et al.*, 2019), adherence to PRISMA-ScR guidance (Tricco *et al.*, 2018), exhaustive searches, blind screening and agreement between independent reviewers. In addition, the data extraction tool was piloted and considered not only outcomes but also the methods or tools of measurement used. Owing to the large number of included articles; data extraction was undertaken by the lead researcher (JC) only. However, the findings were verified by a second reviewer (KMMG) who independently extracted data from 10% of included articles with agreement. The search only includes articles up to 2018, however research published since is unlikely to change the list of outcomes given the extensive repetition experienced in this review. New outcomes identified from interviews with parents (Chapter 5) will be added before undertaking the Delphi survey.

3.7 Conclusion and next steps

The results from this systematic scoping review demonstrate that there is significant variability in outcomes reported in studies of drug resistant childhood epilepsy treated with KD and the methods by which they are measured. Equally, functioning and QoL outcomes are infrequently measured and reported despite the likely importance of these in day-to-day life for the child and wider family. This indicates a clear need for the development of a core outcome set for this clinical area. The 90 unique outcome

categories identified in this review were combined with outcomes identified through a series of semi-structured interviews with parents of a child with epilepsy (Chapter 5) to produce a comprehensive list of outcomes. The list was reviewed in the pre-Delphi consultation process and used to populate the Delphi survey (Chapter 6) conducted in Phase 4 of the study.

Chapter 4: A qualitative study to explore parents' experiences of epilepsy and ketogenic diet therapy

Preface

Chapter 1 illustrated that families experiences of epilepsy treated with KD therapy are not well understood. In this chapter, the results of the phase 2 semi-structured qualitative interviews with parents are presented. The family's experiences of epilepsy and ketogenic diet are explored, including the impact of epilepsy and KD therapy on the family, the everyday challenges of managing KD therapy, and the factors that may assist future families in managing this type of therapy. Understanding these experiences will assist in providing context and insight for parents' views regarding outcomes and prioritisation, as discussed in chapter 5. Work arising from this chapter has been published (open access) in Seizure – European Journal of Epilepsy (Carroll *et al.*, 2022b). A further manuscript is in preparation for submission to Epilepsia focussing on families' experiences of epilepsy and KD therapy. Sections of this chapter have been taken directly from the edited manuscripts. The researcher led the data collection and analysis and wrote the original draft of the manuscripts, which was edited by the supervisory team and then subject to peer review. The published manuscript is available in Appendix P.

4.1 Introduction

Drug resistant epilepsy is a life-changing diagnosis for the child and their family, requiring them to adjust to a new 'normal', characterised by the unpredictability of seizures and the coexistence of comorbidities (Harden, Black and Chin, 2016; Bruce *et al.*, 2017). It is widely accepted that chronic illness, such as epilepsy, presents additional burdens and care needs for parents, increasing their anxiety, stress, and depression (Kerr, Nixon and Angalakuditi, 2011; Reilly *et al.*, 2018b). However

insufficient attention has been paid to how KD therapy might impact upon day-to-day life for families. KD therapy can offer hope to families when ASMs, surgery or VNS have failed or are not viable treatment options. However, it requires substantial changes in routine and dietary habits, even when more liberal and relaxed diets are used, such as modified Atkins or modified KD.

Webster (2018, 2019a) investigated the experiences of parents and siblings with childhood epilepsy and, together with Gabe (2016), examined the identities of parents when using the KD for their children. Parents were able to maintain their identity as good parents by medicalising KD and treating food as medicine, despite the restrictions KD imposed on their child. This qualitative study aims to build on these earlier findings by exploring family experiences throughout the child's epilepsy journey, from diagnosis to management of KD therapy. A deeper understanding of these experiences will assist us in providing the appropriate support to families. The clinical implications of the findings are discussed, concluding with recommendations regarding how families using KD may be better supported to access and manage this therapy.

4.2 Aims and objectives

This qualitative descriptive study aimed to broaden our understanding of the impact of epilepsy and KD therapy, providing insight into parents and family experiences.

Research question

How do parents describe their families' experiences of epilepsy and KD therapy?

Objectives

1) Explore the impact of drug resistant epilepsy on the child and wider family

2) Identify parents' expectations of KD therapy and the extent to which these were met

3) Identify the effects of KD therapy

4) Explore the day-to-day management of KD therapy

5) Identify strategies which have supported families with KD therapy

6) Make recommendations for clinical practice.

4.3 Summary of methods

Chapter 2 outlined the detailed methodology. In summary, participants were eligible if they were a parent or carer to a child aged 0-18 years with drug resistant epilepsy being treated with KD therapy or had weaned from KD in the past year, were English speaking and were able to consent and participate in an interview. Participants were recruited from across the UK and internationally via gatekeepers at three primary sources: 1) Nine UK Participant Identification Centres, 2) Charity organisations: Matthew's Friends, Young Epilepsy and Epilepsy Action, 3) Epilepsy – the Ketogenic way: a family support group on Facebook. The study was also regularly advertised on social media platforms Twitter and Facebook. Written consent was gathered for participation in a semi-structured interview conducted via telephone, video call or in person. During the interview, each participant was invited to share 'the story' of their child's epilepsy. Naturally, this often began with the epilepsy diagnosis, followed by the subsequent impact on the child and wider family. Parents' hopes and expectations of KD therapy, day-to-day experiences, outcomes of treatment and helpful strategies to manage KD therapy were explored using a semi structured interview schedule (Section 2.6.4 Table 10). All interviews were audio-recorded,

professionally transcribed (intelligent verbatim transcription), and uploaded to NVivo 12 (QSR International, Burlington, Massachusetts, United States). Thematic analysis was undertaken to investigate the detailed contextual descriptions of families' experiences (Braun and Clarke, 2006). The data was minimally theorised, instead, it is an account of the experiences of the families, what it meant to them, what they think and believe.

4.3.1 Patient and Public Involvement and Engagement (PPIE)

Table 15 summarises the ways in which PPIE was incorporated into this Qualitative phase of the study and the outcomes it influenced.

Table 15. PPIE in the parent interviews - Phase 2 of the CORE-KDT study
Reported in accordance with the GRIPP2-SF (Staniszewska *et al.,* 2017)

Section and topic	Item
1. Aim Report the aim of the study	- To explore how parents describe their families' experiences of epilepsy and KD therapy - To identify which outcomes parents regard as important when undertaking KD therapy to treat refractory childhood epilepsy
2. Methods Provide a clear description of the methods used for PPI in the study	- Lay research partners and the study advisory group reviewed the interview schedule - Lay research partners helped to develop a procedure for providing support to parents if they became upset during the interview - Lay research partners supported recruitment of parent participants via their charity forum, a closed Facebook group and social media - Lay research partners and the study advisory group reviewed the newly identified parent outcomes and supporting quotes - Lay research partners and the Study Advisory group provided critical review of the write up of the results from phase 1 and 2 of the CORE-KDT study
3. Results Outcomes – report the results of PPI in the study, including both positive and negative outcomes	- A demographic question regarding the number of ASMs trialled prior to commencing KD therapy was added to the interview schedule - The interviewer had a procedure to support any parents who might have become upset during the interviews, however this was not needed - Labelling of 7 new outcomes and the language of associated descriptors was agreed - Two posters were prepared and presented at Global Keto 2021 and a paper published in Seizure - Lay research partners contributed to a plain English summary, approved its inclusion in the Matthew's Friends Newsletter and

Section and topic	Item
3. Results cont.	supported an open online update meeting for parents where the findings of the CORE-KDT were shared
4. Discussion Outcomes – comment on the extent to which PPI influenced the study overall. Describe the positive and negative effects.	- PPI influenced the design of the interview schedule which improved the reporting of the demographics of the participants later in the study. KD therapy is often used as a 'last resort' therapy so collation of data on the number of ASMs trialled pre-KD enabled us to assess where in the journey of treatments for drug resistant epilepsy, KD was implemented. Meaningful dissemination to both parent and professional audiences was enabled by PPI.
5. Reflections Critical perspective – Comment critically on the study, reflecting on the things that went well and those that did not so others can learn from the experience	- PPI in this phase of the study was very effective and influenced key aspects of the study. The interviewer felt more prepared when undertaking the interviews. There was a real sense of teamwork and accomplishment in disseminating the results from the first two phases of the study. However, there were limitations. - The lay research partners and study advisory group members did not receive formal training to support their involvement in study design, planning and delivery. Instead, the lead researcher set expectations and provided support and guidance when needed. While no member raised this as an issue, the lack of formal training could have caused anxiety regarding their ability to contribute effectively. However, formal training may have also increased the burden on them commanding more of their time - This study was largely unfunded, so representatives did not receive remuneration for their time owing to resource constraints - The study advisory group did not meet at any point during the study. This was mainly due to the fact we did not have the resource to offer remuneration for the members or support reimbursement of travel expenses. They did often see each other's feedback as documents with tracked changes were shared but the lead researcher coordinated their involvement seeking ad-hoc input at each phase of the study as needed rather than hosting regular meetings. The bulk of their involvement was prior to the covid pandemic when the use of video calling technology was not so widespread, but this could be used as a cost-efficient way of bringing representatives together in future studies.

4.4 Results

4.4.1 Participant demographics

Thirty-eight parents registered their interest to take part in the study by completing a contact form on the study webpage or emailing JC. In total, 21 parents were recruited and interviewed (19 individuals and 1 couple), representing 21 children as one

mother had two children following a KD. Table 16 lists how parents found out about the study. Advertising by charities on their social media platforms and in closed parents' forum (Matthew's Friends only) proved to be the most successful recruitment strategies. No participant withdrew from the study.

Table 16. Successful recruitment strategies for the qualitative interview phase

Recruitment strategies	N
Advert shared by Matthews Friends on social media, newsletter or parents' forum	13
NHS Participant identification centres	3
Social media advert shared by Young Epilepsy	2
Social media advert shared by Dravet Syndrome UK	1
Advert shared on Epilepsy Action website	1
Facebook (unknow source)	1

Of the 17 participants not recruited, four parents were initially willing to take part but were later unable to owing to their child being hospitalised, a family bereavement, pressures owing to the Coronavirus pandemic and a response lost in their junk folder. Two further participants were ineligible as their child's age group was already well represented or had weaned from KD greater than one year earlier. Finally, 11 parents failed to respond to the initial contact from the researcher and subsequent reminders. The contact form on the study webpage proved the most popular method of contact with 19 participants registering their interest via this route, only two emailed the researcher directly.

Semi-structured interviews were conducted between January and June 2020, with a median duration of 72 minutes (35-131 minutes). Table 17 summarises demographic data for parents and their children together with treatment related characteristics. In

contrast to the literature identified in the scoping review, 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 (67% male, 34% female) ranged in age from 2-17 years (median 8yrs 7mths) and had trialled between one to seven ASMs (median 4) prior to commencing KD therapy. The duration of KD treatment ranged from 4 months to over 5 years (median 1yr 10mths), during which nine children achieved complete seizure freedom and the remaining 12 experienced seizure reduction.

The majority of participants lived in the UK (N=15 across England, Scotland and Wales). International participants were recruited from New Zealand (N=2), Australia (N=2), America (N=1) and Ireland (N=1). Fifteen participants opted for a telephone call, four chose a video call and two chose to meet in person. One scheduled in-person interview had to be rescheduled to a video call due to the Coronavirus pandemic.

4.4.2 Emerging themes and sub-themes

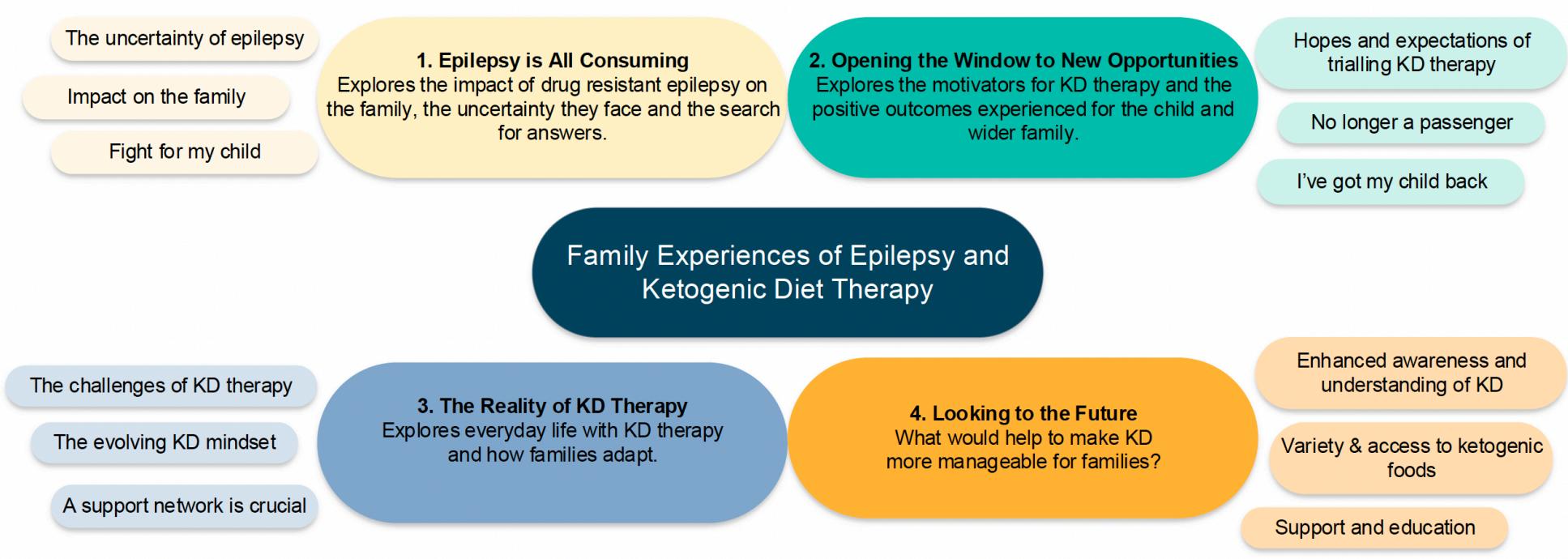
Thematic analysis identified four broad themes and 12 sub-themes, mapped in Figure 9. A narrative overview will follow of the journey families face from the diagnosis of epilepsy, through to commencing KD therapy, day to day life managing a KD and finally looking to what the future holds and how KD might be made easier for families. Appendix Q expands on figure 9 by mapping example codes and illustrative quotes to the themes to demonstrate the systematic process of coding undertaken.

Table 17. 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 8m 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 F	6y 3m 9y 0m	Drug resistant epilepsy	MKD MKD	Oral Oral	6m 6m	Seizure free 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 chain triglyceride ketogenic diet.*

Figure 9. Mapping of four themes and twelve subthemes



4.4.2.1 Theme 1: Epilepsy is all consuming

This theme explores the impact of drug-resistant epilepsy on the family, the uncertainty they face and often their fight to access KD therapy. All parents described the all-consuming nature of their child's clinical condition and the difficulties the wider family faced. The impact of epilepsy on the child, their parents and siblings will be considered. A quote from one mother illustrates this broad theme very well;

> *"So yeah, I guess if you asked what the impact of seizures on our life was - it was our life for quite a number of years. That's what we read and that's what we did, and it was all based around the children, and my husband and I didn't really get a look in. Plus, we're at the hospital every two weeks with appointments. We worked full time throughout that as well, both of us, so it was quite a lot going on in the house." (FP10)*

The uncertainty of epilepsy

In sharing their child's epilepsy story, parents recalled the first seizures, the initial diagnosis, and the 'spiral' that followed as they struggled to come to terms with and navigate their family's new reality. They described their experiences of watching their child seize regularly when ASMs failed as 'scary, devastating, worrying, and exhausting'. Parents faced many uncertainties, a 'constant unknown' that manifested itself in day-to-day and future uncertainties. Parents anticipated and worried about the next seizure and its impact, as well as the possibility of having to call an ambulance and their child be hospitalised. There was a sense of grieving for what might have been in the future, as it became clear that life would not turn out as they had planned;

> *"So yeah, 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. The unknown [with Dravet syndrome], even if he's doing well now, that can change overnight. Prior performance is no guarantee of future outcome. I'm a program manager, I plan. I have plans, and… I have my backup plans. Not being able to even envision or plan anything concrete – I know technically you can't for any kid – but it's just extra hard here." (FP11)*

Parents were faced with difficult decisions along the way and they didn't always feel equipped with the knowledge to address these. Using the internet, medical journals and expert professional opinion, they searched for answers and solutions to help identify their child's diagnosis or potential treatments. As one mother put it, she was 'a mother on a mission.'

> *"It was awful, actually….. I did everything I could and anything I could to help X to ensure that he would be seizure free. So I was a mother on a mission." (FP10)*

As a coping strategy, this drive to "find the answer" may have been helpful to address a sense of helplessness, attempting to bring some order to the uncertainty and unpredictability faced.

The impact of epilepsy on the family - parents

When asked how epilepsy had affected their lives, all parents described how it impacted on their physical health, mental health and wellbeing. Despite their best efforts to find answers and solutions, epilepsy 'was their life', with little control over their circumstances. One mother described the emotional toll of seeing her child's development regress and how difficult that was to cope with;

> *"It's really hard to know that the bright kid you had a month ago is going to turn into something like a disabled person. I don't want to be rude and say something more, but yes, to be someone that is just breathing. I've seen X twice in a condition like that. That's definitely, no parent wants to see that. …How we felt? Awful. You've seen heaven, that your kid can be okay, and then everything was torn to pieces and he was such a mess." (FP5)*

Parents had to be highly vigilant and couldn't risk leaving their child unsupervised in case they had a seizure. There were frequent medical appointments and hospitalisations for investigations, illness or seizures. It became increasingly necessary for parents to take on additional responsibilities, becoming medicalized as such for the sake of their child's routine care and safety. This was particularly evident

among parents who witnessed and managed their child's tonic clonic seizures. It was a highly stressful situation, which required parents to be prepared to resuscitate if necessary, while they awaited the arrival of an ambulance to take over the situation. A father described his experiences of having to be a ‘’life saver’ for his daughter, a role he did not expect to need as a parent;

> *“In terms of us having to resuscitate her at home before the ambulance is there and, yes, sucking obstructions out her airways, and giving her mouth to mouth. None of that is stuff that a parent wants to do but - well should never have to do, attending advanced life support training sessions. That’s all the stuff that has had a lasting impact on us. It’s good that we’ve got those skills but to have to be at the hard - the pointy end of the stick of not being a parent just being a life saver and having that training it’s taken away the sheen of what parenting could have been.” (MP1)*

Many parents reported having difficulty sleeping for a variety of reasons. Parents expressed general concern and anxiety regarding their children, and the additional workload and care required to meet the complex needs of their children often stretched into the night. It was common to use a night time monitor in order to alert parents if their child was distressed or seizing, which negatively affected their sleep quality.

> *“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…it’s like I’m tuned to hear them, my body now wakes up at about 3 in the morning and I can’t go back to sleep. So, it’s a huge impact.” (FP1)*

It was challenging for couples to spend quality alone time together; instead, families tended to do activities together. This was further compounded when families were isolated and didn’t have extended family close by to offer support. Although some were reluctant to allow others to care for their child especially when KD commenced. Some had seen their relationship fail, while others felt the challenges they faced 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 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.

> *"Well I gave up my career, probably that's the hardest thing for me because I was a kindergarten teacher..it wasn't just a job for me, it was a career, but I have to give it up to be his full time carer." (FP12)*

> *" she ([wife] had a very successful career and was on a good trajectory, earning good money…and something she was quite passionate about…well she said she always felt cheated out of the future she could have had…I think it's a grieving process for her." (MP1)*

This has understandably been a loss for those affected. As FP8 highlighted, when we meet people, our natural question is often 'what do you do?'. It is not uncommon for people to define themselves and each other by their roles, therefore, identifying with a profession, such as being a teacher or a scientist. Losing this professional role may exacerbate feelings of loss of identity. In addition to the personal loss, it is also likely to have a negative impact on the household's income. MP1 describes how he psychologically feels the burden of being the sole earner and the worry that brings;

> *"I've been worrying about losing my job all the time because if that happens then the whole thing falls apart and we lose the house, we lose the car, we lose the holidays et cetera. And also then try to marry that with not making [wife] feel like I'm keeping her- I'm allowing her to spend money…because inherently she feels like she's not earning any money, she's not contributing in the traditional – even though the hardest job in the world is being a mother, so she is doing the harder of the two jobs." (MP1)*

The impact of epilepsy on the family – child with epilepsy

Epilepsy affected children's physical health, their development and ability to learn, their social skills, and their QoL in many ways. Parents' explanations of what constitutes a good QoL varied, but FP18 described it as 'a normal type of life or being able to do activities of daily living'. It was felt that children were missing out on the opportunity to participate in everyday life because they were experiencing uncontrolled seizures on a regular basis. Children were more susceptible to illness, which in turn often aggravated the frequency and severity of seizures leading to

hospitalisations. Those with Dravet syndrome struggled to control their temperature and parents had to be careful with baths, warm weather and managing fever during illness. Injuries were common, especially for children with drop attacks or tonic clonic seizures. FP15 shared her reluctance to let her daughter participate in activities owing to the injuries she sustained from drop seizures and another mother (FP14) described the fear and panic her son experienced when a tonic seizure was coming on;

> *"Like if she's eating, she'd always hit her mouth and she would cry because she didn't - it's like blacking out, she doesn't know for a second what happened and she'd sometimes hit her mouth or her teeth or her head and she'd get a bruise or she'd fall down and it really limited what I would let her do." (FP15)*

> *"So when I say his seizure, 45 minutes on average, I'm talking about the tonic seizures. They call it a tonic, a so-called tonic hypermotor seizure because he's aware they're coming. He's frightened. He knows that he's going to stop breathing. He panics. He tries to fight through it." (FP14)*

Following a seizure, children often experienced fatigue and occasionally other symptoms like retching. They needed time to rest and recover which in turn impacted on their ability to participate in day-to-day activities like school. The ability to form social connections and friendships was affected and children struggled to gain the same independence as their peers without epilepsy. Their ability to participate in activities like swimming, rugby, gymnastics and sleepovers was often greatly limited due to fatigue, the risk of seizing during the activity, limited mobility, balance or coordination.

> *"..he missed a lot of schooling. He missed a lot of friendships and a lot of social growth that children would have throughout that time, just because you miss out, and he was obviously not actually present because of the seizures for a lot of it as well. But he's come out the other side, and yes, he's doing well." (FP10)*

Epilepsy also had a profound impact on children's cognitive development, affecting their learning and speech and language development. FP7 shared how her sons'

learning disabilities affected everything and in many ways the impact of this was worse than his seizures;

> *"I don't know how to quantify it really…he's been diagnosed so long the seizures themselves - it's hard to say this without sounding really callous. The seizures don't really bother us so much, it's the learning disabilities and the things that come with it that do… A lot of what comes with it, the learning disability impacts absolutely everything." (FP7)*

It was evident that parents had strong concerns about the side effects of ASMs. All but one described at length the side effects their children experienced. The child with no reported issues started KD therapy shortly after his first birthday having trialled just one ASM. Arguably, it was less likely he would experience side effects than children who had tried multiple ASMs in different combinations over an extended period of time. Appendix R contains an extensive list of the side effects parents attributed to individual ASMs, many of which were reported by St Louis (2009) in Table 3, section 1.5.1. Cognitive function, appetite, mood, behavior, sleep, and mental health were negatively affected, with one child experiencing suicidal thoughts. Children were described as being dazed and disengaged, often referred to as being in a 'zombie-like' state or being in a state of 'brain fog.' A minority of parents reported positive experiences, where ASMs improved seizure control or other symptoms such as brain fog or behaviour. However, these were overshadowed by the breadth of adverse effects parents shared and the debilitating impact of these on their children;.

> *"..You start looking at quality of life as well, because you're doing all these medications, you're going up, you're being advised perhaps if you want to go up, go up a bit higher, you want to go up to this. So, you're going up and you're seeing the impact in the behaviour, the education. Just everything really, quality of life. But they're wiped out and they're a bit of a zombie. That's not fair either." (FP6)*

It is important to interpret this data with caution since it is based on observations by parents over often long periods of time, and it is possible that adverse effects are incorrectly attributed to specific ASMs. The data does, however, provide a clear

indication of the breadth of adverse effects that children who have received polytherapy have experienced. There were some parents who felt their neurology team did not adequately inform or prepare them for the side effects of ASMs. When considering the wide range of adverse effects associated with ASMs, some parents expressed frustration that the ketogenic diet had not been considered earlier.

> *"Their view of the drug is if the drug works, we don't care about the side effects. It's almost like that's just what you have to live with; that's the price you pay. You might have an option of the diet, which would give you the same results, 50 per cent seizure freedom if that's what it is, but you don't have the side effects, then to my mind how is that not a better option?." (FP1)*

It was difficult to ascertain if the adverse effects experienced over time were solely attributable to the epilepsy, the ASMs or most likely a combination of both. Nevertheless, parents were highly motivated to wean their children from ASMs in an effort to reduce the symptoms they were experiencing.

Impact of epilepsy on the family – siblings

Over half of parents interviewed referred to their child's siblings and how epilepsy had 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 children 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)*

When the KD was started, siblings had to be educated and trusted not to swap or share food, which as FP2 describes, is difficult for a five-year-old twin sister to understand, yet she has. Like their parents, siblings too were often medicalised, many had witnessed their brother or sister seizing, seeing paramedics and ambulances arrive to their house. They spent more time in the hospital environment

than other children their age and this showed in their language and how they reacted to situations.

> *"Typically, its either the nanny or my husband who picks her [5-year-old sibling] up from preschool. I picked her up one day and she immediately was like what's wrong? Where's Daddy? Is he at the hospital? Did X have a seizure? How long was the seizure? What type was it? She knows. So, it's quite sad to see that in a kid who shouldn't have to worry about that." (FP11)*

Parents understandably worried that this may have a lasting impact and some sought professional help to support their children with their experiences. FP9 described how her little boy would shout and alert them if his twin brother had a drop seizure but despite his brother becoming seizure free on KD, he still worried about him. For example, he would become very anxious if he saw his brother climbing on a frame at the park. Having him assessed by a therapist, reassured his parents that there would likely be no lasting impact. In contrast, two of MP1's children (8 and 12 years old) have required longer term support from a therapist to help them process their experiences. Y found her sister mid seizure and frothing at the mouth and Z held an untrue memory where he believed his sister had a seizure and he was left at home alone while everyone else went to the hospital

> *"So for Y it's bound to have a lasting impact…she has anxiety problems about people dying when she is not around, about what's happening to her brother or sister or her mum and dad while she's at school, while she's asleep….she has massive control issues because of obviously what she's seen and not been able to help." (MP1)*

> *"Z…he's got a low sense of self-worth…it seems to stem from a sense of being abandoned at times when X had a seizure and mum and dad had to go away and look after her rather than one of us staying with him or whatever it is. So, the impact on the family has been quite tremendous." (MP1)*

Day to day life was affected with family plans changing last minute, stress surrounding mealtimes and siblings' friends not visiting. Despite their resilience and maturity, siblings were most often young children or teenagers and occasionally demonstrated jealousy or frustration at the situation. FP12 emphasised the wider

implications, particularly regarding genetic epilepsies and how DNA testing had been a concern for her older daughters to try to determine if their future children might experience epilepsy. Despite this, she was able to draw some positives from their difficult family experiences when she described how her two daughters are;

> *"very strong independent women' who don't worry about the small things in life." (FP12)*

Fight for my child

Almost half of the parents interviewed described how they had to initiate a discussion about KD therapy with their child's paediatrician or neurologist. If they hadn't done so, then their child might not have accessed the KD. Some managed to access KD therapy quite quickly therafter but many parents reported a lengthy 'battle' and 'fight for their child' to access the diet. It seems that the need to fight for their child was established during diagnosis or in the failure of early treatment strategies, and then continued into the pursuit of KD therapy as a possible treatment.

> *"Everything's a battle, that's one thing we learned. Nothing is easy, nothing's straightforward. A lot of people are nice, and they mean well, but it's a paid job, they don't live it….I'll do whatever it takes for X, I don't care. Every back door, stamp on anyone's feet, do whatever. It doesn't' matter. I will do whatever it takes to get X the right care that he needs. Plead or offend, it just is what it is." (FP14)*

The primary reasons given for delays in access to KD therapy were insufficient or non-existent local KD services or unsupportive health professionals. Some professionals held outdated views regarding the diet, including the belief that it was unpalatable, too difficult, only useful for tube fed children, and ineffective. Essentially, making the decision on behalf of the child and family rather than providing useful information and involving them in the decision-making process;

> *"The neurologist that we see was no, it doesn't work, it's not used for that, it's never been used for absence epilepsy, blah blah blah. She put me off and off for months.. I took in a whole tonne of documents and in the end she referred me…. So its [KD] still very much the poor relation, in my experience It feels like the diet's not given an even - that it's not an even playing field, which I think is a shame because there are people out there*

who could benefit from it who are potentially not being because they're not as pushy as I was and they haven't done the research that I did because of my own background and my own interest. If I didn't have that I wouldn't have done it either." (FP1)

One father recalled how they were told that there were no other options for his teenage daughter, beyond the ASMs she had already trialled. Nine years later they moved area, a new neurology team took over their daughters care and they suggested KD therapy. However, the uncontrolled seizures she endured during those nine years had a profound impact on her QoL as well as that of her parents and siblings. She went on to achieve complete seizure freedom and successfully weaned from KD. Her father shared the anger and frustration he and his wife felt knowing that KD could have been started earlier.

"Yes and I think first in our minds is the what if? So drugs [ASMs] for 10 years. What is the effect of that? Affects personal growth, regardless of the fog…But it feels like pumping her full of drugs for nothing. Then we feel very angry about the doctors in X telling us there's no intervention at all beyond drugs when clearly there was." (MP1)

It was interesting to observe that some families, despite the many difficulties they faced, were able to find the positives. They maintained that things could be worse than they were and demonstrated empathy for those 'who have it worse' than they do. This was possibly a coping strategy to help manage the challenges they were facing.

4.4.2.2 Theme 2: Opening the window to new opportunities

Drug resistant epilepsy can bring feelings of frustration, uncertainty, and helplessness. Trialling different ASM doses or combinations can leave parents feeling powerless and frustrated by the lack of improvement in their child's seizures. However, KD offered parents hope and the opportunity to possibly regain some control in the management of their child's drug-resistant epilepsy. Chapter 1 outlined

the broad range of seizure and non-seizure related benefits that may occur as a result of KD therapy. These were, however, not investigated in great depth qualitatively, nor were parents' perspectives on the benefits of KD explored in past literature. Hence, this theme explores parents' motivations for trialling KD therapy, the positive results their children have experienced, and the impact these outcomes have had on their families. One mother captured the essence of this theme when she described the KD as 'opening the window'. It was providing her son with the opportunity to unlock his potential and that offered her hope for what the future could hold;

> *"Be that little bit proud, yes, you're actually doing stuff now. Because it means, it's almost opening the window up to him learning new skills that he never had that possibility before…..the keto diet has just given me a bigger window of hope for there's still options out there for him." (FP12)*

Hopes and expectations of trialling KD therapy

Participants described their hopes and expectations of undertaking KD therapy for their child and what it would mean to them if these were achieved. Interviews revealed that several factors can influence parental expectations, including the severity of the epilepsy, associated comorbidities, and timing of KD therapy during the treatment pathway. Parents expectations can broadly be grouped into seizure related and non-seizure related outcomes. As might be expected, most participants hoped for improvement in seizure control.

> *"We didn't expect to be completely seizure free, we just wanted to be better than where we were at." (FP4)*

Many parents expressed their hope for seizure freedom and a return to some 'normality'. They almost apologised for anticipating this possibility before acknowledging that any reduction in seizure frequency would be welcome and likely more realistic.

> *"Ideal world that the seizures were going to stop and then after two years we'd wean him off the diet and have this normal child that would then play, speed catch up and get to where he should be in terms of his milestones, so that's the idealistic …but my personal realistic goal was, if we can reduce the seizures by half- or anything- any reduction in seizures." (FP19, MP2)*

Yet for a minority, KD would only be successful if complete seizure freedom was achieved. FP1 described how her son began KD treatment after two failed ASMs, with the hope of being seizure-free. His seizure activity was reduced by greater than 50%. However, KD therapy was having a negative impact on his QoL which they felt outweighed the seizure reduction experienced. His independence was still constrained regardless of how often his absence seizures occurred, and crucially, there were other ASMs that he could try. In contrast, FP12 expressed concern and fear that her son was out of treatment options after trying all ASMs and taking three at maximum doses before the KD began. The use of KD was almost seen as a 'last resort' in this case. Her expectations were somewhat lower; hoping seizures would improve enough to be manageable and less exhausting for her and her son. As a result of KD, his seizures were less severe, and he required fewer emergency rescue medications. This, along with improvements in cognitive, social, and emotional functioning, made continuing the KD worthwhile.

Beyond improvements in seizure control, parents hoped for reductions in the dose and number of ASMs, developmental gains, cognitive gains, improved social and emotional functioning and overall QoL. As FP8 indicated, parents need support and guidance from their keto team to establish realistic hopes and expectations of KD therapy and to recognise the gains achieved. On reflection, she realised that she was focussed solely on seizure related outcomes prior to KD therapy and didn't think beyond that.

> *"I think that's managing people's expectations and also reminding them that actually, that other stuff you're seeing is due to the diet." (FP8)*

Most parents felt their expectations of KD therapy were met or exceeded. There were, however, two families who were disappointed with the results, particularly in terms of seizure control. While one child remained on KD for two years before returning to a normal diet, the other weaned from KD after six months.

No longer a passenger

A strong subtheme throughout the interviews was the need parents felt to take an active role in managing their child's epilepsy and to gain some control over the situation. KD therapy was something they could 'actively' do that in turn might help their child;

> *"It was something we could do. It would take work and effort, whereas everything else was just kind of out of our control... it gives you a bit of control in the scenario, that you've got no control over." (FP11)*

A KD is a medical diet that has the potential to cause short and longer term adverse side effects. However, parents seemed to derive satisfaction from the knowledge that the diet was 'just food', and not an additional medication. This was not surprising given the range of reported adverse effects of ASMs described earlier. Food in essence was becoming medicine for their child. KD therapy is a significant undertaking, even when highly motivated and the responsibility of preparing every meal and snack correctly can be 'daunting'. Despite the challenges, there was a sense of accomplishment and pride among those interviewed when they felt they were mastering KD therapy. Likely, their self-efficacy, that is the belief in their capacity to manage KD was improving, as their confidence and skill grew. This in turn enhanced their sense of control and mastery of their situation. FP7 demonstrated this in her account;

> *'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)*

However, with that control comes additional pressure to 'get it right'. While the uncertainty of drug resistant epilepsy may have improved, everyday life was more complex which may have added to the stress and pressure parents felt. FP19 described the pressure she felt by being her son's medicine;

> *"I would say personally I feel pressured because I feel like I am his medicine, so I can't afford to mess things up or just go, you know what, I'm not doing it today, I can't be arsed, because I am his medication really." (FP19 MP1)*

Although the workload and burden increased with KD therapy, all but one parent interviewed were motivated to continue.

I've got my child back

The purpose of this section is to discuss the positive outcomes of KD and how they relate to this theme and the broader narrative of how families experience KD therapy. KD therapy outcomes will be revisited in chapter 5 and systematically presented in more detail, based on a content analysis of the outcomes identified by parents and their priorities.

All participants described the benefits their children had experienced as a result of KD therapy. These are summarised in a simple word cloud in Figure 10. Although it is a basic representation of a complex and large dataset, it provides a visual representation of the benefits parents reported with KD therapy. These benefits can generally be divided into seizure-related and non-seizure-related benefits, although they are often interrelated. It was common for parents to share the sentiment: 'I got my child back' when asked if their expectations of KD therapy were met. The benefits

experienced were undoubtedly positive for the child with drug-resistant epilepsy, but also for the wider family.

Figure 10. Parent reported benefits of KD therapy for children with drug-resistant epilepsy

All 21 children experienced a reduction in seizure frequency, while nine (42%) achieved complete seizure freedom. Achieving seizure freedom was described as ‘a dream come through’ as it positively impacted upon many other outcomes for the child. There was then a feeling among parents that keto teams were willing to consider weaning from an ASM, which was seen as another positive step towards 'lifting the fog' or 'zombie like state' experienced by their children.

Non seizure related outcomes also improved including behaviour, alertness and concentration. Children were described as being more ‘clear headed’ and ‘engaged’ at home, when interacting with their siblings and during school activities. People outside of the family including friends, health professionals and teachers, noticed the changes and would comment that ‘he/she is a different child now’. Parents found this to be very reassuring and rewarding, positively reinforcing their efforts with KD therapy. FP7 had come to terms with the fact that her teenage son would not

become seizure free, instead she described how the cognitive gains with KD therapy were the most impactful for her;

> *"For me progress, just the cognitive ones for me were the biggest ones. I can live with the seizures, I think I've got that used to the seizures being there, they're just part of what he is and they're always going to be there. But the cognitive benefits for me were the biggest. That was worth anything we go through." (FP7)*

Seeing their child smiling again or elements of their personality coming through was immensely rewarding for parents;

> *"Yep, she's just - because she's more alert and she's funny and she's a bit more chatty as well. So, just that person - you just see the personality again, I think, is what I find." (FP8)*

Clearly when KD therapy is successful it can lead to many positive benefits for the child. Equally, though it can be life changing for the entire family. When asked how they felt about the outcomes their children experienced, parents responded that it was 'life changing, unbelievable, surprising, incredible, amazing and blissful'. Feelings such as these serve to illustrate the magnitude of the benefits that were achieved. FP9 illustrated this when recalling the impact of her child achieving complete seizure freedom;

> *"Oh, it's completely changed our lives, completely and utterly. People don't understand it. I think people at school don't understand because they didn't see him when he was having seizures". (FP9)*

When asked about the impact on her and her husband, another mother explained that now her child's seizure control has improved, life feels almost normal for her and her family;

> *"I think the fact that our lives aren't revolving around which of us is staying awake at night with him to make sure he's not seizing because of the fever. Which of us is ready to go to the hospital. Constantly handing our daughter off to other neighbours and friends, to make sure she doesn't have to come to hospitals with us, until the other one of us can get home from work. It's made life feel almost normal. If you ignore the part that I constantly have to weigh out food, and spend my weekends baking, it's made life feel normal, and that's been amazing". (FP11)*

Interestingly there were some suggestions that it was challenging to identify if the benefits seen were because of KD therapy, weaning ASMs or a combination of both.

4.4.2.3 Theme 3: The reality of ketogenic diet therapy

So far, the profound impacts of epilepsy on the family have been considered. It has been demonstrated in the existing literature (chapter 1), as well as in the present study, that caring for a child with drug-resistant epilepsy imposes a greater burden on parents, caregivers, and siblings. While KD therapy can achieve positive results, it can also pose several challenges for families. In this third theme, 'the reality of KD therapy', I examine how families manage day-to-day with KD therapy and the challenges they face. A quote from FP19 illustrates this theme well, in which she described the positive impacts of KD therapy, but also emphasizes that it was not always easy;

> *"Its monumental, its huge…the impact that the diet has made on his life in a positive way – don't get me wrong though, it's really hard, our life is not like most other people. We don't have a normal life but it's so worth it." (FP19, MP2).*

A deeper understanding of these experiences could help to enhance our clinical management and support for families.

The challenges of KD therapy

The participants described a variety of challenges associated with the daily management of KD therapy (Table 18). As a consequence, they experienced additional stress, pressure, and anxiety during the early stages of therapy. A common view was that KD therapy is time consuming, rigid and inflexible, especially in the early months when there is so much new information to take in and new ways of thinking. One way to cope with change was to keep things simple by preparing and eating similar meals. Having meal plans and suggestions from their dietitian was

helpful, but parents felt frustrated if these were not tailored to their child's individual needs or were perceived to be too restrictive. There was little time to relax with daily tasks stretching late into the night including KD meal preparations, updating KD tracking and monitoring spreadsheets and online research regarding KD or epilepsy. Some had to dedicate a weekend day to KD meal prep in order to 'get ahead' for the following week.

> *"I think the first probably six to eight weeks is very difficult because you are completely changing everything and there's a lot of concentration involved.. I had to have complete quiet." (FP17)*

Parents recalled their disappointment if their child disliked or refused to try a keto meal after the effort that went into its preparation. Furthermore, the frustrations associated with trying to systematically identify potential sources of error when ketone levels fluctuated. Managing routine illness like viruses and infections was challenging for parents, trying to encourage their child to eat and managing their fluctuating ketone levels. Parents wanted to provide food that made their child happy while unwell but were restricted by the medical demands of the KD.

KD therapy changed the wider families eating habits in several ways. Some parents chose to adopt similar KD principles as their child, regardless of the risk of adverse effects to their heath, including weight loss or gain, raised cholesterol and vitamin or mineral deficiencies (Cervenka *et al.*, 2021). Those who did so felt strongly that this was a way for them to be a role model for their child and support them to not feel alone or different. Parents and siblings chose to avoid carbohydrate rich snack foods or to eat them away from the child on KD. Some felt this was a positive change, as they consumed less sugar and they were introduced to foods they would not normally consume, such as avocados (high fat, low carbohydrate) and celeriac (low carbohydrate).

Table 18. Challenges associated with ketogenic diet therapy

Challenges
Time consuming
Rigid and inflexible
Unindividualised meal plans
Trying to identify the mistakes or errors
Change in family eating habits
Missing out on favourite foods
Feeling different and excluded
Expensive
Access to suitable foods and drinks
Eating out and holidays
Lack of understanding from others
Difficult to trust others with the management of KD
Managing illness

Parents spent a great deal of time, energy, and planning on replacing missed or prohibited foods in order to prevent their child from feeling different. In view of the increased workload of KD therapy, it is not surprising that parents often put all their energy into their children's care and wellbeing, thereby neglecting their own.

> *"Yeah, the other - the other thing that was a bit - still is a bit of a challenge and when she first started, was our nutrition. So, my husband's and I - because everything was about her and what she was eating and all of that energy - my energy, went into her food and we were eating really poorly because you sort of - everything's going towards this food that we were just sort of oh, let's have toast for dinner." (FP15)*

In some cases, parents expressed concern about the extra cost of KD therapy, having to purchase foods that are high in fat or low in carbohydrates that they would not normally buy. This may be particularly challenging for single income households.

Several reported difficulties obtaining keto-friendly food, having to visit several supermarkets and order from multiple online stores in search of specific ingredients;

> *"Some weeks and some months have been harder than others. This current scenario we're in [COVID-19 pandemic] has been extremely stressful because we can't get online shopping slots. I go to Asda to get his extra special pesto sauce because it's the lowest in carbs I've found and the highest in fat. I go to the Co-Op or Tesco's to get his extra-thick double cream because of his dysphasia- it's thicker. Because it's the lowest carb, highest fat. I go to Sainsbury's to get his celeriac because it's the only place they do it…. I have to go in even further to Holland & Barrett to get seitan flour. None of these places are anywhere near us." (FP14)*

A small number of interviews were conducted during the early stages of the Coronavirus pandemic, and parents were anxious about the availability of even the most basic keto-friendly foods, such as eggs, cream, and butter. Substituting these required complex recalculations of meals.

Parents described the restrictions KD therapy imposed on their families' social activities, family fun and occasionally relationships with immediate family. When eating out, it was difficult to identify suitable meals on a menu that could be reconstituted into a keto-friendly meal, so some families avoided going out. Others felt the worry and pressure of managing these challenges while away on holidays was too great and it prevented them from going. It is not uncommon for parents of children with complex needs to struggle to entrust their child's care to others. As might be expected, KD therapy exacerbated this. It was felt that there was a general lack of understanding about KD therapy and the necessity of it – it wasn't just a 'fad diet'. Some parents have had excellent support from friends and family, while others have found it a 'lonely experience' and have been disappointed by the reactions of others. There was a fear that the dietary restrictions would not be understood or sustained by others, including family, friends, caregivers, school and respite providers. An account provided by one mother illustrated this challenge, as a few

strawberries given by well-meaning grandparents caused stressful consequences for her later;

> *"So the grandparents were the hardest because they obviously like the treats, the sweets, the chocolates. You know?...so say she had a sleepover and I pack all of her food and label all of the containers and then I say oh, did she eat her food? Yeah, yeah. Did she have anything else? Oh, she had a couple of strawberries. How many strawberries did she have? Oh, three or four. Meanwhile, I'm like oh my God, three or four strawberries, do you understand that's like - that's her whole meal of carbohydrates. Okay, you know she's not meant to have anything else and then I'd have to take it off her dinner so she can only have eggs for dinner because she's had extra. That caused her drama at night-time when she couldn't have anything else. That was probably the main thing." (FP15)*

Few parents reported side effects associated with KD therapy. Among the most common symptoms were constipation and gastrooesophageal reflux disease, with only one child experiencing raised cholesterol and a rash attributed to KD. However, these were managed with dietary adjustments. More difficult to manage was the behaviour feeding difficulties experienced by a minority of children.

It is important to note that not all parents experienced challenges during KD therapy. There was a small minority of individuals who were surprised at how well they adapted to KD therapy and attributed this to the fact that their child was young and/or compliant. Those interviewed were highly motivated to overcome any challenges they faced and make the necessary sacrifices in order to maintain a KD for their child. Ultimately, they felt it to be worthwhile and the same was true for parents whose child had achieved some improvement in seizure control and complete seizure freedom. This sentiment was illustrated very well by two mothers;

> *"Socially it's awkward, financially it's a bit hmm, shopping's a bit hmm, but at the end of the day there's no chocolate bar out there that's worth going back to how he was". (FP7)*

> *"But the downsides are manageable and minor compared to impact… It's amazing. The diet gives you the possibility - the limitations are so minor compared to the possibility to live a normal life. I believe this is valid for kids and adults. It gives you the opportunity - the limitations are not that*

frightful. It gives you the opportunity to live. That's it, to live, because the other one is existence. It's not living." (FP5)

In the following sections, the change in mindset required to enable parents to cope and adapt to such challenges will be examined and how they might be supported to do so.

The evolving KD mindset

Over the course of the interviews, 'the evolving KD mindset' emerged as a subtheme, exploring how parents' mindsets changed over time in order to effectively manage KD therapy for their children. By doing so, parents were able to achieve a greater sense of control over their child's epilepsy management, a concept closely associated with the subtheme "no longer a passenger". It appears that parents felt like they were on a journey of sorts with KD therapy, initially trepidatious but optimistic, gradually developing their confidence and skills, confronting and overcoming challenges along the way. Parents were faced with new ways of thinking about food, the ingrained principles of a low-fat healthy diet no longer applied and they 'picked their battles' with regard to food choices.

"You give your kids a really healthy diet and suddenly you throw al l that out the window and do the opposite…That business of, do you know what, if [keto] cake for breakfast works, then so be it." (FP8)

Many described how they 'threw themselves' into the KD education and preparation sessions and how over time the KD became easier. Early in the diet, FP2 described her initial tunnel vision; however, as time and experience progressed, she developed more confidence to adapt to her son's behavioural problems with food;

"The thing we ended up doing for his breakfast, which was the most challenging meal, is I figured out – because that was the other thing I noticed with the diet starting that got easier – I think I had a bit of tunnel vision going on. I think I had a bit of a lack of being able to think outside the box. I don't know if that's common." (FP2)

Parents initially followed the meal plans provided, fearing deviation in case of mistakes, but as their confidence grew, so did their ability to develop their own techniques and strategies to integrate KD into their daily life. Even so, this usually required good organisation and planning skills, with both partners taking on specific roles and sharing KD-related responsibilities wherever possible. 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. Firsts such as these were extremely formative, as they contributed to their sense of achievement and increased self-efficacy, which in turn enhanced their confidence and ease with KD.

> *"I mean, the first time we manage to go out for a meal, that felt like a win. So we went to Nando's and we just had plain chicken and broccoli. But, yeah, that felt like, oh actually we can do normal things you know?..We've had family to stay and we've managed to do fry ups and his hasn't looked noticeably different to anybody else's. So with a bit of planning and prep you can have food and join in and feel part of a social occasion." (FP18)*

A support network is crucial

A common view among those interviewed was that a support network was crucial to help families to cope with KD therapy. This network included a broad range of individuals and services including family members, friends, carers, other families with shared experiences, KD charities and their keto team. Some of the most valuable support was provided by those who listened and made an effort to understand and assist the family. Connections with families with shared experiences were particularly valued and these were generally via online forums and groups or social events like coffee mornings or keto cookery days.

> *"I attended two to three cookery days, yeah just to meet other people actually who were on a diet. Because that was one of the biggest things, you feel quite isolated and nobody else really understands…so just to have that link to a few people you meet on the cookery days was really invaluable." (FP6)*

Interestingly, parents had mixed experiences with online forums and groups. Some found them a helpful way to connect with others with shared experiences, while others felt posts often focussed on negative experiences. They were particularly helpful to one mother who lived in New Zealand, where there was only one keto service covering a wide geographical area where parents were unlikely to be able to meet in person. In contrast, a minority felt that they could become 'dragged in' and more panicked reading the worst-case scenarios. A mother shared that, on reflection, she realized she only posted when she was in need of support and usually, she posted 'the awful stuff'. Recognising this motivated her to think more positively about the small wins she and her child were achieving. There was a sense that people who used online forums and groups needed to find methods of managing and processing the information, recognising that sometimes the information will be helpful and at other times it won't be;

> *"I mean obviously people put on there if they have a good day, which is great, and it's great to hear success stories. But equally, sometimes like social media, that can make you feel oh, things aren't going so well. So, it's both really. It depends how a person is feeling really, I suppose. If you're feeling really upbeat that day and things are going well, you then think oh, brilliant news, and you think not too much of it. But somebody else might think, oh gosh, we're having a terrible time and nothing is going right and I'm not feeling great." (FP6)*

The experiences shared were primarily related to online groups rather than virtual parent meetings that some charities arrange. The virtual meetups may provide a more supportive and balanced environment because they are often facilitated by individuals with experience in epilepsy and KD treatment.

In the UK, Matthew's Friends and the Daisy Garland are both charities that provide support for families with KD therapy, with Matthew's Friends branches also in New Zealand, Canada, and the Netherlands. A similar service is provided by the Charlie Foundation, a US-based charity. Families found that a variety of supportive

resources were available to them, including recipes, one-on-one help, online peer support, keto starter kits, written information, and samples of ketogenic foods, provided by these trusted charity organisations. Parents valued these and felt supported by the community.

> *"I think the websites are really good, the ketogenic website and Matthew's Friends were really helpful. Obviously, they sent a pack at the beginning which was really lovely." (FP6)*

> *"..the Daisy garland group on Facebook, which is really good too, if I need recipes." (FP13)*

In addition, another organization, Young Epilepsy, supports families with epilepsy, and one parent emphasized the significant research they conduct and how encouraging that is for parents; 'it gives us hope'.

Keto teams including a consultant paediatric neurologist, specialist keto dietitian and epilepsy specialist nurse provided education, monitoring, fine tuning of the KD and sample recipes and meal ideas. Families were often supported by the same health professionals for many years and good relationships were formed as a result of this

> *"We have her [dietitian] on a pedestal because, well, we- maybe not directly, but we actually do feel like she's saved X's life, and that she's given X the opportunity to have as normal an adulthood as she could possibly have. So, yes, we kind of owe her everything, I guess." (MP1)*

Parents welcomed the support and motivation they received and in particular; timely responses to their queries, monitoring of the risk of adverse effects and bespoke individualised recipes and meal plans. Interestingly, they really respected and valued when their dietitian had trialled the KD and they had that shared experience. However, issues arose when parent's felt unheard, had to wait for long periods for follow up or were provided with recipes or meal plans which they felt would not work for their child.

4.4.2.4 Theme 4: Looking to the Future

Having gained a deeper understanding of KD therapy's impact on families, theme four 'looking to the future' aims to identify factors that may make the therapy more manageable for families. In particular, the researcher was interested in how they might be more effectively supported with KD therapy, and if it would be possible to summarise their suggestions into key recommendations for the keto community to consider. During the interviews, parents were asked to envision what it would be like if they had a magic wand that could help make KD easier. They shared a variety of experiences, ideas, and strategies, which were analysed and grouped thematically. A narrative overview is presented below describing parents' perspectives on topics such as; access to KD therapy, KD foods, support and education, transitioning from paediatric to adult KD services, and discontinuing KD therapy. Furthermore, this overview serves to contextualise and justify the five recommendations that follow in section 1.4.2.5. The goal of these recommendations is to provide guidance to the keto community of healthcare professionals, KD services, commercial medical nutrition companies, and charities on ways in which to optimise the support given to families when managing KD therapy.

Enhanced awareness, understanding and access to KD therapy

Some families were not aware of KD therapy prior to their neurology team suggesting it, which raised the concern for some that if they had not been informed, their child might never have accessed the diet. As one mother stated, 'it's about empowering parents with the knowledge that it's out there'. A number of families experienced significant delays in the initiation of KD therapy, as illustrated by the median number of four ASMs tried before starting KD therapy, which is double that suggested by clinical guidelines (Kossoff *et al.*, 2018).

Several parents expressed frustration, anger, sadness, and/or disappointment regarding what could have been achieved had a KD been initiated earlier. It was hoped that improved awareness and understanding of KD therapy among paediatricians, epilepsy nurses, and neurologists would result in fewer future families having to fight so hard or wait so long for a referral to a specialist keto team. A significant number of parents were passionate about raising awareness regarding KD therapy, and it was felt that participating in this study would contribute to this goal.

"So yeah, whatever I can do to shed light on how or why it works or at least to get more people on it, so we've got more data to collect, I'm here to help." (FP11)

More broadly, beyond access to KD therapy, parents would like family, friends, services like school and respite and the general public to have a greater understanding of KD therapy. Although this is arguably a tall order for such a niche treatment, people demonstrating a willingness to learn and understand would go a long way towards making KD therapy easier to manage for families.

Variety and access to ketogenic foods

The challenges of KD therapy were discussed earlier, with time being one of the greatest issues for parents; the time required to plan and calculate recipes, shop for specialty ingredients, and then prepare the meal. Consequently, it is not surprising that parents would welcome improvements in the convenience of KD therapy, including a greater variety of prescription medical nutrition products and store-bought options. Foods for Special Medical Purposes (FSMPs) are evidence based nutritional solutions for disease related malnutrition and/or other clinical conditions. FSMP status has been granted to a wide range of ketogenic milkshakes, deserts, macronutrient supplements including MCT oil, vitamins, minerals, and food products like cereal bars and muesli that can be prescribed for children in the UK. The range

and accessibility vary in other countries. As these foods are usually very high in fat and low in carbohydrates, they can be very useful in helping children to meet their daily fat goals without using up too much of their daily carbohydrate allowance. Most parents interviewed shared their experiences of at least one ketogenic product, describing their child's tolerance and how they incorporated them into the diet. Like many nutritional supplements, their acceptability varied over time, but parents generally regarded them as helpful. A creative approach to flavouring and incorporating them into savoury and sweet recipes helped to improve palatability. There were however some who experienced gastrointestinal side effects and had difficulty obtaining them locally, which added to their stress. In addition, one mother argued that these products are full of 'chemicals' and should be avoided, while another was worried if the stated ketogenic diet ratio could be trusted. There was a general sense that a wider variety would be welcomed and in particular a prescription flour;

> *"..more prescription items. So instead of all these fancy fours and stuff, why doesn't someone come up with one and put it on prescription? Make our lives easier." (FP14)*

It was noted that the range of foods available in health food stores and general supermarkets had improved considerably. However, families do not have access to keto ready meals, which if available would be very convenient. Unfortunately, product development for such meals would be very challenging given the bespoke nature of each individuals KD prescription. It was difficult for parents to get reliable information on new ketogenic foods or drinks without having to consult their dietitian each time they found something. It was suggested that a centrally held list be established, where parents could find out about new products and their suitability. However, given the rapid growth of the keto foods market, maintaining such a list would be extremely challenging for a keto team or charity.

Support and education

This subtheme examines parent perspectives on what constitutes quality support and education for families, including support from their keto team and KD charities. There is significant overlap in the earlier subtheme ‘a support network is crucial’ particularly in relation to the support that KD charities provide. In addition, the benefits of social group education are discussed where parents are able to interact with and learn from each other, as well as the potential for peer mentoring or support via a 'keto buddy' program.

i) Support from KD charities and the keto team

Earlier the immense practical and emotional support that charities such as Matthew's Friends, Daisy Garland, The Charlie Foundation, and Young Epilepsy provide families with was discussed. The keto team, however, has a responsibility to provide families with information about these organisations, rather than expecting parents to identify these organisations independently. There was a recurring theme in the interviews regarding the importance of supportive health professionals within the keto team who listened to parents and worked with them collaboratively. Negative experiences of being ignored, unheard, and unsupported had a lasting effect on families. Moreover, parents emphasised the importance of health professionals adopting a holistic approach to supporting families to access and manage KD therapy, as well as ensuring that a variety of optimal outcomes are considered. FP8 described this as ‘looking at the whole child and how everything impacts’. FP19 and MP2 expanded on this by encouraging health professionals to look beyond the numbers;

> *“we look at whole package, we look at other channels. There’s no measurement for that. I mean I could say, at the moment he’s at 90 per cent in terms of how I feel he’s doing in comparison to other days potentially. But I think for healthcare professionals, I would just like them to*

look more at the overall picture rather than being so number focused. [Partner in agreement] - Yeah look at the child. It's the child, isn't it? It's see the child." (FP19 MP2)

The need for support from the keto team extends to what is typically the final stage of KD therapy, that is weaning from the diet and returning to a more typical, standard dietary intake. It is common to consider this after two years of KD therapy, and usually the positive outcomes gained on KD are sustained after returning to a normal diet. However, the timing should be determined by the keto team and the family, rather than the family feeling pressured to discontinue the KD. In this stage of KD therapy, parents understandably often experience mixed feelings and emotions. It can be challenging to consider stopping KD therapy after successful treatment and a range of positive outcomes have been achieved. A mother whose child was on KD for over five years shared how she took two years to come to terms with the idea of slowly weaning her child off the diet. While she is now ready to make the transition, it is tinged with fear and nervousness in case the seizures worsen again, yet excitement at the opportunities to eat out and go on holidays more easily;

"Yes, I wasn't keen, they've pushed more than I have. I think it's taken me two years to get to okay, let's give it a go, put it that way… I'm terrified and excited at the same time. It would very much be nice to be able to just go out for a meal with the family, to have a social experience…. just to be able to hop on a plane and go actually do you know what, we'll pull in there and it's going to be fine, that would be great."

"Yes, I am nervous about it, I'm very, very nervous that when we get to a point where he's off it completely and we start introducing foods back that he's going to go back to how he was. I am at the point now where I don't think I can do that again, I really don't think I can do that again. So that scares me. I'm hoping, because you are supposed to stay on it for two years and then the benefits are supposed to stay and that's it, I'm hoping that that's going to be the case." (FP7)

One mother whose child was in the process of weaning from KD, described it as a 'feeling of liberation'. She and others shared FP7's views that eating out and holidays would become so much easier;

> *"…also coming off the diet has also contributed to just a feeling of liberation, in some ways. Every now and then I'm like, oh God, yeah, actually, this is quite a big deal, but generally I'm just feeling quite excited about moving to the next stage of him being able to eat as much pasta as he wants.. a bit more spontaneity and ability to go and do things and not have to worry about taking food with us." (FP4)*

Among those whose children had successfully weaned from KD, half continued to follow a lower carbohydrate diet with limited intake of free sugars suggesting a maintenance of some KD principles.

Only one participant (FP7) had a teenager undergoing transition into adult services. She expressed fears and concerns that echoed those we frequently hear in clinical practice, and consequently it was felt important to share these and consider the ability to transition to an adult keto service in the recommendations that follow later. Adult epilepsy services do not have the expertise or resource to support transitioning teenagers with KD therapy and few adult keto services exist in the UK and internationally. At the time of writing there were just three KD services in the UK, and they are all heavily oversubscribed with long waiting lists. Paediatric KD services have many teenage patients approaching the age of transition who will have to wean from KD therapy if a place in an adult service cannot be secured. This places undue stress and anxiety on the family, but also the paediatric keto team. Turning eighteen brings with it lots of other changes too in terms of school ending and welfare benefits changing. FP7 was particularly worried about whether she would receive support from an epilepsy nurse, if there would be changes in consent and guardianship and what the procedure would be when her son was admitted to an adult ward. She usually stayed overnight and tended to his care in hospital but expected she wouldn't be able to do this on adult wards;

> *"Nervous, very very nervous. I don't know who we're transferring to. The people at my local epilepsy support have mixed reviews on their care, so*

that's that. There's an awful lot I need to wrap my head around. He's my one and only and I've not done this before, so I kind of feel I am just feeling my way around in the dark." (FP7)

A UK based adult KD service is in the process of developing a transition pathway, which will be shared nationally once complete, so we await the outcome of this service development initiative.

ii) Social learning and education

Parents consistently expressed that they enjoyed and valued keto cookery days where they met with an experienced keto chef, other families, and often a dietitian. The sessions could be considered a form of social education where parents could practice recipes, receive hints and tips from keto chefs, and share their experiences with others in a relaxed learning environment;

"We had a keto cookery workshop on Saturday with chef X who was fantastic. That's the first one we've had. I would say if there was more of those.. Fantastic, not just helpful, absolutely amazing.. So many little tips that I picked up for her." (FP8)

"…when your new to it, I think it's really important for you to hear the positive stories and speak to the parents that have gone through it and actually hear that it really isn't as bad as it sounds." (FP9)

In general, the chefs who conduct keto cooking sessions with families are employed by the medical nutrition companies that manufacture prescription ketogenic products, and so they share creative ways in which these products can be used in baking and cooking. It could be argued that these sponsored sessions for parents are a marketing strategy to increase product use and profitability of the ketogenic product ranges. Nevertheless, a more pragmatic approach would be to consider the convenience and variety the products can provide families in meeting their children's nutritional needs, as well as the opportunities for social learning provided. Rather than imposing the use of ketogenic products on families, it is important to provide them with the knowledge and choice to make their own decisions.

iii) Support from a peer support program

Families that I have supported with KD therapy often ask if they can be linked with another parent who has 'been there, done that' with KD therapy. The feasibility of such a program has been discussed in professional meetings, and while there may be some benefits for families, there may also be challenges related to data protection, the burden placed on families and the appropriate criteria for matching families. I was interested to explore whether parents would value being connected with another experienced parent for peer support, and if so, what the perceived benefits would be for them.

When asked if a peer support system like a mentor or 'keto buddy' would be helpful, many parents agreed. It was felt that they could share their 'real' insights as 'families who are living it'. Online forums went some way to providing this but not to the degree that one to one support could provide. This might include motivational support, practical tips and reassurance. Two parents shared their experiences as informal mentors, supporting new families to KD therapy and how they enjoyed their role. They acknowledged that they would have really welcomed similar support when they were starting out with KD therapy. Interestingly, as interviewees thought about the question and considered it further, they highlighted some of the challenges that an initiative such as this might face. As an example, FP13's account illustrates this well. Her initial reaction was very positive, but she subsequently acknowledged that, in order for it to work, she would need to be matched with someone who faces similar challenges;

> *"So, to have somebody that - yes, that's, come on, keep going, it's worth it, and we've all been there, we've all been there, you'll get through to the other side, just something like that, that actually had the experience of starting the diet and knew about the constipation, they knew about the reflux, and all their suggestions. That would have been really good, actually, yes. …. Yes and I suppose its matching somebody up with– would*

there be somebody else on the diet like [child's name] who isn't a great eater? …I'll be better to have a parent who's had similar struggles that I would have had." (FP13)

Similarly, it was suggested that having a keto mentor who has extensive experience and is further along in their keto journey would be more beneficial. If both parents had children at the same stage of KD therapy, then they may be limited by their shared lack of experience or confidence. It was also possible that it would create a burden for the mentee if the mentor was not fulfilling their role and needed support when the mentee had 'enough on their plate'. This suggests the need to consider the expectations associated with the arrangement. A 'keto buddy' potentially suggests an informal connection with someone in a similar position or stage of KD therapy. While a keto mentor may suggest a more formal arrangement with someone more experienced and knowledgeable.

4.4.2.5 Recommendations to support families in the management of ketogenic diet therapy

The perspectives of parents, described above, have helped to shape the five recommendations presented in Table 19. A number of actions are proposed to facilitate the implementation of these recommendations, and stakeholders who may be best positioned to assist with the implementation are identified. Several examples of excellent care and support have been included, driven largely by the experiences that parents shared. However, some proposed actions take a broader view of how the keto community might tackle the problem of access to KD therapy.

It is anticipated that recommendations one, two and three, will be feasible to implement in clinical practice with many centres or organisations likely already following these principles. Recommendation four relates to peer mentoring and

despite its perceived benefits, there remains much to be considered regarding the logistics and necessary resources to support the implementation of an effective peer mentoring system. Similarly, recommendation five relies largely on the food industry and medical nutrition companies. It will be easier to engage the latter group since they are interested in developing keto products that patients will use as well as building meaningful relationships with charities and keto teams in the keto community, supporting educational events for families and health professionals. These recommendations will be revisited in chapter 7 when the overall implications of this study and future directions are discussed.

Table 19. Recommendations to support families with the management of ketogenic diet therapy

Recommendations	Actions	Stakeholders to contribute
1. KD therapy should be more easily accessible for children, and they should be able to transition to adult KD therapy services if necessary.	• Increase awareness of the evidence supporting KD therapy among non keto professionals via CPD webinars, education days, patient testimonials, local outreach and collaboration. • Liaise with our colleagues in adult epilepsy services to support business case development for growth in services. • Participate in initiatives that have a national and international reach in reviewing or setting epilepsy research and treatment priorities, such as consultations and evidence reviews conducted by NICE and partnership priority setting surveys.	• Keto teams • KD charities • Ketogenic Dietitians Research Network • International Neurological Ketogenic Society
2. Children and their families should receive quality support and education prior to and during KD therapy	• Keto teams to take a holistic patient-centred approach to care, considering a variety of seizure and non-seizure related outcomes of KD therapy. • Connect families with KD charities and the range of excellent resources and services they offer. • Provide emotional support for parents, especially when approaching the time to discontinue KD therapy.	• Keto teams • KD charities
3. Children and their families should have opportunities for social education and learning	• Consider the ability to offer group education sessions in the preparatory phases of KD therapy where families can meet and learn together. • Offer opportunities for families to meet and learn together in an informal setting such as keto cookery sessions, coffee mornings or informal virtual meetings.	• Keto teams • KD charities • Medical nutrition companies
4. Explore the feasibility, costs and interest in developing a peer mentoring system for parents new to KD therapy to receive support from parents experienced in this therapy.	• Further explore the perceived need and feasibility of a peer mentoring programme via a focus group with parents and professionals.	• CORE-KDT research team • KD charities
5. Expand the range of ketogenic foods, both on prescription and store-bought to improve the convenience of KD therapy for children and families.	• Medical nutrition companies to continue to broaden the range of keto products available. • It is challenging to access and influence the wider food industry but keto teams and KD charities to be responsive in supporting parents to identify suitable keto friendly foods.	• Medical nutrition companies • The food industry • Keto teams • KD charities

4.5 Discussion in the context of existing literature

This qualitative descriptive study aimed to explore how families experienced epilepsy and KD therapy as told by parents. Their personal accounts revealed four main themes and twelve subthemes, spanning the period from the diagnosis of epilepsy to the use of KD therapy as a therapeutic intervention and finally, weaning from the diet. The findings demonstrated that KD therapy can provide parents with a sense of control over an otherwise unpredictable situation, and when successful it can offer significant benefits to the child and the family as a whole. The findings also support those described in Chapter 1 relating to the impact of epilepsy on the child and wider family. While much is understood about the experiences of families with epilepsy, only one other research group has conducted similar qualitative research addressing both epilepsy and KD therapy (Webster and Gabe, 2016; Webster, 2019b). However, this was from a sociological perspective which focused on the meaning of food within the family and did not address the practical aspects of KD therapy for families. As a ketogenic dietitian, the researcher was highly motivated to examine and if possible, enhance the care that they and their colleagues provide to families. Consequently, this study builds upon the work of Webster and Gabe by exploring in greater detail how KD therapy benefits families and how future KD therapy management may be improved.

Drug-resistant epilepsy was characterized by persistent and uncontrolled seizures, an unstable condition that created a great deal of uncertainty for parents. Webster (2019a) described this as 'a cycle of uncertainty' marked by day-to-day uncertainty, future uncertainty, and symptomatic uncertainty. Several examples of these uncertainties were similarly reported by parents who participated in this present

study. They worried about their child's diagnosis, treatment options, when the next seizure would occur and what the future might hold. Unsurprisingly, parents of children with epilepsy, particularly mothers (Shore *et al.*, 2002) have higher rates of stress, anxiety and depression owing to the additional burden of care associated with having a child with a complex illness (Kerr, Nixon and Angalakuditi, 2011; Reilly *et al.*, 2018b). There is often no respite from the all-consuming and unpredictable nature of their child's epilepsy.

As parents became aware that their child's future would not unfold as they anticipated, they described grieving the loss of what might have been. Dyson and Fewell (1986) suggested that parents are dealing with the inevitable loss of the image of an 'ideal child'. The diagnosis of epilepsy likely intensifies these feelings and may result in a period of mourning, described as a state of chronic sorrow. This can be a long-term, cyclical sadness or grief experienced by parents and caregivers in response to a situation with no predictable end (Olshansky, 1962; Lindgren *et al.*, 1992), independent of epilepsy severity and other comorbid conditions (Hobdell *et al.*, 2007). To help manage feelings of chronic sorrow, parents need to develop ways of coping with their child's epilepsy. To cope means to deal with or to attempt to overcome difficulties. It was suggested by Miller and colleagues (1992) that the fluctuating distress associated with epilepsy may affect the type of coping strategy parents employ. The use of emotion-focused coping strategies was more common when distress levels were high, while problem-focused coping strategies were more common when distress levels were lower. Hobdell (2007) argues that parents experiencing intense grief and sorrow are more likely to seek social support from others, make attempts to deal with psychological tensions and strains and maintain feelings of self-esteem.

The subtheme 'no longer a passenger' illustrated how KD therapy provided parents with a problem-focused coping strategy and a new focus for their effort to help improve their child's health. It offered hope that the treatment could be successful and gave parents the opportunity to take the lead in the treatment's provision. Parents with more positive attitudes towards epilepsy have been found to use more positive coping behaviours like seeking social support, strengthening family relationships and being optimistic about life in general (Austin and McDermott, 1988). KD therapy may help parents to have a more positive attitude and optimism about their children's future. While they acknowledged that it would be different from the normalcy they had originally anticipated and planned for prior to their child's diagnosis of epilepsy, there remained positive outcomes. With time, parents' confidence grew, and pride in their ability to attain the expertise and skills required to cope with epilepsy and KD (Smith *et al.*, 2014). This was evident in the subtheme 'the evolving KD mindset.

Children had been treated with a median of four ASMs (one to seven) prior to referral for KD therapy, so most families had experienced drug resistant epilepsy for an extended period before meeting with the keto team. As a result of the delay in access to KD therapy, parents experienced feelings of helplessness, anger, and frustration, which were similar to those shared by four families when recalling their experiences with KD therapy (Williams *et al.*, 2012). Parents questioned why KD therapy had not been offered earlier and how different their child's condition might have been had KD been made available earlier. As a result, it is likely that parents experience multiple emotions during those first consultations, so it is essential that keto teams listen and acknowledge families' prior experiences. The needs of parents should be considered, as well as the support they may require in order to adapt to new coping

strategies. In the same way, parents need support to help guide their expectations and hopes regarding KD therapy in order to address any misconceptions that may compound existing feelings of helplessness. Our perception as health professionals is that many parents expect full seizure freedom, but this is not always the case. In fact, many hope for smaller, perhaps more achievable gains including seizure reduction and improved alertness (Bruce *et al.*, 2017). As health professionals, it is our responsibility to take the time to discuss these individualised hopes and expectations with our patients.

The goal of KD therapy for childhood epilepsy is to improve a broad range of seizure as well as non-seizure-related symptoms and, ultimately, to improve global quality of life for children by enabling them to build upon their existing strengths. The theme 'opening the window to new opportunities' demonstrated the ways in which children benefited from KD therapy, which included learning new skills, engaging in activities, and building and maintaining social relationships. Bruce *et al's.* (2017) small study of an unvalidated questionnaire was used to explore what would constitute improved QoL for parents and their children. The reported results are similar to those presented earlier in Figure 10, with significant overlap in the reported outcomes that resulted in improved QoL for children and parents. These included the child being happy and smiling again, improved alertness and recognition of those around them, developmental progress, reduced seizures, reduced ASMs and toilet training. More recently, an online survey distributed via social media platforms assessed 192 parents or caregivers' perspectives of KD therapy (Sarlo and Holton, 2021). The median score for quality of life was 9 on a scale of 0-10 (10 being much improved), which suggests parents felt their children's quality of life was much improved when treated with KD therapy. Although, this study was limited by the lack of a comparison

baseline score of QoL prior to KD. Given the reported improvements in QoL it is not surprising that treatment with KD therapy has been conceptualised as a ‘saviour’ for children, particularly for those who experienced a reduction in seizures and emergency hospital admissions (Webster, 2019b). Similarly, parents in this present study described the sense of ‘getting their child back’. Despite the challenges they faced, they were able to establish a sense of normalcy for their child and family through KD therapy. Interestingly though it has been observed that ‘the goalposts can shift’ over time where parents sub-consciously increase their expectations of KD therapy, overlooking the positive achievements gained (Bruce *et al.*, 2017). It is important that keto teams explore these evolving expectations and encourage parents to reflect upon the gains achieved with KD therapy in order to support ongoing motivation.

Woodgate *et al.* (2015) describe a state of intense parenting, where parents of children with complex care needs took on more roles than parents of healthy children and they had to work more intensely at these roles. Theme 1 ‘epilepsy is all consuming’ illustrated how 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, findings that have also been echoed by Harden *et al.* (2016). While KD therapy offered hope when other treatments had failed; it imposed additional roles and challenges for interviewed parents which affected wider family life. According to Sarlo and Holton's survey (2021), on a scale of 0-10 (10 being very challenging), parents ranked KD therapy as somewhat to very challenging with a median score of 7. Moreover, 99% of respondents reported experiencing more than one diet-related difficulty. There were several challenges reported that were similar to those identified in 'the reality of KD therapy' theme,

including a lack of clinical support, a lack of time, family stress, restrictions on social outings, cost, and caregiver stress.

Similarly, the findings of this study are consistent with those of Webster and Gabe (2016), who investigated the impact of KD on children with epilepsy and the subsequent effect on their families. In the subtheme 'impact on the family', the gendered nature of KD therapy 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 I interviewed, the impacts on family life extended to their other children. Siblings often provided assistance and support in the daily care and management of their brother or sister with epilepsy (Webster, 2018). Parents expressed their concerns regarding the burden of care siblings faced and this grew when KD therapy was introduced. Siblings' food choices, mealtimes and activities outside the home were affected. 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. The 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 (Webster, 2018).

There is a great deal of emphasis placed on the potential adverse effects of KD therapy by health professionals, and these are monitored regularly via bloods and imaging. Yet, it was interesting to observe how little emphasis parents placed on these. They were only briefly mentioned when discussing the challenges associated with KD therapy. The findings of this study are broadly similar to those of Schoeler *et*

al. (2014), who examined parental attitudes towards KD therapy. Parents who believed in KD therapy did not overly worry about the side effects associated with the diet during periods of positive outcomes with the diet. Possibly, parents feel reassured by knowing that the keto team monitors closely for adverse effects, and in a sense, they delegate that responsibility to them, trusting that they will handle it.

In contrast, parents expressed strong concerns about the range of adverse effects associated with treatment with ASMs, and some felt that their keto team dismissed these concerns. After observing positive results of KD, parents were eager to reduce the dose and number of ASMs and were frustrated if their keto team was cautious. This has implications for how health professionals discuss expectations of KD therapy with families, and for their willingness to challenge the status quo and attempt to wean an ASM. When preparing families for KD therapy, it should be discussed as a partnership with ASMs and not as a substitute. This is especially important in light of the fact that 86% of a cohort of 232 children treated with KD therapy remained on at least one ASM during and after treatment with KD therapy (Shah *et al.*, 2019). Among the 14% who achieved drug free status, most were younger children, often diagnosed with GLUT1 deficiency syndrome or Doose syndrome, on fewer medications and had achieved >90% improvement in seizure control or seizure freedom with KD therapy. Anecdotally, there is sometimes a misconception among health professionals that children must be seizure free before attempting to reduce ASMs. This is not the case (Kossoff *et al.,* 2018; Shah *et al.*, 2019), and working with families to determine the best timing and order for attempting ASM weaning may help to strengthen the relationship with their keto team.

While KD therapy assisted families in managing some of the uncertainties associated with epilepsy, the final theme ‘looking to the future’ revealed that many parents expressed concern and fear that weaning from KD therapy would worsen seizure control. It was difficult for parents to ‘let go’ of this successful treatment. By initiating open conversations and exploring the potential benefits and risks of weaning from KD therapy, health professionals can assist patients in managing this stress and worry. Few studies have continued to follow patients up post KD therapy, but those that have suggest that 75-80% of children who are seizure free on KD therapy will sustain this once KD is discontinued. (Martinez, Pyzik and Kossoff, 2007; Caraballo *et al.*, 2011). Similarly, 75% of children who achieved a 50% reduction in seizure frequency maintained these benefits following the discontinuation of KD therapy (Caraballo *et al.*, 2011). Families should be informed of these encouraging results to provide reassurance when considering weaning from KD therapy. It is recognised that longer term studies of KD therapy are needed (Martin-McGill *et al.*, 2020), however it has been suggested that tolerability and adverse effects should be the focus of such research. Arguably though, longer term follow up should also include review of efficacy outcomes post KD to advance the earlier work of Martinez *et al.* (2007) and Caraballo *et al.* (2011).

4.6 Strengths and limitations

International recruitment was a key strength of this study, with six participants recruited from outside the UK. Considerable time was devoted to registering nine NHS keto centres as participant identification centres in order to maximize recruitment for both the parent interviews and the Delphi study. However, recruitment was highest from social media posts and advertising via charity organisations suggesting these are key channels for recruitment for future studies. In light of the

burden of care for families, it was considered that recruitment might be challenging, but the majority of participants were recruited and interviewed within four months. By extending recruitment to six months, additional participants were recruited. The study fulfils key criteria for quality in qualitative research as defined by the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist (Appendix S) (Tong, Sainsbury and Craig, 2007). Among the criteria addressed are the design of the study, researcher reflexivity, and the transparency of the methodology. The use of NVivo software ensured that the stages of analysis were retained, and a clear trail could be mapped through these.

There are some limitations to this study. Due to time and budgetary constraints, the study was conducted only 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 that perhaps represents the parent who has the most to say on the topic. Similarly, Jensen *et al.* (2017) had difficulty recruiting parents, especially fathers, to participate in their focus group investigating the impact of severe childhood epilepsy on caregivers. A total of 51 parents were eligible for participation, 19 were recruited, but only 12 were able to attend, two of whom were fathers.

Most of the children in this study were over two years of age when KD therapy began, so the views of parents of young infants are not included in this study. KD therapy is safe to be administered to infants, and clinical guidelines are available to guide its management (van der Louw *et al.*, 2016). However, at the time of

recruitment, the first RCT investigating KD therapy in infants was still in progress, and the final results have not yet been published (Titre-Johnson *et al.*, 2017). During the coming years, KD therapy will likely be used more frequently in infants as this and other studies report on its successful implementation (Armeno *et al.*, 2021). The majority of children were consuming their KD orally, with the exception of one child who received top-up enteral feeds through a gastrostomy tube. Consequently, the experiences shared represent those who have managed a KD orally and the challenges involved. It is reasonable to suggest that enteral tube feeding of a KD using a commercially available keto feed may present fewer challenges for parents in terms of cost, inconvenience, and preparation time, as well as fewer changes in the household dietary habits. However, if a child is solely dependent on enteral tube feeding, different challenges may arise, including gastrointestinal intolerance. It would be beneficial to explore this topic further with parents whose children are exclusively or predominantly tube fed. The children of interviewed parents all experienced some degree of seizure reduction and nine achieved full seizure freedom. Only two parents were disappointed with the outcome of KD therapy, so overall they were arguably a motivated group, keen to share their views on outcomes and experiences of epilepsy and KD. While there is potential for bias in their responses, their viewpoints are generalisable to the population this core outcome set represents; children with epilepsy who trial and continue KD therapy.

The sampling frame guiding recruitment for parent interviews considered their child's epilepsy diagnosis but omitted developmental status and learning difficulties. In hindsight, consideration and collation of this data may have provided further insights to the study population. The data collated focussed on the child's epilepsy and use of KD, failing to consider broader socioeconomic data such as household income,

parent education level and marital status. Deprivation data could have been obtained for UK participants using the Index of Multiple Deprivation if postcode data was collected. Broader family demographic details could have considered the primacy of the child with epilepsy and their number of siblings. Collation of this additional demographic data could have informed recruitment, ensuring a broader range of background characteristics of the sample and improved transferability of the data set. The use of ASMs and associated adverse effects was an emotive topic for parents. In hindsight it would have been beneficial to have more robust data on the use of ASMs for all participants. Firstly, the perceived adverse effects experienced with individual ASMs and secondly if attempts were made to wean from an ASM and the outcome of this. A short pre-interview questionnaire could have been used to explore this issue; however, this would have increased the burden on families and might have been off-putting during the recruitment process. Finally, all interviews and the majority of the analysis were conducted by one researcher which increased the risk of researcher bias. However, this was mitigated in a number of ways in order to strengthen the trustworthiness and rigor of the findings. For example, a semi structured interview schedule was used to ensure consistency in the core questions asked of participant. The coding approach and emerging themes were regularly discussed with the supervisory team and a researcher with expertise in qualitative data analysis. Finally, appendix Q provides detailed mapping of themes, subthemes, codes and illustrative quotes to demonstrate the systematic process undertaken.

4.7 Conclusions and next steps

This chapter provides deep and meaningful insights into families' experiences of epilepsy and KD therapy enabling us to better understand their perspectives on outcomes which follows in chapter 5. Examples of supportive clinical practice were

shared as well as areas in which health professionals can work more collaboratively with families to help them prepare for and manage KD therapy. These included many aspects of patient-centred care, but in particular; the development of coping strategies, the setting of goals, consideration of the process of weaning from ASMs, and preparation for the process of weaning from KD therapy. Parents were asked to reflect on their experiences managing KD therapy on a daily basis and to share any suggestions they felt might make the management of the diet easier for future families. Their suggestions informed five recommendations aimed at improving access to paediatric and adult KD services, improving access to KD foods and enhancing support and education for parents in preparation for and during KD treatment. The implementation of these recommendations within clinical practice will be discussed further in chapter 7 when considering the broader implications of this project.

Chapter 5: Qualitative study to identify outcomes of importance to parents

Preface

Chapter 1 highlighted that parents' priorities may not be adequately represented in existing studies of childhood epilepsy treated with KD therapy. Consequently, the results of the phase 1 scoping review (chapter 3), may not capture all outcomes of importance to parents for their child. While outcomes were discussed in the previous chapter in the context of the benefits of KD therapy, they will be revisited in greater depth here. This chapter therefore begins by identifying the most important outcomes to parents through a series of semi-structured interviews (phase 2), before considering whether these important outcomes were represented in the scoping review. The findings are discussed in the context of the development of the core outcome set and are used to inform the phase 3 pre-Delphi consultation described in chapter 6. Work arising from this chapter has been published (open access) in Seizure – European Journal of Epilepsy (Carroll *et al.*, 2022b) Sections of this chapter have been taken directly from the edited manuscript. The researcher led the data collection and analysis and wrote the original draft of the manuscript, which was edited by the supervisory team and then subject to peer review. The published manuscript is available in Appendix P.

5.1 Introduction

To date, there has been no unified attempt to assess parent views into the choice of outcomes, and consequently there is no consensus among healthcare professionals, parents and researchers regarding what should be measured and reported. This qualitative descriptive study aims to contribute to a comprehensive list of outcomes which will be prioritised by parents, health professionals and researchers in an international two-round Delphi study in order to achieve consensus on a core set of outcomes. The scoping review (chapter 3) identified a list of outcomes reported in published studies of childhood epilepsy treated with KD therapy. However, 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 scoping review as a single source to populate a comprehensive long-list of outcomes may overlook potentially important and relevant outcomes to parents.

5.2 Aim and objectives

This qualitative study aimed to identify the outcomes of importance to families when undertaking KD therapy to treat drug resistant childhood epilepsy.

Research question

Which outcomes do parents regard as important when undertaking KD therapy in the treatment of childhood epilepsy.

Objectives

1) Explore outcomes of importance to families

2) Assess whether the scoping review outcomes list adequately reflects parents' perspectives or if there are any additional important outcomes that have not yet been identified.

5.3 Summary of methods

Chapter 2 outlined the detailed methodology. In summary, participants were eligible if they were a parent or carer to a child aged 0-18 years with drug resistant epilepsy being treated with KD therapy or had weaned from KD in the past year, were English speaking and were able to consent and participate in an interview. Participants were recruited from across the UK and internationally via gatekeepers at three primary sources: 1) UK Participant Identification Centres, 2) Charity organisations: Matthew's Friends, Young Epilepsy and Epilepsy Action, 3) Epilepsy – the Ketogenic way: a family support group on Facebook. Written consent was gathered for participation in a semi structured interview conducted via telephone, video call or in person. Outcomes were identified directly by asking participants to describe the important results or outcomes 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, a content analysis was undertaken to identify outcomes indirectly in the transcripts when exploring families' experiences of epilepsy and KD therapy. Together, this enabled the identification of all possible outcomes. All interviews were audio-recorded, professionally transcribed (intelligent verbatim transcription), and uploaded to

NVivo 12 (QSR International, Burlington, Massachusetts, United States) for deductive content analysis (Hsieh and Shannon, 2005).

5.3.1 Patient and Public Involvement and Engagement (PPIE)

Table 15 (section 4.3.1), reported on the ways in which PPIE was incorporated into the qualitative phase of the study and the outcomes it influenced in accordance with the GRIPP2-SF (Staniszewska *et al.,* 2017).

5.4 Results

5.4.1 Participant demographics

As outlined in section 4.4.1 and Table 17, 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 minutes (35-131mins).

5.4.2 Existing outcomes identified by parents

In total, parents identified only 39 of the outcomes identified in the scoping review (Table 20) suggesting the remainder may be of less importance to them.

Table 20. Existing outcomes identified in parent interviews categorised according to domain (N=39)

Domain (Dodd *et al.*, 2018)	**Outcome**
Physiological/Clinical	Seizure reduction
	Seizure freedom
	Electroencephalogram (EEG) findings
	Anti-seizure medication use
	Side effects of anti-seizure drugs
	Constipation
	Gastro oesophageal reflux disease
	Kidney stones
	Cholesterol
	Growth
	Ketogenic rash
	Bone health
Diet and Nutrition	Ketone levels
	Palatability of KD formula and supplements
	Feeding difficulties physical
	Feeding difficulties behavioural
	Food preference
	Appetite
Resource Use	Accident and Emergency department attendance
	Unplanned hospital admission
	Cost effectiveness of KD
Physical Functioning	Activities of daily living
	Movement ability
	Manual ability
	Balance and coordination
	Fatigue
	Time spent asleep
	Daytime sleepiness
Cognition	Developmental milestones
	Speech and language
	Learning
	Memory
Social and Emotional Functioning	Alertness
	Concentration
	Behaviour
	Emotional development
	Mood
	Social skills
Global Quality of Life	Quality of life for child on KD

5.4.2.1 Physiological clinical outcomes

Parent identified outcomes in this domain can be categorised into two broad groups. Firstly, the potential positive impact of KD therapy on seizure control and secondly the potential adverse effects that may be experienced from both ASM use and KD therapy. These benefits of KD can generally be divided into seizure-related and non-seizure-related benefits, although they are often interrelated.

Seizure reduction and seizure freedom

Improvement in seizure control was described as 'the fog lifting' for the child. All children in the study experienced *seizure reduction* with nine achieving full *seizure freedom*. Parents recalled the point at which it became apparent that the KD was helping their child. For some this was quite soon after KD commenced and for others it took longer to establish. Their initial disbelief was evident and hesitancy to acknowledge the improvement in seizure control in case it was just a coincidence or a short-lived improvement.

> *"Yeah, we didn't go in too fast…after about two days, it was like, oh my god, he's seizure free. Yeah, and then we started speaking about it." (FP10)*

> *"Yeah. For quite a long time, we weren't even really able to acknowledge that to ourselves, because you just don't want to almost tempt fate." (FP4)*

Anti-seizure medication use and side effects

It is recommended that children be referred for consideration of KD therapy when two or more ASMs have failed to adequately control seizures (Kossoff *et al.*, 2018). Yet, participants described how, prior to commencing KD therapy, their children had trialled between 1-7 ASMs in a bid to control their epilepsy. Consequently, referral for KD therapy was delayed past the recommended trial

of two ASMs for the majority of children (N=17). Parents described how their children had experienced a range of side effects which they attributed to *ASM use* (Appendix R). These included memory loss, fatigue, behavioural problems, loss of appetite, a 'dulling' or 'zombie like' state, poor sleep and suicidal thoughts in one case. If successful in controlling seizure activity, KD therapy offered the potential to reduce the dose or number of ASMs and associated side effects (Kossoff *et al.*, 2018). For many, this was a motivating factor to trial KD therapy. In fact, one felt strongly that if anti-seizure medications were not reduced, then the KD wouldn't be worth continuing.

> *"I was hoping to get them off the medications, basically. I was pretty up front with the neurologist and my husband that if we couldn't get them off any medications, I didn't want to put them through the side effects of the medication and potential side effects of the diet unless it has some very clear gains." (FP16)*

Adverse effects of ketogenic diet therapy

Parents described how their child was regularly monitored for adverse effects via blood tests and scanning (renal ultrasonography and DEXA), which was reassuring for them. The most commonly experienced side effects were *constipation* and *gastro-oesophageal reflux*, similar to that in Neal *et al's.* (2008a) RCT cohort. For some, already existing reflux was worsened by the high dietary fat intake. However dietary manipulation and fine tuning led by the dietitian, resolved these adverse effects. Only one child experienced *raised cholesterol* and another *ketogenic rash.*

> *"We dropped it [carbohydrate] down, we dropped it down, we dropped it down, we upped the fats. It really really exacerbated his reflux and he's already got very very severe reflux anyway." (FP14)*

> *"He went through awful awful constipation in the early weeks." (FP2)*

One teenager weaned from KD after 6 months of treatment despite experiencing greater than 50% reduction in seizure activity. KD therapy was having a negative impact on his QoL which he and his parents felt outweighed the seizure reduction seen, especially when there were other ASM options that he had not yet trialled. This highlights the challenge families may face in deciding between treatment options and the individual nature of expectations of KD therapy.

5.4.2.2 Diet and nutrition outcomes

Ketosis

Over half of the participants made reference to their child's *ketone levels* and the role monitoring of these played in guiding fine tuning to the diet or managing illness. For some this was a source of stress as they struggled to identify any patterns between ketones and seizure control.

> *"Yeah so I think at one point when I didn't even know what to do and we were on that holiday and he'd had a 7.7 reading of ketones or something like that and I gave him the Maxijul thinking I need to get his ketones down…." (FP9)*

While for others, close monitoring of ketosis guided food choices and decisions later in the day. This ability to adjust and adapt afforded parents some control in optimising their child's *ketone levels* and ideally seizure control.

> *"Don't feel you're a bad mother and you're hurting your child with that [finger] prick. You're doing the best because you have the data and you know what to do. If I now measure that the glucose is 4.4, I will change the next meal." (FP5)*

Palatability of ketogenic foods and supplements

There was a range of experiences in the group with Foods for Special Medical Purposes and over the counter ketogenic products ranging from powdered and ready make milkshakes, desserts, snack bars, baking mixes and savoury

meals. It is not surprising that personal taste influenced preferences for products with some really valuing them; 'an absolute life saver', 'gives us flexibility', and others ‘couldn’t tolerate’ them or used them initially but less so as they have found their own meals and recipes. Interestingly, the product and extensive delivery packaging was raised by one participant as a concern for parents trying to be more sustainable and use less plastic.

Feeding difficulties

A total of four parents reported their children had experienced challenging *physical or behavioural feeding difficulties* when on KD, which greatly increased their mealtime workload. They described their efforts to develop their child’s feeding abilities over long periods of time; the joy they experienced from the little successes and disappointment when they felt like things were regressing.

> *“Feeding X is like feeding a baby still, he needs a high level of intervention, its very time consuming….Its hard work but it meant that then he’d progressed in his development to feeding himself and to enjoying food which was brilliant. Then we started the diet and things slipped right back….”(FP2)*

> *“We had lots of food refusals… it was really stressful. It got to the point where I was literally prising his mouth open to get any food in in… it’s just really stressful, it was awful. I phoned [dietitian] and said something’s got to change. I can’t do this anymore it’s breaking me, it’s breaking him.” (FP14)*

Parents wanted to develop their child’s independence with self-feeding and give them the opportunity to move through the appropriate textures developmentally. However, they felt conflicted with the demands of the KD and the need to finish the fat portions. This resulted in them resorting to spoon feeding their child soft meals to ensure they finished ‘every morsel’ of the meal.

5.4.2.3 Resource use outcomes

Unplanned hospital attendance

Only 6 participants discussed *unplanned hospital admissions or accident and emergency visits* and how these together with their need to call an ambulance declined when KD commenced.

> *"pre diet, we were quite the regulars there [hospital], there was the [child's name] suite at the hospital!… yeah, everyone knew him because he was there so often. He had so many illnesses and they all seem to have improved…every month more or less we'd be up in A&E for something or other." (FP19, MP2)*

One felt this may also be related to their uncertainty around the new diagnosis of epilepsy, feeling 'fairly new to it and panicky' around managing epilepsy but with time and treatment with KD therapy, comes a sense of 'calm'.

5.4.2.4 Physical functioning outcomes

Activities of daily living and mobility

Physical functioning is considered to be the ability to perform both basic and instrumental *activities of daily living*. The majority of parents described at least one physical outcome that was important for their child. Activities and tasks included their child being able 'to feed themselves', 'to be able to sit independently and crawl', 'to move across the room from sofa to sofa', 'to start or improve walking' and 'to keep up with friends physically'. Nursery and school teams were often highlighted as playing a key role in supporting these developments. FP12 eloquently describes how the KD 'opened a window to learning new skills' that her 13-year-old son never had the possibility of before;

> *"the fact that he can crawl more now and he's drinking a baby bottle to other people means nothing, but then you know he never could do those things, that's huge for me… For me, I'm looking at that and I still get a kick out of seeing him do that." (FP12)*

FP19 and MP2 detailed how their sons *balance and coordination* improved to the point where he could join in a parkrun without his helmet and being attached to a parent via reins. His improved physical abilities also unlocked *independence* for him.

> *"as an example with the parkrun and the amount of seizures. When we first went along, he was on reins and in a helmet, we were literally no more than a foot away from him. Now he's running it free, no helmet on. Obviously, we're still right by him, but it's all the park and it's providing a platform for him to lead a life as normal as possible with whatever he can achieve." (FP19, MP2)*

Sleep

Half of the participants identified that *fatigue* and *sleep* were important outcomes to consider when monitoring KD. Improvements in *fatigue* was described as an outcome in its own right, however this in turn often opened the door to further progress as the 'fog had lifted' and the child had the energy to do more, such as physical activity, engage in school and playing with siblings. FP8's family loved walking together but would often end up carrying their child with epilepsy as she would tire so quickly. Within a few weeks of starting KD and achieving optimal ketosis, her energy levels improved significantly;

> *"We started walking and after about 10 minutes, my husband looked at each other and went, she's still walking. She walked the whole way around. We said nothing. We got home and she said Mummy, look, I walked the whole way and I'm not even tired. So, she noticed as well." (FP8)*

For FP18, their child experienced nocturnal seizures which negatively affected his night-time sleep and led to *daytime sleepiness* which affected his ability to attend and engage in school activities. KD reduced the frequency of his night-time seizures, improving his sleep, and in time, allowed his parents to sleep better as they didn't have to get up as often to attend to him seizing. Parent's sleep is captured in the *parental he*alth outcome, but this demonstrated how much the child's care impacts on the wider family. For others it was less clear

cut, and it was more difficult to ascertain the causes of *fatigue* and what led to improvement. There is a possibility that it was simply the KD helping, or it may have been due to a combination of treatment with KD and a reduction in the dose or number of ASMs;

> *"So she's off the Frisium and she's weaning off the Epilim but in terms of her, look, it's really hard to say where she's at in terms of improvement and side effects. She's definitely less fatigued than what she was." (FP1)*

5.4.2.5 Cognition outcomes

Developmental milestones

Almost all participants interviewed identified at least one cognitive outcome as important to consider and measure. These encompassed *developmental milestones, learning*, *speech and language skills* and *memory*. The majority of children had experienced some degree of developmental delay owing to their epilepsy or other related diagnoses, so their parents were acutely aware of the areas in which their child struggled. This was often a source of anxiety owing to the uncertainty that epilepsy brings and what the future might hold for their child (Webster, 2019a). However, making progress in these areas offered the opportunity to achieve to their potential and open doors to wider experiences. FP7 described how her child could only do 2 of the 20 things on a checklist of tasks and abilities that children should be able to do before they start nursery. The other parents in the room ticked everything for their children. Assessments like these, while often a necessity for screening or monitoring progress, can serve as a regular reminder of what a child cannot achieve which can be disappointing and affronting for families.

Speech and language

Children's *speech and language* development play a major role in establishing their independence and enabling them to communicate their needs. In addition, it supported their wider *social skills* and interactions which will be discussed in the Social and Emotional functioning domain.

> *"It was a big one for X, yeah the speech was. But because he struggled with his speech always, even now he talks with a lisp, he still has speech therapy, but I look at him now and he just amazes me sometimes." (FP9)*

> *"He wasn't able to hold a conversation, he was just – how to put it? The child I had after keto is nothing like the child I had before." (FP7)*

Children engaged more when playing with their toys; making choices, role playing and making appropriate noises like 'vroom' for a car or 'shush' to the baby doll.

Learning

Similar to physical functioning; schools were often commended for supporting these developments. FP5 spoke about how happy her son was to go to school 'like a regular kid' and not have to study alone. FP9 agreed that school brings 'normality' for the child so even if seizures are continuing, being in school and *learning* were key. Our focus is largely on how these functional outcomes affect the child with epilepsy being treated with KD. However, when taking a wider more holistic view, developmental gains for the child may also have a profoundly positive impact for their parents, siblings, extended family and the professionals supporting their progress. Understandably, it was a great source of pride for parents when the developmental and cognitive gains were noticed by individuals external to the family;

> *"the teacher, a couple of times in the early months of the diet when I was talking to her on the phone,….she said to me X's absolutely*

flying in the classroom at the moment. So, flying is like no one's ever said that about X." (FP2)

"so in terms of education the teachers at school have noticed that she's developed in leaps and bounds. You know she was struggling to keep up with the children in the specialist school and now she's in the top sets for everything." (MP1)

5.4.2.6 Social and emotional functioning outcomes

The majority of parents identified at least one outcome in the social and emotional functioning domain including *alertness, concentration, behaviour, emotional development, mood* and *social skills*.

Alertness

Children were described as 'being more switched on, brighter and aware' and this was often interlinked with personality, mood and engaging socially with those around them. Being more alert indicated that they were 'back to their old self' or engaging like they had before the epilepsy presented, and had since been 'clouded' or lost;

"she just seems more with us, she's not disengaged.. She's more like the child I remember…just more in the family." (FP3)

"..because she's more alert and she's funny and she's a bit more chatty as well. So, just that person – you just see the personality again"…" (FP8)

Social skills

Friendships flourished, as did relationships with siblings and the ability to interact with peers in nursery and school. FP12 described how her son who attends a specialist school was in a standing frame alongside another little girl, and they tried to swap and share their toys. The teacher was so surprised as she had not seen them try to do that before and she attributed this to a positive

impact of KD therapy. However, despite success on KD, some may still struggle to achieve the same social skills as their peers without epilepsy. MP1 explained how his daughter struggled to form social connections, despite being seizure free, and he felt this was related to the reduced mental function and processing ability she experienced while being so 'clouded' in her primary school years. She is now a teenager and feels frustrated and alone at times.

Behaviour

Four parents highlighted behaviour as an important outcome in the context of their child being more settled or calmer;

> *"we think, we do think he's calmer. Actually, people have said what have you done – somebody said, what have you done to him? He's a much calmer child." (FP18)*

FP16 described how she would like the social and emotional impact of following a KD to be measured and not just the potential change in these areas developmentally. She acknowledged how fortunate she felt that her two young daughters, both on KD were so compliant and resilient, making 'her job particularly easy'.

5.4.2.7 Global quality of life outcome

Half of the parents interviewed stated that their child's *quality of life* was an important outcome. Nevertheless, *quality of life* is a broad concept, and while the remaining participants didn't explicitly state it, many of the outcomes they cited as significant would also lead to improved quality of life if improvement was experienced. FP18 captured this ambiguity when they described quality of life as being 'whatever constitutes a normal life', yet individuals' definition of what constitutes a normal life would likely vary significantly. FP8 explained how

quality of life is 'looking at the whole child and how everything impacts'. This supports the need to consider the wider holistic construct. When asked what would signify improved *quality of life* parents listed a range of activities (Table 21). Many of these represented independence, participation, choice and freedom with gains in these areas symbolising progression and improvement in *quality of life* for the child with epilepsy. MP1 captures this overlap in outcomes

> *"so there ae some things we have been able to do and she has gone on a couple of sleepovers now. So, for her personally, quality of life is immeasurably better. I really couldn't say it was 10 x 100, or 1000, it's just immeasurable. She feels so much more independent." (MP1)*

Table 21. Parent reported activities that would lead to improved quality of life if achieved

Activities
An easing of existing restrictions or limitations
To be able to go out and play
To have friends and the interactions this brings
To ease suffering
To go out and about as and when you want to
To go out for a meal as a family
To be able to be happy and live
To be actively involved and make choices
To have a sleep over
To be able to go to bed late
To watch a movie and sleep well

5.4.3 New outcomes identified by parents

Parents identified seven new outcomes not previously identified in the scoping review, listed in Table 22, 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.*

Table 22. New outcomes identified by parents

Domain (Dodd *et al.*, 2018)	**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)*	4
	7. Seizure duration	*We did have a decrease in seizure times, slightly. (FP6)*	4

5.4.3.1 Global quality of life outcomes

Parent or primary carers health

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)*

For many parents, their sleep was negatively affected for a variety of reasons. Their child might experience nocturnal seizures which would wake them up in the night to respond to a seizure or any disturbance. In addition, the extra workload and wider care for their child with complex needs, on top of 'normal' day to tasks often stretched late into the night. Examples included KD meal preparations, updating KD tracking and monitoring spreadsheets, medical appointments and online research regarding KD or epilepsy. Finally, general worry or anxiety was reported to affect sleep.

> *"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…it's like I'm tuned to hear them, my body now wakes up at about 3 in the morning and I can't go back to sleep. So, it's a huge impact." (FP1)*

Family life

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. Chapter 4 explored these impacts on the family in great detail. In summary, couples struggled to spend

alone time together, for some their relationship failed under the burden, while for others they felt their relationship was strengthened by the challenges they faced. Household income was reduced as mothers felt the need to leave their jobs or work part time to care for their child. Siblings took on extra responsibilities to support their parents with the care of their brother or sister with epilepsy.

> *'I think you have to make sure that the whole family is involved and the whole siblings are on board with it. It can't just be a parent and that child event'. (MP1)*

5.4.3.2 Social and emotional functioning outcomes

Participation

Participation is defined 'as involvement in a life situation' (World Health Organization, 2001) and represents how one functions in society with a health condition. Twelve parents discussed *participation* as a new outcome for their child, one not previously identified in the scoping review. 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 they felt their child was missing out on.

FP15 discussed how her 5-year-old daughter had to give up swimming and gymnastics, she wouldn't let her climb anything and felt she had to follow her around the playground for fear of anything happening to her. When she was seizure free for almost a year, she re-joined swimming classes and gymnastics and she 'can do everything now'. Birthday parties, sleep overs and school trips were challenging owing to the array of non-ketogenic food and the risk of a child seizing when unsupervised by their parent. Sometimes the reluctance to attend

was driven by the child's parents out of worry but on other occasions the child with epilepsy was excluded

> *"..one of the parents did say to me that they weren't going to invite – or they hadn't invited him to a birthday party because they were worried that there would be lots of sweets and cakes and so on there. So that made me feel quite-that was a bit sad." (FP6)*

It was clear there were many factors influencing a child's ability to participate. Some were beyond the control of parents and included the willingness of others to make adjustments and support the child to take part. For example, nursery, school, sports coaches and other parents of child's friends. A lovely demonstration of this was when FP19 and MP2s local parkrun group made the necessary adjustments to welcome and support their 7-year-old son to take part

> *"..he loves the fact that he comes last because everyone now knows him and he'll pause about 20 metres before the finish line and wait until he has everyone's attention, they're all clapping him and then he sprints across the line.. he's a little celebrity down there." (FP19, MP2)*

Independence

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. An example of this was walking to school alone and overcoming the hurdles this presented, particularly when crossing the road. Those who highlighted this example had experienced their child walking out in front of traffic or seizing with the subsequent loss of control and awareness.

> *…"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…he's 12 at some point he's going to want to go out with his mates into town on a Saturday to go to the cinema with his friends and he can't do any of those things." (FP1)*

FP10 described how limited her 14-year-old son was when having regular seizures and how he didn't have the 'same 'freedoms as a normal child'.

However, his independence has increased greatly since becoming seizure free with KD therapy. He chose his own secondary school and travelled there alone every day, which involved a walk, train and bus journey. She described how 'he is his own person, he's independent'. Parents used bathing or toileting as an example of where their child could or had gained independence and the importance of this, particularly as their child got older. 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.

5.4.3.3 Diet and nutrition outcomes

Parents confidence with ketogenic diet

Almost half of parents interviewed identified that their confidence with preparing and managing the KD should be considered as an outcome. It is a significant undertaking, and the responsibility of preparing every meal and snack correctly can be 'daunting'. FP3 described how she 'burnt out' only three weeks into starting KD as she stayed up very late to prepare keto meals and put a lot of pressure on herself to get it right. Taking some time off work helped and she along with others felt that 'it got easier as times gone on'

> *"Yes, because I suppose it is our responsibility, like these children can't do it for themselves." (FP2)*

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 sub theme 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)*

FP17 discussed how this felt especially pertinent for her as a mother, she felt she was doing something positive every day for her little girl that was helping. 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.

> *"we've always loved eating out, we love food. To go out on keto diet we thought, we're never going to be able to do it. So, it must have been a good year we left it before we started trying…those sorts of things to us, they're literally huge, you've just done that, we've just gone out an had a family meal and it makes it more normal." (FP19, MP2)*

5.4.3.4 Physiological clinical outcomes

Status epilepticus and rescue medication use

Status epilepticus is a state of persistent seizures. Typically rescue medication such as midazolam is administered after five minutes to try to interrupt the seizure cycle. Four parents highlighted the importance of monitoring the use of this medication as reduction in use would suggest an improvement in seizure control. This was therefore classified as a new outcome. 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)*

Seizure duration

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 minutes in duration when treated with KD therapy.

5.4.4 Parents priority outcomes

When asked to prioritise the outcomes they identified (Table 23), 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)*

These outcomes largely revolved around parents seeking to monitor their child's development and progress in different activities and in turn monitoring their successes. This was very individual for each child, but it was apparent that each 'small step' was celebrated as a step forward. For some these were viewed almost as an additional bonus on top of the seizure control while for others they were the priority.

> *"For me I was thinking of the diet as this was going to help control her seizures. So then with all the other benefits [personality returning and improved energy levels], I was really quite surprised, obviously pleasantly surprised. But I think either it hadn't sunk in there was going to be other potential benefits, or I just focussed on the seizures that I'd forgotten there might be other benefits." (FP8)*

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

Table 23. Parents priority outcomes

Domain (Dodd *et al.*, 2018)	**Outcome**	**N identified**
Physiological Clinical	Seizure reduction	6
Cognition	Learning and cognition	6
Physiological Clinical	ASM 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

5.5 Discussion in the context of existing literature

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 (Washington and Lipstein, 2011). To the authors knowledge, this is the first in depth qualitative study, exploring parents' views on outcomes of importance. The findings demonstrate 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 with fibromyalgia and rheumatoid arthritis (Kirwan *et al.*, 2003; Arnold *et al.*, 2008) and parents of critically ill children (Fayed *et al.*, 2020) highlighted new outcomes not previously identified through systematic 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 (Kerr, Nixon and Angalakuditi, 2011). 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.* (2015) describe a state of intense parenting, where parents of children with complex care needs took on more roles than parents of healthy children and they 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 (Harden, Black and Chin, 2016). While KD therapy offered hope when other treatments had failed; it imposed additional roles and burdens for parents and affected wider family life.

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 the dietitian and wider keto team 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 (Smith *et al.*, 2014). 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.

S*eizure reduction* was prioritised as a primary outcome in both published research (Chapter 3) 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. Ultimately, these findings suggest that the secondary outcomes assessed in published research do not reflect parents' priority outcomes.

5.6 Strengths and limitations

In section 4.6, the strengths and limitations of the qualitative phase of this study were discussed, and these factors are equally applicable here. A significant strength of this phase of analysis is that it is the first to examine the opinions and priorities of parents regarding the outcomes of KD therapy for children with epilepsy. Content analysis was used to ensure all possible outcomes were identified and not only those that parents identified as outcomes when asked about the most important outcomes for their children. The analysis is systematic, reliable, and repeatable, while maintaining the meaning of the message as it was intended by the interviewee. In this way, the parents' terminology and descriptors of outcomes could be utilised in the later Delphi study, thus improving accessibility.

5.7 Conclusions and next steps

These 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 long list of outcomes identified from the scoping review (chapter 3) and the parent interviews (chapter 5). The outcomes identified in this phase of the CORE-KDT study were reviewed in the pre-Delphi consultation process (Chapter 6) that follows in preparation for a two-round international Delphi study to seek consensus on a core outcome set for this clinical area.

Chapter 6: Identifying a core outcome set

Preface

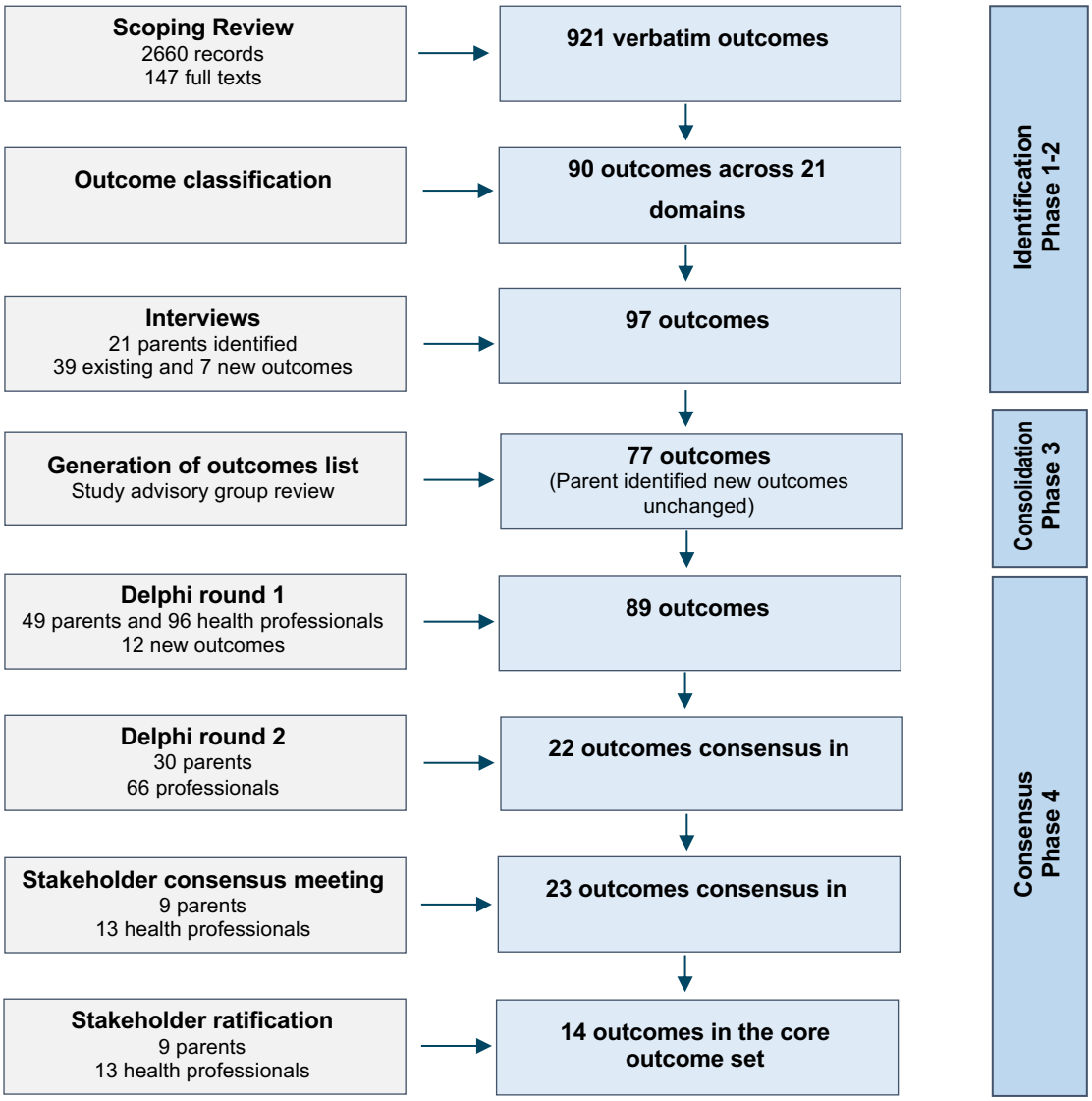
This chapter describes the consensus process undertaken to agree upon a core outcome set for children with drug resistant epilepsy treated with KD therapy. Outcomes from the scoping review (chapter 3) and parent interviews (chapter 5) informed the pre-Delphi consultation between the study advisory group and the research team. An international Delphi survey and stakeholder consensus meeting followed, during which participants prioritised the core outcomes. The chapter concludes with the presentation of the agreed core outcome set. Work arising from this chapter has been published (open access) in Epilepsia (Carroll *et al.*, 2023). Sections of this chapter have been taken directly from the edited manuscript. The researcher led the data collection, data analysis and wrote the original draft of the manuscript, which was edited by the supervisory team and then subject to peer review. The published manuscript is available in Appendix T.

6.1 Introduction

The earlier scoping review (chapter 3) identified that there is considerable variation and lack of consistency in reported outcomes, definitions and measurement approaches in past clinical trials of drug resistant epilepsy treated with KD therapy (Carroll *et al.*, 2022b). Furthermore, parents' perspectives on outcomes had not been examined, and it was unclear if researchers' and health professionals' priorities aligned with those of parents. To address this gap in knowledge, interviews were conducted with parents to explore their perspectives. The findings (chapter 5) indicated that the outcomes traditionally

used in research do not adequately reflect parent priorities for their children (Carroll *et al.*, 2022b). To address these challenges in outcome selection and reporting the first international parent, health professional and researcher consensus was established, to develop a core outcome set for drug resistant childhood epilepsy treated with KD therapy. Figure 11 provides an overview of the development of the core outcome set.

Figure 11. Overview of core outcome set development



6.1.1 Aim and objectives

Research question

What are the most important outcomes to include in a core outcome set for drug resistant childhood epilepsy treated with KD therapy?

Aim

1. To seek agreement within the study advisory group and the research team regarding the list of outcomes and descriptors (Phase 3), to go forward to the Delphi survey of parents, health professionals and researchers who will rate the critical importance of each included outcome (Phase 4).
2. To reach consensus on a core outcome set for drug resistant childhood epilepsy treated with KD therapy, from the perspective of key stakeholders including parents, health professionals and researchers (Phase 4).

Objectives

1. To minimise overlap between outcomes and ensure that the language used is accessible for participants
2. To undertake a two-round Delphi survey where stakeholders are invited to rate the list of outcomes
3. To identify three sets of outcomes from the Delphi survey;
    i) with a consensus for inclusion in the core outcome set
    ii) with a consensus for exclusion from the core outcome set
    iii) without a consensus – undecided outcomes
4. To convene a stakeholder consensus meeting to discuss and vote upon the undecided outcomes and agree the core outcome set.

6.2 Summary of methods

Chapter 2 outlined the detailed methodology, which is summarised briefly here for ease of review.

6.2.1 Pre-Delphi consultation to agree the list of outcomes (phase 3)

The outcomes identified in the phase 1 scoping review and phase 2 parent interviews were combined to create a comprehensive long list of outcomes and associated descriptors, then reviewed and ratified by the research team and the study advisory group (phase 3). 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. Reviewers commented on a shared document so all could view each other's commentary. The feedback was reviewed, implemented, and recirculated for final agreement. The consolidated outcomes list was used to populate the Delphi survey, which was then piloted by parents and professionals to ensure ease of use and accessibility for participants.

6.2.2 Patient and Public Involvement and Engagement (PPIE)

Table 24 reports on the ways in which PPIE was incorporated into the pre-Delphi consultation and the outcomes it influenced, in accordance with the GRIPP2-SF (Staniszewska *et al.,* 2017).

Table 24. PPIE in the Pre-Delphi Consultation - Phase 3 of the CORE-KDT study
Reported in accordance with GRIPP2-SF (Staniszewska *et al.,* 2017)

Section and topic	Item
1. Aim Report the aim of the study	- To seek final agreement within the CORE-KDT study advisory group and research team regarding the list of outcomes and descriptors to go forward to the Delphi survey of parents, health professionals and researchers, who will rate the critical importance of each outcome. - To minimise overlap between outcomes and ensure that the language used is accessible for participants
2. Methods Provide a clear description of the methods used for PPI in the study	- Lay research partners, the study advisory group and the research team reviewed the 90 outcomes identified in the Phase 1 scoping review and the seven outcomes identified in the Phase 2 parent 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 - Reviewers commented on a shared document so all could view each other's commentary - Lay research partners and the study advisory group piloted the Delphi study developed using DelphiManager
3. Results Outcomes – report the results of PPI in the study, including both positive and negative outcomes	- PPI involvement helped to reduce the list of 97 outcomes to 77 outcomes for inclusion in the Delphi study - Clear rationale was identified and mapped for the expansion, merging or removal of an outcome (Appendix V) - User experience of the Delphi study was improved when feedback was implemented
4. Discussion Outcomes – comment on the extent to which PPI influenced the study overall. Describe the positive and negative effects.	- PPI improved the language and accessibility of the Delphi study for both parent and professional participants
5. Reflections Critical perspective – Comment critically on the study, reflecting on the things that went well and those that did not so others can learn from the experience	- PPI in this phase of the study was very effective and influenced key aspects of the study. The list of outcomes was reduced, removing repetition and language improved. However, there were limitations. - One parent representative was 'lost to follow up' in the study advisory group, electing not to respond to emails or requests for involvement. It was decided not to replace this member as the study was in progress for two and a half years at that point. As such a new parent representative may struggle to adapt given the degree of design, planning and implementation they would have missed. - The lay research partners and study advisory group members did not receive formal training to support their involvement in study design, planning and delivery. Instead, the lead researcher set expectations and provided support and guidance when needed.

Section and Topic	Item
5. Reflections cont.	While no member raised this as an issue, the lack of formal training could have caused anxiety regarding their ability to contribute effectively. However, formal training may have also increased the burden on them commanding more of their time. - This study was largely unfunded, so representatives did not receive remuneration for their time owing to resource constraints - The study advisory group did not meet at any point during the study. This was mainly due to the fact we did not have the resource to offer remuneration for the members or support reimbursement of travel expenses. They did often see each other's feedback as documents with tracked changes were shared but the lead researcher coordinated their involvement seeking ad-hoc input at each phase of the study as needed rather than hosting regular meetings. The bulk of their involvement was prior to the covid pandemic when the use of video calling technology was not so widespread, but this could be used as a cost-efficient way of bringing representatives together in future studies.

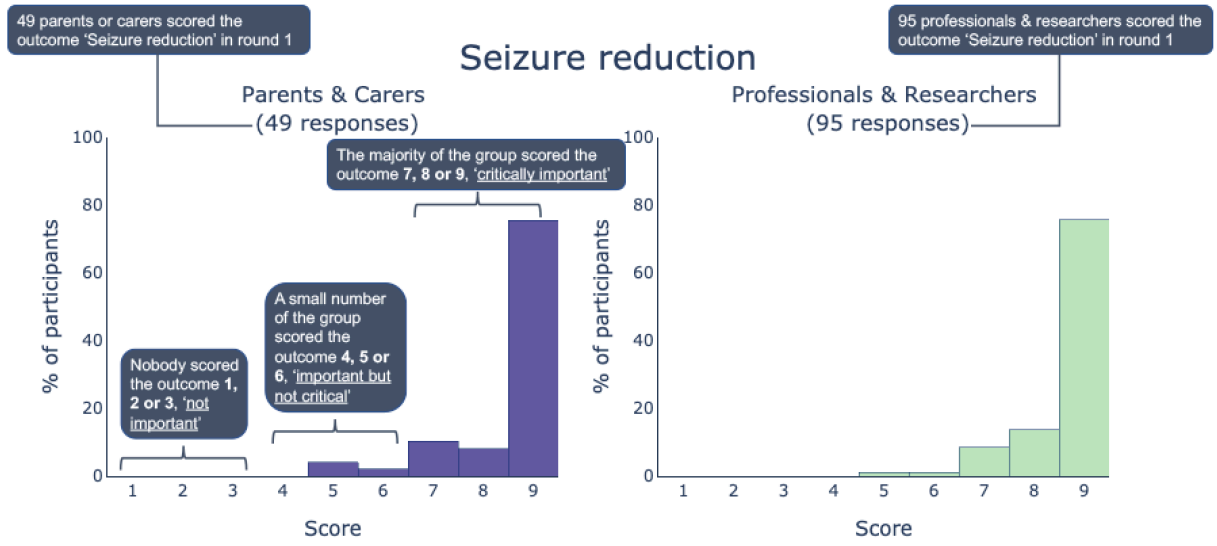
6.2.3 Stakeholder participants and eligibility

International parents, health professionals, researchers, industry and charity representation were sought. Participation was open to stakeholders with lived experience of childhood epilepsy and KD therapy or supporting families to undertake KD therapy. Parents were recruited from nine KD centres operating as Participant Identification Centres (UK only), and via charity organisations (Matthew's Friends, Young Epilepsy and Epilepsy Action), Epilepsy the Ketogenic Way and social media (UK and international participants). Health professionals were recruited internationally via professional networks (Matthew's Friends Professionals mailing list, Ketogenic Dietitians Research Network, Ketogenic Professional Advisory Group and the Epilepsy Nurses Association) and social media.

6.2.4 Delphi Survey (phase 4)

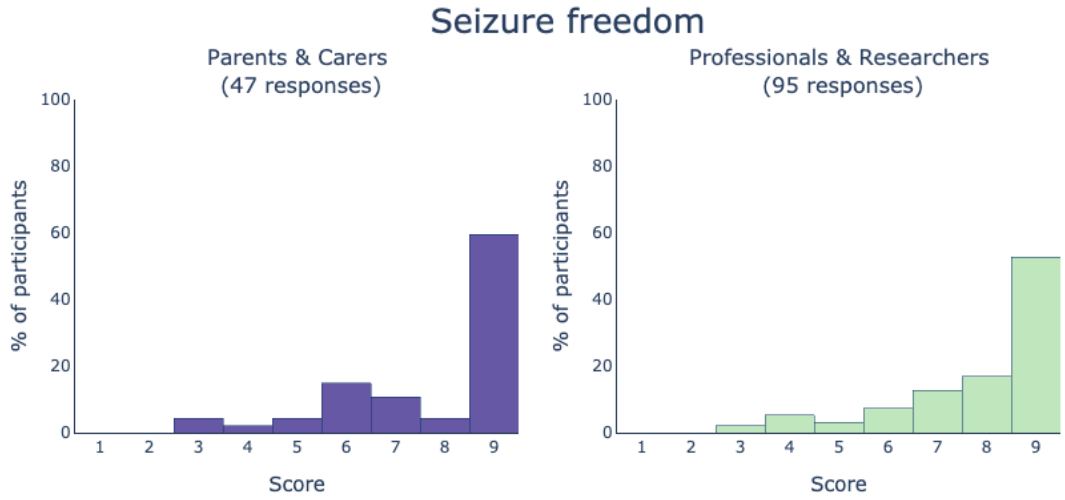
Participants were asked to rate the importance of each outcome on a Likert type scale ranging from 1-9 (1-3 not important; 4-6 important but not critical and 7-9 critically important to include in the core outcome set). In round one, participants were offered the opportunity to propose additional outcomes not addressed by the existing list of outcomes. The scores for each stakeholder group, (i) parents and (ii) health professionals or researchers, were analysed separately, including partial responses. Descriptive statistics summarised the results of each round, including the percentage of participants scoring 1-9 for each outcome. All participants were invited to participate again in round two, where their individual round one score and the group scores of each stakeholder group were presented on histograms (Figure 12a and 12b). They were asked to reflect on the scores of others, rescore each outcome again and share their reasoning for any changed scores. Consensus criteria for inclusion or exclusion from the core outcome set were defined *a priori* (Williamson *et al.*, 2017). 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 core outcome set. Conversely, outcomes scored not important (1-3) by 70%, or more and critically important by 15% or less in both stakeholder groups were *excluded* from the core outcome set. Outcomes that failed to reach a consensus using these criteria for inclusion or exclusion were categorised as undecided.

Figure 12. Histograms shared in round two summarising the round one outcome scores from each stakeholder group
(12a)



The graph for the first outcome 'Seizure Reduction' had explanatory notes to guide participants on how to read and interpret the graph. Thereafter, the notes were removed as in (12b).

(12b)



6.2.5 Consensus meeting (phase 4)

Participants were invited to attend an online stakeholder consensus meeting, purposely sampled to ensure representation of key stakeholders. Participants discussed and voted upon:

(i) undecided outcomes where 70% or more of one stakeholder group scored it critically important but not the other

(ii) undecided outcomes proposed by a participant prior to the consensus meeting

The Likert type scale (1-9, not important to critically important) used in the consensus meeting voting process was the same as that used in the Delphi survey. Scores were calculated separately for both stakeholder groups to mitigate the imbalance in numbers between parents and professionals. Results were shared with participants within one week and feedback was sought (JISC online survey) at two time points. Firstly, following the consensus meeting to assess their satisfaction with the process and secondly, following review of the proposed core outcome set to evaluate their views and gather any final feedback.

6.2.6 Patient and Public Involvement and Engagement (PPIE)

Table 25 reports the ways in which PPIE was incorporated into the Delphi study and consensus meeting and the outcomes it influenced in accordance with the GRIPP2-SF (Staniszewska *et al.,* 2017).

Table 25. PPIE in the Delphi and consensus meeting – Phase 4 of the CORE-KDT study
Reported in accordance with the GRIPP2-SF (Staniszewska *et al.,* 2017)

Section and topic	Item
1. Aim Report the aim of the study	- To reach consensus on a core outcome set for drug resistant childhood epilepsy treated with KD therapy, from the perspective of key stakeholders including parents, health professionals and researchers.
2. Methods Provide a clear description of the methods used for PPI in the study	- Lay research partners supported recruitment of parent participants via their charity forum, a closed Facebook group and social media - Lay researchers supported recruitment of professional participants to the two round international Delphi study via the Matthews Friends Professionals email list serve and social media - Lay research partners reviewed the materials for the consensus meeting, were in attendance and voted - The healthcare professional representative of the study advisory group attended the consensus meeting and voted - Lay research partners provided critical review of the write up of the results from phase 3 and 4 of the CORE-KDT study and dissemination.
3. Results Outcomes – report the results of PPI in the study, including both positive and negative outcomes	PPI contributed to this phase of the study in many ways. - Attrition of parent participants between Delphi round one and two was high but improved when lay research partners sent email reminders - The lay researchers and health professional representative of the study advisory group made valuable contributions to the consensus meeting - The lay researchers made themselves available to speak with any parents post the consensus meeting if in need of support - The lay research partners co-developed a poster on the role a charity can play in PPIE, presented at the British Paediatric Neurology Association Conference and accepted for presentation at Global Keto in San Diego 2023 - Lay research partners provided critical review for the article published in Epilepsia - Lay research partners contributed to a plain English summary, approved its inclusion in the Matthew's Friends Newsletter and supported an open online update meeting for parents where the findings of the CORE-KDT were shared
4. Discussion Outcomes – comment on the extent to which PPI influenced the study overall. Describe the positive and negative effects.	- Representatives made valuable contributions to recruitment and the finalised core outcome set and supported the dissemination of this. The benefits of PPIE were shared with professional audiences via a poster to enhance awareness and encourage incorporation of PPI into future studies.

Section and Topic	Item
5. Reflections Critical perspective – Comment critically on the study, reflecting on the things that went well and those that did not so others can learn from the experience	- PPI in this phase of the study was very effective and influenced the development of the finalised core outcome set. Recruitment would have been reduced without the involvement of our lay researcher partners and our ability to disseminate to a lay audience in particular would have been limited. However, there were limitations. We omitted a formal evaluation of PPI partners views and experiences on their engagement with the study. This would have informed the evolution of PPIE in future work. The lay research partners and study advisory group members did not receive formal training to support their involvement in study design, planning and delivery. Instead, the lead researcher set expectations and provided support and guidance when needed. They were keen to share their views and support the study, however it is possible that the lack of formal training may have caused anxiety that they were contributing effectively. However, formal training may have also increased the burden on them commanding more of their time. - This study was largely unfunded, so representatives did not receive remuneration for their time owing to resource constraints - The study advisory group did not meet at any point during the study. This was mainly due to the fact we did not have the resource to offer remuneration for the members or support reimbursement of travel expenses. They did often see each other's feedback as documents with tracked changes were shared but the lead researcher coordinated their involvement seeking ad-hoc input at each phase of the study as needed rather than hosting regular meetings. The bulk of their involvement was prior to the covid pandemic when the use of video calling technology was not so widespread, but this could be used as a cost-efficient way of bringing representatives together in future studies.

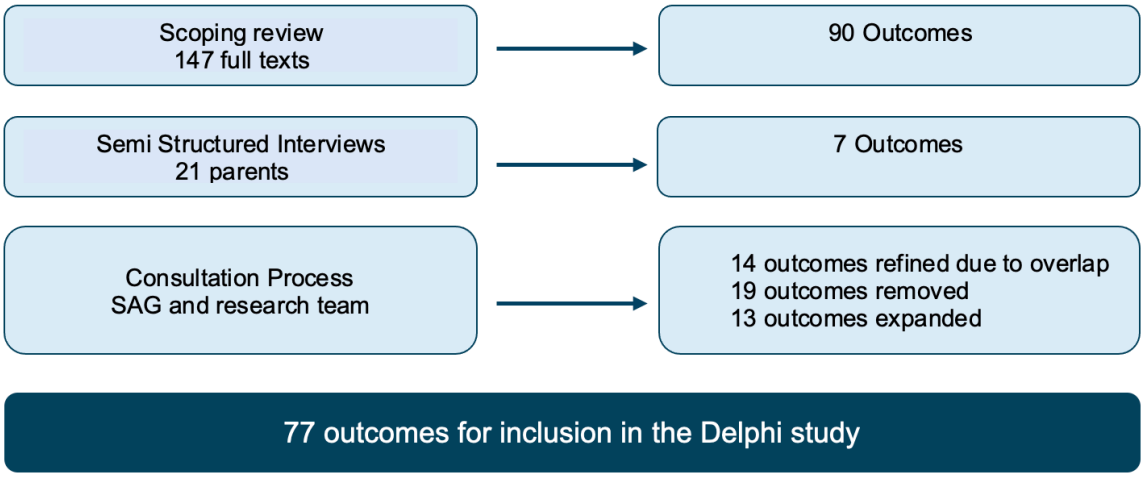
6.3 Results

The results of the CORE-KDT study are reported in line with the Core Outcome Set-STAndards for Reporting (COS-STAR) guidance (Kirkham *et al.*, 2016). The checklist is available in Appendix U. Figure 11 summarizes each phase of the study, including the number and grouping of participants and the systematic prioritisation of outcomes.

6.3.1 Phase 3: Pre-Delphi consultation

Figure 13 provides an overview of the steps taken to identify and consolidate the outcomes in phases one to three of the study. The research team and study advisory group reviewed 97 outcomes and plain language descriptors identified via the scoping review and parent interviews. Parent identified outcomes (N=7) remained unchanged. Appendix V presents the rationale for the removal, merging, or expansion of individual outcomes. Nineteen outcomes were removed as they were influencing or predictive factors rather than true outcomes. For example, predictors of growth or predictors of response to KD therapy. Fourteen outcomes were merged owing to overlap with other outcomes. For example, the outcome *long term seizure outcomes* was merged with *seizure reduction* and *seizure freedom* as this outcome was related to follow up duration rather than a separate outcome in itself. Thirteen outcomes were expanded to reduce ambiguity for participants, for example *cognition* was expanded to three outcomes: *speech and language, memory,* and *learning* and *seizure frequency* was expanded to *seizure reduction* and *seizure freedom.*

Figure 13. Identification and consolidation of the outcomes list



SAG – study advisory group

Adverse effects were initially grouped according to the system affected, for example *adverse effects gastrointestinal* as it could prove overly onerous for participants in the Delphi study to rate a list of hundreds of outcomes if each individual adverse effect was listed as a discrete outcome. Listing outcomes individually may also hinder the ability to reach consensus on the core, most important outcomes. Consequently, the finalised core outcome set would be too long and unrealistic for researchers or keto teams to implement. However, a compromise employed by Fish *et al.* (2018) in the development of a core outcome set for anal cancer was to name any adverse effect as a discrete outcome if it was identified in the parent interviews alone or in the parent interviews and scoping review together. This approach was utilised to ensure the inclusion of adverse effects parents felt were important in the Delphi study. Adverse effects identified by parents and listed individually as a discrete outcome for the Delphi survey included *fatigue, bone health, bone fractures, renal stones, cholesterol, gastro oesophageal reflux disease, constipation, ketogenic rash and feeding difficulties*.

Plain language descriptors were refined following insightful feedback from parent co-investigators and study advisory group representatives. The consultation process concluded with 77 outcomes and representative plain language descriptors ratified for inclusion in the Delphi study (Table 26).

Table 26. 77 Outcomes classified according to the COMET Taxonomy
with associated descriptors and mapping of parent identified outcomes (✓) from the scoping review 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.	✓
	Seizure freedom	Not having seizures	✓
	*Seizure duration	How long a seizure lasts	✓
	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 minutes or more it is called status epilepticus or 'status'.	
	*Use of rescue medication for status epilepticus	How often rescue medication is used	✓
	Anti-seizure medication use	Number and dose of anti-seizure medications to reflect recent changes such as weaning from an ASM	✓
	Ani-seizure medication blood concentrations	The concentration or level of anti-seizure medications in the blood	
	Side effects of anti-seizure medications drugs	Side effects experienced with the use of anti- seizure medications	✓
	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.	✓
	Growth	Changes in weight, length, height or growth centile	✓
	Cholesterol levels	The concentration or level of cholesterol in the blood. This can increase for some children treated with KD	✓
	Gastro oesophageal reflux	High fat intake can exacerbate existing reflux for some children	✓
	Constipation	Difficulty in passing a stool (poo) or going to the toilet less often	✓
	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.	✓
	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	✓
	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.	✓
	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	
Diet and nutrition outcomes	Appetite	Change in the desire to eat food or drink	✓
	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	✓
	Physical feeding difficulties	For example, difficulty swallowing or unable to consume the necessary volume and hence requires tube feeding	✓
	Behavioural feeding difficulties	Challenges with feeding, for example food fussiness, food refusal, difficulty with textures and long mealtimes	✓

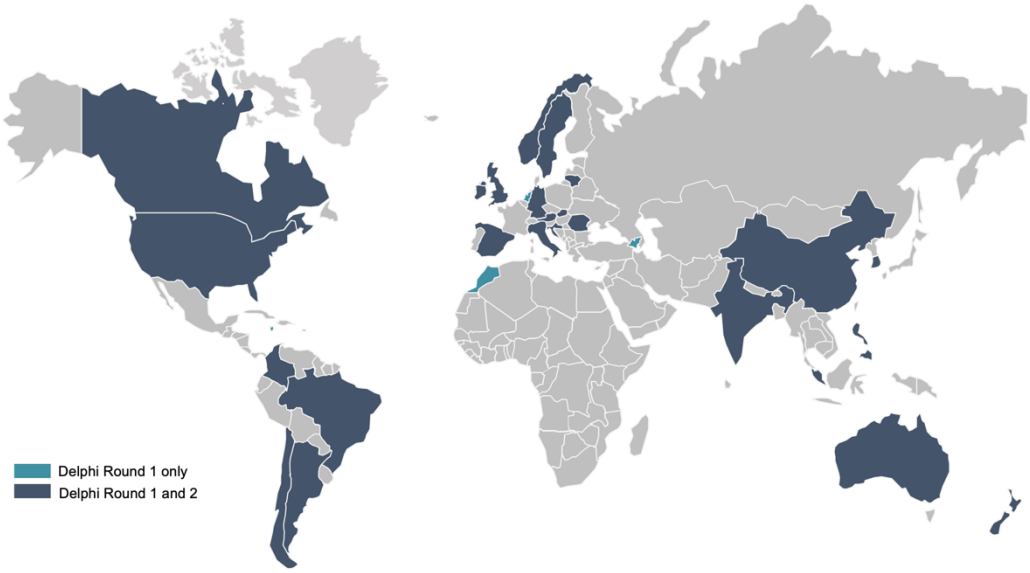
Diet and nutrition outcomes Cont….	Tolerability of KD	How well the child can manage the KD and its challenges	
	*Parents confidence with KD	Parents feelings towards being able to cope and manage the KD	✓
	Palatability of KD formula and supplements	Acceptability of the taste of prescribed KD formula, supplements or additives (for example ready meals, snacks, milkshakes, desserts, vitamins and minerals, fat, protein or carbohydrate shots and powders)	✓
	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)	✓
	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	✓
	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	✓
	*Family life	Impact of epilepsy and KD on family life including siblings, parents relationship, work and career opportunities	✓
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	✓
	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	✓
	Concentration	Change in ability to focus on a given task while ignoring distraction	✓
	Social skills	Change in ability to engage and interact with others, for example siblings and friends	✓
	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.	✓
	*Independence	Child becoming as independent as they can, for example; needing less supervision or walking to school alone	✓
	Mood	Change in general sense of positive or negative mood	✓
	Emotional development	Change in child's understanding of who they are and what they are feeling	✓
Cognition outcomes	Memory	Change in short and long-term memory	✓
	Speech and language	Change in ability to make oneself understood & understanding when spoken to	✓
	Learning	Change in ability to gain new skills and knowledge	✓
	Developmental milestones	Progress in meeting milestones such as smiling, sitting without support, responding to requests, sorting shapes and colours	✓
Physical functioning outcomes	Activities of daily living	Change in ability to carry out activities like feeding, toileting, washing	✓
	Movement ability	Change in ability to sit, crawl, walk, run or jump	✓
	Coordination and balance	Change in ability to use parts of body together & efficiently, e.g. riding a bike	✓
	Manual ability	Change in dexterity in handling objects like cutlery and toys	✓
	Fatigue	Lacking in energy, feeling more tired or 'drained' than usual	✓
	Time spent asleep	Total time spent asleep in each 24-hour period	✓
	Daytime sleepiness	Feeling sleepy or actually sleeping during the day	✓
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	✓
	Unplanned hospital admissions	Unexpectedly needing to be admitted to hospital for epilepsy or KD related issues	✓
	Length of hospital stays	Number of inpatient days in hospital in a given period, e.g. last year	
	Cost effectiveness of KD	is KD a cost-effective treatment for epilepsy	✓

Resource use cont.	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)
	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.

6.3.2 Phase 4: Delphi Survey

In total, 145 participants from 33 countries participated in round one, 96 of which went on to take part in round two, representing 29 countries (Figure 14).

Figure 14. Map of international participation



The characteristics of participants included in the analysis are summarised in Table 27. Most professional participants indicated their primary profession as a clinician, with only seven identifying as a researcher or academic. However, it is likely that many others were also involved in research as part of their clinical roles. Most professional participants were paediatric dietitians or paediatric neurologists, and 40% of these professionals reported more than 10 years' experience working with KD therapy. For parents, 90% were mothers, a similar pattern of recruitment to the qualitative interview phase.

Table 27. Delphi participant characteristics and demographic data

Stakeholder group	Variable	Round 1 (%)	Round 2 (%)
Parents	**All**	**49**	**30**
	Sex		
	Female	44 (90)	26 (86)
	Male	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)
Professionals and researchers	**All**	**96**	**66**
	Sex		
	Female	73 (76)	51 (77)
	Male	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 or black British	1 (1)	0 (0)

Stakeholder group	Variable	Round 1 (%)	Round 2 (%)
Professionals and researchers cont.	**All**	**96**	**66**
	Profession	48 (50)	33 (50)
	Dietitian	2 (2)	1 (1)
	Dietitian and researcher	2 (2)	2 (3)
	Nutritionist	15 (16)	9 (14)
	Paediatric neurologist	6 (6)	5 (8)
	MD neurology	1 (1)	1 (1)
	Neuropaediatrician	4 (4)	3 (5)
	Paediatrician	2 (2)	2 (3)
	Physician	1 (1)	1 (1)
	Prof of paediatric neurology	1 (1)	1 (1)
	Clinical fellow paediatric epilepsy	5 (5)	3 (5)
	Clinical/epilepsy specialty nurse	1 (1)	1(1)
	Paediatric nurse practitioner	3 (3)	1(1)
	Academic	2 (2)	1(1)
	Researcher	1 (1)	1(1)
	Neuropsychiatrist	1 (1)	1(1)
	Neuropsychologist	1 (1)	0 (0)
	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)

6.3.2.1 Delphi round one

Eight participants submitted an incomplete set of scores for round one, six of whom were parents and carers, the smaller of the two stakeholder groups. The scores which they did complete were included in the analysis to ensure their views were represented. Participants could choose an ‘unable to score’ option, which would result in fluctuations in the total number of participant scores for each individual outcome. Therefore, the inclusion of partial datasets would not adversely influence the results. Table 28 lists the voting results for both stakeholder groups following rounds one and two, classifying outcomes as undecided, included or excluded from the core outcome set. Participants proposed 68 additional outcomes during round one, of which 12 were added to round two for scoring (total N=89 outcomes). The remaining proposed outcomes (N=56) were duplicates of existing outcomes or influencing factors

rather than outcomes. Appendix W outlines the justification for their inclusion or exclusion from round two.

6.3.2.2 Delphi round two

Scores from 96 round two participants were analysed (30 parents and 66 health professionals and researchers), which included two parents and three health professionals or researchers who did not complete the entire round. The attrition rate between round one and round two was 34% (49 participants: 19 of 49 parents [39%] and 30 of 96 health professionals and researchers [31%]). In total, 22 outcomes reached consensus for inclusion in the core outcome set. No outcomes met the original criteria for exclusion (>70% score 1-3 and <15% scored 7-9). Fish *et al.* (2018) established a precedent when they defined new exclusion criteria to address the issue of nil outcomes meeting the *a priori* exclusion criteria. Using their criteria, outcomes were excluded if 50% or less of participants in both stakeholder groups scored the outcome as critically important (7-9). When applied, 17 outcomes were excluded from the outcome set. The remaining 50 outcomes did not meet the criteria to be included or excluded from the core outcome set and were classified accordingly as *'undecided'*.

Table 28. 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	100	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

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 (%)	
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

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 (%)	
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
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	2	28	69	1	34	66	UNDECIDED	4	23	74	0	23	77	IN

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 (%)	
Resource Use Cont.														
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.

6.3.3 Phase 4: Consensus meeting

The consensus meeting was held online via Zoom on February 23rd 2022. Twenty-five participants registered to take part, however three were unable to attend on the day (two parents and one epilepsy specialist nurse). As a result, 22 participants (9 parents and 13 health professionals) attended the meeting, representing nine countries, although the majority lived in England. Contributors and their roles are listed in Appendix X. All voting members were experienced with epilepsy and ketogenic diet as a parent, health professional, charity or industry representative. Fourteen participants (seven parents and seven health professionals) had completed both rounds of the Delphi study. Of the remaining eight participants, three were voting members of the research team, one represented Young Epilepsy and four were members of an expert international working group convened to explore the measurement of non-seizure related outcomes.

Following the Delphi survey, 19 of the 50 undecided outcomes were scored to be critically important by ≥70% of one stakeholder group but not the other. The remaining 31 outcomes were not deemed to be critically important by the majority of either group. It would not be feasible to discuss all 50 outcomes during the consensus meeting so the group of 19 outcomes were prioritised for discussion and scoring. Prior to the meeting, participants proposed 8 of the remaining 31 outcomes for discussion and scoring, resulting in a final total of 27 outcomes put forward to the consensus meeting. Table 29 outlines the voting results, one additional outcome reached consensus for inclusion in the core outcome set - ‘Unplanned hospital admissions’. Fourteen outcomes reached consensus for exclusion when the 50% exclusion criterion was applied.

Table 29. 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

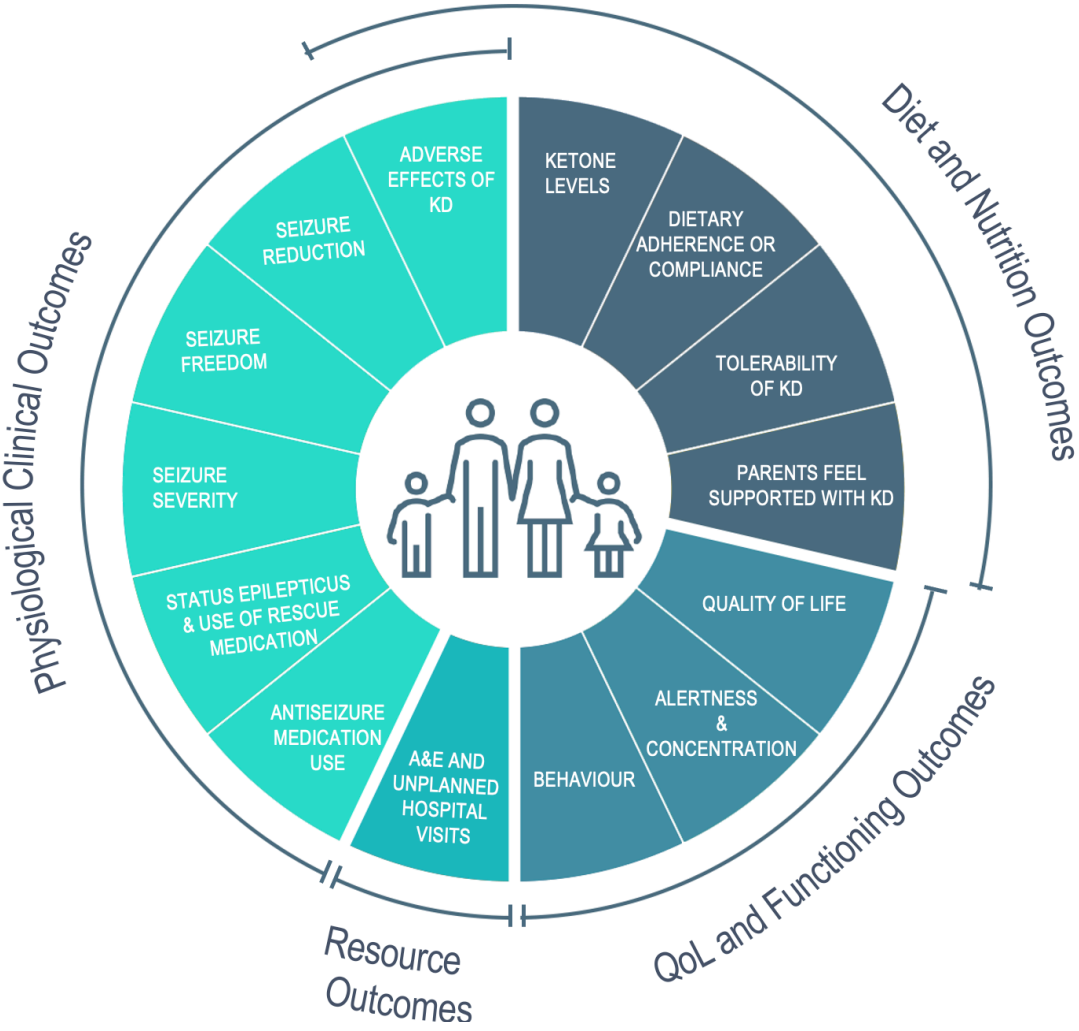
During discussions, participants shared helpful opinions and views on outcomes that could potentially be merged in order to reduce the overall number of outcomes in the core outcome set. Interestingly, following the Delphi study, three broad adverse effects outcomes were voted into the core outcome set;

‘side effects that affect the heart’, ‘side effects that affect the liver’ and ‘side effects that affect the respiratory system’. Yet arguably as important and more frequently occurring side effects such as growth, constipation, reflux and kidney stones were scored out or undecided. During the consensus meeting, parents voiced their opinion that all side effects should be considered as they felt reassured by the keto team monitoring these for their child when following a KD. Health professionals felt there were additional potential renal issues beyond renal stones alone and the value of respiratory side effects was questioned. In response to these valuable insights, the research team finalised the provisional core outcome set which was then shared with the consensus meeting participants one week after the meeting. Appendix Y outlines the reasoning and justification for final amendments to the core outcome set.

6.3.3.1 A core outcome set for childhood epilepsy treated with ketogenic diet therapy

The finalised core outcome set (Figure 15) includes 14 outcomes across five domains including physiological clinical, diet and nutrition, global quality of life, social and emotional functioning and resource use. Table 30 expands on this and lists the agreed descriptors for each outcome.

Figure 15. The CORE-KDT core outcome set



The potential adverse effects of KD may manifest as physiological clinical or diet related outcomes so the potential overlap is demonstrated in Figure 15.

Table 30. The CORE-KDT core outcome set

Domain	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 anti-seizure 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 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.

6.3.3.2 Participant feedback

Feedback was sought following the consensus meeting to assess participant satisfaction with the process (18 completed; 7 parents, 11 health professionals) and following their review of the core outcome set to confirm their agreement with the outcome set (20 completed; 8 parents, 12 health professionals). All (100%) participants were satisfied with the process used to agree the core outcome set and the facilitation of the meeting. All (100%) felt able to contribute to the meeting and 94% felt comfortable to communicate their views. When initially asked if the consensus meeting produced a fair result, 56% agreed or strongly agreed, 44% neither agreed nor disagreed. This was likely because the results of the consensus meeting and provisional core outcome set had not yet been shared when this feedback was sought. The same question was repeated one week later when the provisional core outcome set was shared, and all participants (100%) agreed or strongly agreed the consensus meeting produced a fair result. These quotes illustrate participants' responses:

> *"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."*

6.4 Discussion in the context of existing literature

The CORE-KDT core outcome set provides the first international consensus on outcomes for children with epilepsy treated with KD therapy. It has been developed encompassing the views of parents, health professionals, researchers, charity and industry representatives from 33 countries. Delphi consensus methodology enabled an inclusive and transparent process facilitating differing viewpoints and avoiding potential over-influence from one type of stakeholder. Seventy percent or more of both stakeholder groups deemed the outcomes in the core outcome set to be critically important. We recommend that all future trials evaluating KD therapy for children with drug resistant epilepsy utilise the CORE-KDT study core outcome set as a framework for outcome selection and reporting. The core outcome set 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. By implementing the CORE-KDT set routinely, both settings will benefit from improved consistency in outcome selection and reporting.

The core outcome set includes a range of both seizure and non-seizure related outcomes across five domains of the COMET taxonomy (Dodd *et al.*, 2018). This includes six physiological clinical outcomes, four diet related outcomes, three quality of life and functioning outcomes and finally one resource use outcome. Commonly reported outcomes such as seizure reduction, seizure freedom and quality of life are included, in line with existing guidelines for children with epilepsy (NICE, 2012; Scottish Intercollegiate Guidelines Network, 2020). There are also shared outcomes with a core outcome set for Rolandic

epilepsy (Crudgington *et al.*, 2019, 2020) and outcome criteria for ASM use in epilepsy (Murugupillai *et al.*, 2018). Unlike drug resistant epilepsy, Rolandic epilepsy is often well managed with anti-seizure medications and many children will outgrow the condition. In contrast to these studies, it was 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 KD therapy use. As expected, the CORE-KDT core outcome set includes outcomes specific to KD therapy as an intervention for drug resistant childhood epilepsy including *adverse effects, tolerability, dietary compliance, ketosis* and *how well parents felt supported to manage KD therapy*. These KD-specific outcomes are not adequately captured in any existing published core outcome set. Core outcome sets include the minimum outcomes which should be measured in any clinical area and as such, they should be a concise and focussed group of outcomes. Although no guidance exists on the ideal number of outcomes, it is likely that larger core outcome sets with many outcomes will be difficult to implement and less likely to be adopted. The CORE-KDT study reduced 89 outcomes to just 14 in the finalised core outcome set. The majority of these are routinely used to evaluate and monitor children with epilepsy treated with KD therapy and so the core outcome set should be easily implemented in research and clinical practice.

Interestingly, *seizure reduction, quality of life, tolerability of KD* and *dietary adherence* were all voted critically important by 90-100% of both groups suggesting these are ultimately the most important outcomes. Our earlier scoping review and qualitative analysis of parent interviews (Carroll *et al.*, 2022b) demonstrated that past research has predominantly focussed on

physiological, seizure related outcomes and adverse effects of KD therapy. However, interviewed parents, prioritised a combination of physiological and functional outcomes for their children (section 5.4.4, Table 23). With the inclusion of six physiological outcomes (four prioritised by interviewed parents) and three functional outcomes (all prioritised by interviewed parents), the CORE-KDT core outcome set 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 KD*, *rescue medication use for status epilepticus*, and *seizure duration* was merged with *seizure severity*.

There were however some unexpected exclusions from the final core outcome set including *sleep* and *cognitio*n domain outcomes. Children with epilepsy have shorter sleep times, more sleep difficulties and decreased sleep efficiency when compared with those without epilepsy (Winsor *et al.*, 2021). Consequently, learning, mood, behaviour, seizures and parents' quality of life may all be affected (Gibbon, Maccormac and Gringras, 2019). Hallböök *et al.* (2007) demonstrated that treatment with KD therapy improved sleep quality and reduced daytime sleep in children with drug resistant epilepsy. In light of these findings, it was surprising that fatigue and two sleep-related outcomes did not come closer to achieving consensus for inclusion in the core outcome set among either stakeholder group. It may be that poor sleep is somewhat expected and accepted for children with drug resistant epilepsy (and their parents) due to the seizure burden and complex care requirements. This acceptance may influence parents perceived importance, but this warrants further investigation. Our findings are similar to Murugupillai *et al.* (2018)

outcomes study where sleep was not prioritised by children, parents, or professionals. However, five sleep-related outcomes were included in the CHOICE core outcome set (Crudgington *et al.*, 2019). For now, it is suggested that sleep pattern could be considered as a factor of the *quality of life* outcome, until the relationship between KD therapy and sleep is better understood.

In round two, the outcome *cost-effectiveness of KD therapy* was very close to being included in the core outcome set, with 67% of parents and 73% of health professionals and researchers voting it as critically important. In the consensus meeting, health professionals voted in a similar way (76%), but only 44% of parents deemed it critical and therefore it was not included as one of the core outcomes. There was a clear divergence in priorities between health professionals and parents for this outcome. In the Delphi, participants could comment on the reasoning for their scores and a common theme in parent responses for this outcome was that cost of therapy should not matter. One parent felt that "all patients should be given access to a therapy that could work… it's not just the cost of the treatment but potential savings in other areas of the NHS and beyond". This parent eloquently captured the challenge encountered in this clinical area of demonstrating the broader cost-effectiveness of KD therapy. This has only been examined by one research group, which compared KD therapy to usual care for children with drug-resistant epilepsy and concluded that KD therapy is not cost-effective (de Kinderen *et al.*, 2016; Wijnen *et al.*, 2017). The generalisability of the findings are limited as the data emerged from Dutch KD centres where it is standard practice to start KD therapy during a five-day hospital admission. In contrast, in the UK, children start KD in their own homes, thereby significantly reducing cost. It is also

possible that the measures used to assess improvement in quality of life and quality adjusted life years were not sensitive enough to detect the small gains and improvements by children that would have a significant impact on their individual QoL, thereby under-estimating the QoL gains. The challenge of measuring QoL outcomes for children with complex needs is considered in chapter seven which follows and will form part of the future work arising from this project. In a recent report, the NICE committee recommended that research priorities be focused on the clinical and cost-effectiveness of KD in children and adults over the short and long term (NICE, 2022b). The time, labour and funding required to conduct health economic studies is considerable, and while a comprehensive cost-benefit analysis of KD therapy is necessary, it is arguably not a core outcome for inclusion in all future trials.

In the course of the interviews, parents discussed in detail the adverse effects their children had experienced when treated with ASMs. There was similar concern expressed in the Delphi survey, where 72% of parents in round one and 85% in round two considered the *side effects of antiseizure medications* to be of critical importance. Health professionals disagreed, however, with only 52% and 48% in rounds one and two voting this outcome to be critically important. This may validate the view shared by some parents during the interviews, in which they felt that health professionals failed to discuss or acknowledge the detrimental side effects of ASMs. While ASMs are often an essential part of the care of children with drug-resistant epilepsy, we could improve our approach to addressing ASMs with parents, exploring the potential side effects, listening to their concerns and involving them in decision making. Of the 12 new outcomes proposed by participants in round one, only one

outcome reached consensus for inclusion in the core outcome set - *parents feel supported to manage KD therapy*. When considering the role parents play in the preparation, provision, and day-to-day monitoring of their child's KD, this is a crucial outcome. Earlier, chapter one and chapter four discussed the additional burden of care that parents face due to their child's drug-resistant epilepsy and a KD therapy regimen. It was therefore surprising that *parental stress associated with the management of KD therapy* was not included as a core outcome. Health professionals and researchers deemed it critically important in round two of the Delphi, yet parents did not, and neither group deemed it critical for inclusion in the consensus meeting. The positive benefits that children experience with KD therapy likely outweigh the challenges and difficulties associated with it, a view that was expressed by parents during the interview process. Health professionals in the consensus meeting were possibly influenced by parents' views on this outcome and downgraded the importance accordingly.

Interviewed parents prioritised *learning and cognition* outcomes equally with *seizure reduction* (section 5.4.4, Table 23), so the exclusion of three cognition outcomes *(learning, memory*, and *speech and language*) from the core outcome set was also surprising. In the Delphi, all three outcomes failed to reach consensus in even one 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 following discussion and voting at the meeting. Prior to the Delphi survey, 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 survey, the domain descriptor clearly stated that these were cognition outcomes, but it may be that these outcomes no longer resonated as strongly with some participants. This demonstrates the difficulty of creating composite outcomes, if over stratified they may lose their meaning and relevance. Robust, repeated review of the outcomes list and descriptive terminology by the research team and study advisory group can go some way to mitigating this challenge. *Alertness* was voted into the core outcome set following the Delphi study and while parents voted *concentration* in at the consensus meeting, it failed to reach consensus for inclusion as only 62% of health 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" as KD continued. Improvements in alertness and concentration were thought to indicate that other areas such as social interactions and academic performance might improve as KD progressed.

Defining outcomes with standard terminology and standardised definitions requires careful consideration. The plain language descriptors (Table 30) were derived from the scoping review definitions and descriptions, together with the language parents used in their interviews. They were refined in consultation with the study advisory group and finally, feedback from the consensus meeting participants. It may be necessary to refine and standardise these further and this will form part of planned future work. Feedback will be sought from

researchers and clinicians who implement the CORE-KDT core outcomes set to determine the need for this.

6.5 Strengths

A significant strength of the CORE-KDT study is that the mixed methodology is informed by consensus guidelines, (Kirkham *et al.*, 2016, 2017, 2019; Williamson *et al.*, 2017) defined in an a priori protocol (Carroll *et al.*, 2022a) and transparently conducted and reported. Consequently, trialists can be assured that the core outcome set has undergone a rigorous development process and is a valid framework for selecting and reporting outcomes in future research involving KD therapy for drug-resistant childhood epilepsy. COMET encourages researchers to include patients with lived experience of the studied condition as members of the research team, in order to develop a core outcome set that is relevant and trusted by patients (COMET Initiative, 2021). Parents played a vital role as partner co-investigators in this study. They supported the international recruitment of parents to the interview and Delphi phases, thereby increasing their participation and enabling the identification of parent-important outcomes. Our study was strengthened by PPIE from the early design through to dissemination and the inclusion of both parents and health professionals in each phase ensured the core outcome set fairly represents their shared priorities. Consistently using the same consensus criteria and electronic voting in both the Delphi and consensus meeting enabled outcome prioritisation to be easily compared and stakeholder views to be equally represented, regardless of differences in participant numbers. The consensus meeting brought together international parents and health professionals for the first time to discuss

outcomes openly. Participant feedback highlighted the importance of the open discussions and the value of hearing each other's views.

Our comprehensive and rigorous approach to identifying outcomes via a scoping review and interviews with parents ensured that outcomes across all domains were considered. It is crucial to maintain transparency in studies such as this, where many outcomes are identified and then reduced and prioritised to a small number of core outcomes. To minimise the impact of a single researcher, the study advisory group and research team were consulted for agreement on key decisions. The reasoning for the inclusion, exclusion and merging of outcomes has consistently been openly shared to demonstrate the systematic short listing of outcomes. There was considerable time spent preparing and engaging with the participants who agreed to take part in the consensus meeting. In advance of the meeting, the researcher met with each parent via Zoom to explain the purpose and agenda of the meeting, answer any questions, and test the voting function. The same opportunity was offered to participating health professionals. The large number of undecided outcomes (50) following the Delphi survey posed a significant challenge as it was not feasible to discuss each of these in the online consensus meeting. Nevertheless, if the research group alone selected a smaller group of undecided outcomes for discussion, it may have biased the results and this approach would contradict the study's ethos to involve stakeholders throughout. The decision was therefore made to i) prioritise the 19 outcomes where one stakeholder group had rated the outcome critically important in the Delphi as these had the most likelihood of achieving consensus among both groups at the consensus meeting and ii) to invite consensus meeting participants to propose

(via an online form) outcomes from the remaining undecided outcomes group for discussion at the meeting. This ensured democratic and shared decision making among stakeholders and it also helped to engage them in the consensus meeting preparation process.

6.6 Limitations

A key strength of this study was the recruitment of international participants to both the Delphi survey and the consensus meeting; however time and budgetary constraints limited the participation of non-English speakers. There was significant participant attrition from round one to two of the Delphi (34%), despite many extensions to the round opening period and regular personalised reminder emails to participants. Intervention, in the form of emails from parent representatives, did increase parent participation slightly.

It was predicted in the PPIE consultation that parents in the study would face time constraints and competing demands. During the interview and Delphi phases, these challenges were further compounded by the COVID pandemic when many parents were home-schooling or had difficulty accessing carer support. For the consensus meeting, finding a time that worked for all participants was particularly challenging. The schools had reopened, so I chose a weekday during school hours to accommodate parents. However, the resultant time difference then limited international participation. As a result of work commitments, caring responsibilities, or other medical appointments, some parents were still unable to attend. Time differences, work commitments and pandemic related pressures prevented some health professionals from attending. Future studies need to consider these challenges when planning.

6.7 Conclusions and next steps

The CORE-KDT core outcome set has identified the outcomes which should be measured as a minimum in future clinical trials and practice. The included outcomes represent the consensus opinion of an international group of parents, professionals, researchers, charity and industry. Implementation in research and clinical settings will serve as a framework to achieve standardisation in outcome selection and reporting, facilitate data synthesis and ultimately enhance the relevance of outcomes to parents, researchers and health professionals. Chapter seven will elaborate on the strategies in place to disseminate, implement and evaluate the use of the core outcome set. The focus of future research is also considered which will include identification of appropriate outcome measurement instruments to assess the outcomes identified in the CORE-KDT core outcome set.

Chapter 7: Overall discussion

Preface

This chapter brings together the individual threads of discussion that have been presented in the preceding chapters. It begins by presenting a review of the aim of the thesis and the four phases undertaken to develop the core outcome set. A brief overview of the findings and their contribution to both research and clinical practice is presented before the dissemination of the core outcome set and future work is considered.

7.1 Summary of main findings

This thesis set out to identify a core set of outcomes which reflected the views of parents and professionals, in order to resolve the problem of inconsistent and inappropriate outcome selection and reporting when evaluating KD therapy. The study represents the first international consensus in this field, and the core outcome set represents the views of a group of parents, health professionals, researchers, charities, and industry representatives. The core outcome set was developed in four phases: (i) a scoping review to identify a list of outcomes from past studies (Chapter 3); (ii) semi-structured interviews with parents to identify outcomes important to them and additional new outcomes (Chapter 5); (iii) a pre-Delphi consultation to agree the list of outcomes (Chapter 6) and iv) a Delphi survey and stakeholder consensus meeting (Chapter 6) to agree the core outcome set.

The findings of the scoping review (Phase 1) demonstrated that there is significant heterogeneity in the outcomes which are reported in studies of drug

resistant childhood epilepsy treated with KD therapy. Equally a wide variety of measurement tools or methods were used to measure the reported outcomes. The use of inconsistent methods for selecting, measuring, and reporting outcomes limits our ability to meaningfully synthesise data via meta-analysis, reinforcing the need for experienced stakeholders to agree upon a core outcome set. Furthermore, the scoping review highlighted the limited attention that has been given to non-seizure-related outcomes of KD therapy.

It was particularly important to explore parents' experiences of KD therapy and their views on outcomes via semi-structured interviews (Phase 2) to assess if the outcomes identified in the scoping review corresponded with their priorities. The first qualitative analysis presented in this thesis provided important insights into families' experience of epilepsy and KD therapy. It was evident that KD therapy enabled parents to take an active role in their children's epilepsy treatment, which often led to an increased sense of purpose and control. Although KD therapy presented some challenges, it provided significant benefits to both the treated child and the family when the therapy was successful. Having gained these insights, it was possible to contextualise parents' perspectives on the outcomes of importance derived from the second qualitative analysis. Parents identified just over one third of the outcomes from the scoping review which suggested that the remainder were of less importance to them. They also identified seven new outcomes that had not been measured or reported previously. These findings indicated that the clinical outcomes traditionally used in research arguably do not adequately reflect parents' important outcomes for their children supporting the importance of this work to establish a core outcome set in order to guide future outcome selection.

During the pre-Delphi consultation (Phase 3), the study advisory group and research team reached a consensus on the final list of outcomes and plain language descriptors to be included in a two-round Delphi survey. Upon completion of the Delphi survey and a stakeholder consensus meeting (Phase 4), consensus was reached regarding fourteen core outcomes across five domains in the core outcome set.

7.2 Contributions to the research field

The research presented in this thesis has advanced the understanding of KD therapy outcomes and proposes a solution, via a core outcome set, for how these outcomes could be improved to better reflect the priorities of parents for their children. This thesis represents the first comprehensive review of all outcomes measured and reported in all studies of childhood epilepsy treated with KD therapy during a ten-year period (Chapter 3). The findings indicated that outcomes are highly heterogeneous and inconsistent, as evidenced by the fact that only 52% of all outcomes have been reported more than once across 147 articles. All included studies were quantitative in nature and did not involve parents in their design or development, thus limiting parental participation and perspectives. In contrast, the CORE-KDT study has included parent co-researchers and parent participants from the beginning of the project through its completion and dissemination and has benefited significantly from their involvement. The effects of KD therapy on seizure related outcomes are well documented (Neal *et al.*, 2008a; Sharma *et al.*, 2013; Lambrechts *et al.*, 2017; Martin-McGill *et al.*, 2020) however non-seizure-related outcomes have rarely been assessed, despite the potential for these outcomes to have a significant

impact on children and families' daily lives. It was surprising to learn of the extent of the problem in outcome selection and reporting in this clinical area.

The qualitative study (Chapter 4) provided valuable insight into how families experience KD therapy, advancing our understanding of their perspectives on the benefits and challenges of this treatment. This study is the largest qualitative exploration of parent perspectives to date and contributes to the limited empirical evidence currently available (Webster and Gabe, 2016; Sarlo and Holton, 2021). It provided an opportunity to evaluate the support families receive and the factors they feel could help to make KD more manageable. For the first time, parents' perspectives on outcomes were investigated (Chapter 5), and the findings reinforced the importance of assessing non-seizure-related outcomes. It is my understanding that the stakeholder consensus meeting (Chapter 6) was the first of its kind in this clinical area, that brought together parents, health professionals, researchers, charity and industry representatives to discuss and agree upon priority outcomes. It was evident that participants valued the process and each other’s opinions, thereby reinforcing the importance of this phase in core outcome set development. Throughout the development of the core outcome set, parents prioritised a range of both physiological and functioning outcomes, however, past clinical trials focussed predominately on physiological outcomes and adverse effects, suggesting they do not fully represent parents' priorities.

The CORE-KDT project provides the first international consensus on outcomes for drug resistant childhood epilepsy treated with KD therapy. It now better reflects the views of all stakeholders including parents. Table 31 compares the

priority outcomes identified in the scoping review and parent interviews with the outcomes included in the finalised core outcome set. Ten of the fourteen outcomes in the core outcome set map to three of the themes which emerged from the qualitative interviews. It is evident that the core outcome set now better reflects the shared priorities of parents for their children, while still maintaining the outcomes typically measured in research. The implementation of the core outcome set in future trials will lead to improved consistency in outcome selection and reporting, which will enhance the ability to synthesise data for meta-analyses. The core outcome set should assist in redressing the imbalance in outcome prioritisation that currently exists between the outcomes reported in research and the priorities of parents for their children. By doing so, a greater body of relevant evidence will be available for use to support clinical decision making. There is still a need for further research to provide guidance on how to measure these outcomes, but this thesis provides a firm foundation on which we can build.

Table 31. Mapping of the core outcome set against the identified priorities in the scoping review and parent interviews

Phase	Outcomes represented in the agreed core outcome set
Priority outcomes in scoping review (Figure 8)	1. Seizure frequency including seizure freedom 2. Adverse effects of KD therapy 3. ASM use
Parent identified new outcomes (Table 20)	1. Seizure severity (duration) 2. Status epilepticus and use of rescue medication 3. Parents feel supported with KD therapy
Priority outcomes to parents (Table 21)	1. Seizure reduction 2. ASM drug use (reduction) 3. Quality of life 4. Alertness 5. Seizure freedom 6. (growth (adverse effects) 7. behaviour
Outcomes reflected in themes and subthemes (Figure 9)	***Theme 2: Opening the window to new opportunities – I've got my child back*** 1. Quality of life 2. Alertness and concentration 3. Behaviour 4. Seizure reduction 5. Seizure freedom 6. Seizure severity (duration) 7. ASM use 8. Status epilepticus and use of rescue medication ***Theme 3: The reality of KD therapy - a support network is crucial*** 9. Parents feel supported with KD therapy 10. Adverse effects of KD ***Theme 4: Looking to the future - support and education*** - Parents feel supported with KD therapy

7.3 Clinical implications

Ultimately, the CORE-KDT project aimed to develop a core outcome set, which will have positive implications for clinical practice. However, the findings derived from the qualitative interviews with parents have also contributed significantly to the impact of this project. While the interviews were an integral phase in the identification of outcomes, they also served a dual purpose of providing deeper insights to how parents and families experience epilepsy and KD therapy. Over the years that I have worked in this field, I have strived to provide families with high quality care and would consider myself to be well informed about their perspectives. However, it was enlightening to listen to parents' experiences as a researcher rather than their keto dietitian; free from the distractions of clinical pressures, problem solving or motivating them during challenging times. This provided clarity and a depth of understanding of their early experiences prior to meeting the keto team and the impact of ASMs, in particular, on their children. Parents shared a variety of experiences, strategies, and ideas regarding how support for families might be optimised when managing KD therapy (Chapter 4). This resulted in the formulation of five recommendations, all of which are applicable to keto teams and their delivery of healthcare to this patient group (section 4.4.2.5 table 19). Among these were the fact that KD therapy should be more easily accessible for children, families should receive quality support and education including opportunities for social learning, parents may benefit from peer mentoring and finally a wider range of keto foods could improve the convenience of KD therapy.

Parents highlighted that delayed access to KD therapy is an ongoing issue that we all have a responsibility to try to address. KD therapy is quite a niche

treatment with relatively small numbers of treated patients and many on treatment waiting lists (Whiteley *et al.*, 2020). It has proven difficult to expand services and access to the treatment primarily due to funding constraints within the National Health Service. The most recent NICE evidence review reinforced this when they concluded that it is necessary to conduct a cost benefit analysis and to gather information on the long-term outcomes of KD therapy (NICE, 2022). More positively, the keto community at large (families, KD services, charities, and medical nutrition companies) all work together to try to raise awareness of the positive benefits of KD therapy but the success of these efforts will likely remain limited unless it can be demonstrated that KD therapy is a cost effective treatment. The UK Epilepsy Priority Setting Partnership (2022) recently published the top ten priorities for epilepsy research, identified via a nationwide engagement programme with health professionals, patient groups and people affected by epilepsy. While KD therapy is not directly addressed in a priority, it will likely be considered as a part of question nine which asks, *'What causes drug-resistant (refractory) epilepsy and how can it be best treated?'.* Priority setting partnerships such as these are designed to drive research funding towards the areas of greatest need so we should use this to underpin our efforts to enhance awareness of KD therapy and attract impactful research funding.

Parents frequently emphasised the importance of holistic family-centered care and how this improved their interactions with their keto team and diet management. Keto teams can demonstrate this family-centeredness by considering the non-seizure related outcomes in the core outcome set and treating each child as an individual when it comes to progress with KD therapy.

By connecting families with other support services, such as keto charities and support groups, keto teams can enhance the support families receive beyond their care team. The concept of social education proved to be very popular among families, where they could learn knowledge and skills in a relaxed social environment such as keto cookery days. Medical nutrition companies, as well as keto charities, are generally eager to support these events. While these events increase the administrative burden for already stretched keto teams, they do prove to be very beneficial for families.

It is clear that these recommendations may benefit families, but there is less clarity regarding the role peer mentoring, where parents provide support to one another, may play. In light of this, I have included it as a tentative recommendation recognising that the perceived need and feasibility requires further exploration, which will be discussed in section 7.5. An important consideration would be whether the initiative should be led by individual KD services or by a charity that has experience in providing similar support through online meetings and social events.

To turn now to the clinical implications of the core outcome set, if clinical trials are designed to include outcomes which are meaningful to patients and relevant to clinicians there is a greater likelihood that the findings will be translated into meaningful benefits for patients. For example, high quality data examining the impact of KD therapy on quality of life, alertness, concentration and behaviour would likely strengthen the case of need for KD therapy, enabling increased funding for KD services and better accessibility to this treatment. The inclusion

of quality of life and functioning outcomes in the set reinforces the importance of these outcomes.

By using this core set of outcomes, keto teams will be able to prioritise their choice of routine monitoring of outcomes and avoid the situation we initially faced when my keto team and I were solely focused on numbers-driven outcomes. While it is important to collect high quality, rigorous data in clinical practice, the rigors of validation and repeated measurements can be less demanding than those in clinical trials. The measurement of outcomes will be addressed further in section 7.5. Ideally, one instrument would measure all outcomes and the same instrument would be used in both clinical practice and research in order to optimise consistency. However, this may be impractical and a more pragmatic approach for clinical practice may be needed such as the one page questionnaire developed by Bruce *et al.* (2017) to measure quality of life. This could be a good starting point in keto clinics.

In the current financial climate, the National Health Service is under considerable strain and pressure with limited funding for the expansion or development of new KD services. Many new KD services are initially funded by charities in order to facilitate service establishment and the preparation of a business case for application to the local clinical commissioning group for ongoing funding. The core outcome set will help to guide new centres on the critical outcomes of importance to measure and include in business cases to justify their impact on patient care and the need for ongoing service provision. Furthermore, a unified approach to outcome data collection may enable data

pooling and improve efficiency and enable benchmarking across services through routine audits, quality improvement projects and service evaluation.

7.4 Strengths and Limitations

The strengths and limitations of each phase of the CORE-KDT study have been discussed at length in the associated chapters, so they will not be repeated here. Overall, the research contributes to the understanding of priority outcomes for children with drug-resistant epilepsy treated with KD therapy. The core outcome set was developed using a robust and transparent methodology (Williamson *et al.,* 2017, Kirkham *et al.,* 2017, Kirkham *et al.,* 2019) and reported in line with relevant guidance (Kirkham *et al.,* 2016). Public involvement and engagement were incorporated from the beginning, collaborating with lay research partners and consulting with the study advisory group to improve the quality and relevance of the core outcome set. The impact of PPIE on each phase has been considered earlier using the GRIPP2-SF and a critical review will follow on how PPIE can evolve in future research activities.

However, there are some limitations. In many cases, core outcome sets are developed for specific conditions rather than for specific interventions (Fish et al., 2018, Crudgington et al., 2019, Maclennan et al., 2017), where the outcomes in the set are generally relevant to a range of interventions. This helps to reduce waste and duplication in research efforts (Williamson *et al.,* 2012). In contrast, the CORE-KDT study set out to develop a core outcome set for the specific intervention of KD therapy. This limits the use and application of the core outcome set to drug-resistant epilepsy treated with KD therapy. However, this is arguably a worthwhile limitation considering the unique nature

of KD therapy, the additional burdens it may place on families and the need for specific monitoring. Although there may be some overlap between KD therapy and other treatments for drug-resistant epilepsy (surgery, vagus nerve stimulation, and ASMs), a condition-specific set for drug resistant epilepsy would not provide the specificity required for KD treatment outcomes. Consequently, the uptake and implementation of a general condition-specific core outcome set would be limited in the area of KD therapy research and practice.

The CHOICE core outcome set (Crudgington *et al.,* 2019) provides a unique opportunity to compare and contrast a condition-specific set (Rolandic epilepsy) with the CORE-KDT intervention-specific set (KD therapy). Only seven of the fourteen outcome domains in the CORE-KDT set are represented in the CHOICE set. These include; seizure *reduction, seizure freedom, seizure severity, quality of life, alertness and concentration, behaviour and unplanned hospital admissions.* These shared outcomes would likely be relevant across all epilepsies; however the absence of any KD related treatment outcomes supports the argument that a KD specific set is needed to capture the relevant diet and nutrition outcome domains. Interestingly, since starting this body of research in 2018, there has been significant growth in the number of core outcome sets under development and the COMET database now includes core outcome set studies relevant to specific healthcare settings (paediatric intensive care and the Emergency Department), interventions (surgeries) and clinical practice (handovers). This suggests the scope of core outcome sets will likely continue to expand beyond just clinical conditions.

The core outcome set represents the views of an international group of stakeholders, although most were based in the United Kingdom (67% in round 1 and 73% in round 2). Even though both Delphi rounds were open for extended periods, it was challenging to increase international participation. Consequently, the extent to which the set is transferable to international settings is not known at this time, but it will be assessed in our ongoing future research.

7.5 Patient and Public Involvement and Engagement

It is critical to reflect upon public involvement in the CORE-KDT study, examining the successes and weaknesses and crucially how it might evolve moving forward. The UK Standards for Public Involvement in Research (NIHR, 2019) provide a framework for the implementation of good public involvement in research. It encourages reflection and learning to identify where improvement is needed in the planning, support and evaluation of public involvement. Table 32 uses the questions in the framework to identify areas of good practice within the CORE-KDT study and examine areas for improvement in future work.

Table 32. Assessment of public involvement in the CORE-KDT study mapped against the UK Standards for Public Involvement (NIHR, 2019)

Standard	Example of good practice in CORE-KDT	Areas for improvements
1. Inclusive opportunities Offer public involvement opportunities that are accessible and that reach people and groups according to research needs	- People affected by and interested in the research were involved from the early design of the study	- Financial resource limited the ability to pay those involved, payment should be considered in future funding applications - Public advertisement of future PPIE opportunities to ensure broader access
2. Working together work together in a way that values all contributions, and that builds and sustains mutually respectful and productive relationships	- Purpose of public involvement was discussed with all individuals, together with the role, responsibilities and expectations - Individual contributions were recognised and implemented throughout the study to ensure members felt valued	- Plan for members to meet at given time points within the research schedule, in person if possible (with consideration for cost, time etc) but at least virtually - Group discussion to develop and record the terms of service
3. Support and learning Offer and promote support and learning opportunities that build confidence and skills for public involvement in research	- The researcher offered support to the individuals; however, this was likely limited by their limited experience with PPIE - As a group we learned by doing, talking and sharing our experiences	- Create a pack of resources for interested individuals and identify training opportunities to support them in their role
4. Communication Use plain language for well-timed and relevant communications, as part of involvement plans and activities	- Our experiences with PPIE were shared via a co-produced poster (with lay researchers) presented at the British Paediatric Neurology Association conference and will be presented at Global Keto San Diego 2023 - Public involvement greatly enhanced the ability to present the findings from the study in plain English summaries for the wider public	- Develop a communications plan to ensure involvement activities are captured and shared - Use a wider range of communication methods to ensure inclusivity

Standard	Example of good practice in CORE-KDT	Areas for improvements
5. Impact Seek improvement by identifying and sharing the difference that public involvement makes to research	- Public involvement in the study was very impactful, influencing the early design, decisions throughout the study implementation and then dissemination of the core outcome set. However, this impact would be better mapped in real time rather than retrospectively - Informal discussions and feedback sought from members indicated that they valued being involved in the CORE-KDT study. They enjoyed the experience and were glad they contributed as lay research partners or study advisory group members. However, this would benefit from deeper exploration via a structured interview or questionnaire to guide future work	- Involve the members in deciding how impact should be assessed - Ensure use of the GRIPP2-SF to map PPIE plans and impacts - Undertaken an assessment PPIE from the perspective of those involved, what went well, what could be improved and how might that be implemented.
6. Governance Involve the public in research management, regulation, leadership and decision making	- Public voices were heard, valued and respected, evidenced by their role in decision making throughout the study. However, resources were not allocated for public involvement which should be considered moving forward given the time members contributed - Minimal personal information was collected, protected and used in a suitable way	- Budget for public involvement in future fundings applications - Regularly monitor, review and report upon the planned PPIE plans

7.6 Dissemination of the core outcome set

Having established the core outcome set, it is now necessary to disseminate this, promote its use and monitor and evaluate its implementation in future clinical trials and practice. The core outcome set will be disseminated in various ways over the coming months, and a subsequent evaluation of the implementation and usage will take place in the coming years. The plain language descriptions outlined in Table 30 were informed by the lay language parents used during the interviews and the descriptions or definitions used in the papers included in the scoping review. However, it may be necessary to refine these further in response to feedback from clinicians and researchers who go on to implement the core outcome set in the future.

In order to fully realise the impact of the core outcome set, we need to provide guidance on the most appropriate outcome measurement instruments to assess each of the fourteen outcomes. In general, an outcome measurement instrument refers to a means of measuring an outcome, such as a single question, a detailed questionnaire, or a laboratory investigation, among others. This will be discussed in greater detail in the next section when future work is described. The COMET initiative works to promote core outcome set uptake and they have successfully lobbied trial funding bodies, regularity authority and guideline development groups to endorse the use of core outcome sets. The CORE-KDT project was registered with COMET and the study page on their core outcome set database has been updated to reflect the project's successful completion and the four publications associated with it. Throughout the course of this project, the findings have been published and presented at key

conferences to inform and engage the KD community. This has contributed to a greater awareness of the work and facilitated collaborations and opportunities for expanding its reach. Currently, I am collaborating with colleagues from the Ketogenic Dietitian's Research Network in the development of an international registry of individuals with epilepsy who have been referred for treatment of KD. The outcomes from the core outcome set have been incorporated into the registry as a means of ensuring that data collection is congruent across centres. Once the registry is fully developed and operational, keto centres will be invited to submit their data, which makes this collaboration a successful first step in improving consistency in both the selection and reporting of outcomes in clinical practice. It is intended that the registry will act as a secure centralised database of health data and serve as a platform for investigating unresolved research questions. This includes examining long-term clinical and safety outcomes of KD therapy, as well as identifying candidates who may be most suitable for dietary treatments.

I am leading an international group of experts to drive forward the future work arising from this thesis which will be addressed in detail in the next section. The group is comprised of some of the most prolific researchers in the field and members hold active positions in various organisations, such as the Ketogenic Dietitian Research Network, the International Neurological Ketogenic Society, Matthew's Friends and the International League Against Epilepsy. This will greatly enhance our ability to disseminate the core outcome set and evaluate its use in the coming years. Participants in the CORE-KDT project were provided with a lay summary of the findings, including links to the key publications (Carroll *et al.,* 2022b, 2023) and Figure 15 to visually illustrate the core outcome

set. The results will be summarised in an article for the Matthew's Friends summer newsletter, which is distributed to parents and professionals, ensuring that the study's reach extends beyond those who participated. I am a mentor and lecturer on the annual KetoCollege training programme which provides training and continuing professional development opportunities for professionals both new to and experienced in KD therapy. This has proven to be an excellent opportunity to motivate keto teams to consider the outcomes they are monitoring and to engage in discussion about how they may be improved to reflect the broader impacts of KD therapy.

7.7 Future work

The CORE-KDT project culminated in the development of the core outcome set presented in this thesis, ultimately identifying the outcomes that should be measured and reported in future clinical trials and practice. Initially, this will assist trialists and clinicians in determining what outcomes to measure. However, for optimal consistency in outcome measurement and reporting, the core outcome set should be supported with guidance regarding the appropriate outcome measurement instruments for each of the fourteen outcomes. The measurement of these multi-dimensional outcomes will require careful consideration, and this will be the focus of the next phase of the project. Among the working group's international experts are consultant paediatric neurologists, keto dietitians, a neuropsychiatrist, and an expert parent and charity coordinator. The members of the group have a broad range of clinical and research experience in childhood epilepsy and KD therapy. This enables us to appreciate the challenges associated with outcome measurement in both settings as well as contribute to practical solutions. We aim to identify measures

that are clinically meaningful and evidence-based, while also making sure they are family-centered and fit for purpose. As we consider the differences in data collection in a research and clinical environment, we will examine the need to develop a bespoke, pragmatic, and focused outcome measurement instrument. Idealistically a measurement instrument would have the capability to gather data on all fourteen outcomes, both electronically and on paper, it would be quick to complete and could be completed by the keto team and parents rather than requiring a neuropsychiatrist, as few KD services have access to this. However, it is unlikely that a suitable tool exists that can meet all of these requirements, and there are a number of factors to consider before beginning the development process.

The process will be guided by the COSMIN guidelines (the COnsensus-based Standards for the Selection of Health Measurement Instruments) for selecting outcome measurement instruments after a core set of outcomes has been established (Prinsen *et al.*, 2016), which they developed in collaboration with COMET. Typically, this involves identification of existing instruments, review of the quality of the instruments and a consensus process to agree a single measurement instrument for each outcome. This process, however, assumes that there are satisfactory outcome measurement instruments available when we know this is a particular challenge in this clinical area, particularly for quality of life (Chapter 1 and 3). It is possible that we will have to compromise reliability and validity initially in order to develop a measure that will be more suitable for this population of children with complex needs.

There were 23 validated outcome measurement instruments identified in the scoping review (section 3.3.4 Table 14) which assessed a range of outcomes including seizure severity, behaviour, cognition, activities of daily living, mood, side effects of KD and quality adjusted life years. It was noted that each of these tools had only been used once by a single research group, and that other well-known patient reported outcome measures (PROMs) had not been utilised. Those omitted included Vineland Adaptive Behaviour Scales, (Sparrow, Cicchetti and Balla, 2005), Peds QL Epilepsy Specific Module (Follansbee-Junger *et al.*, 2016), Quality of Life in Childhood Epilepsy (QOLCE-55) (Goodwin *et al.*, 2015) and finally Health Related Quality of Life Measure for Children with Epilepsy (CHEQOL) (Ronen, Streiner and Rosenbaum, 2003). It is difficult to draw conclusions as to the applicability or feasibility of these 27 outcome measurement instruments without an in-depth review, especially when considering that the agreed outcome measurement instruments for the core outcome set would ideally serve both research and clinical purposes. However, they can serve as a starting point for our review of existing tools. A recent systematic review collated outcome measurement instruments for children undergoing epilepsy surgery (Chisolm *et al.*, 2022), in total 46 tools were identified but only 13 were reported to be validated for use in paediatrics, five of which were identified in our scoping review. Similarly, Crudgington *et al.* (2020) identified and mapped 11 epilepsy specific PROMs of health related quality of life to a core outcome set for Rolandic epilepsy, concluding that the QOLCE-55 and CHEQOL were the most appropriate PROMs to cover the majority of included outcomes. We will be guided by these findings in our search for potentially appropriate instruments for KD therapy.

Of the fourteen outcomes in the core outcome set, eight are largely objective in nature and could be measured by counting (seizure frequency, status epilepticus frequency, ASM use, accident and emergency or hospital visits), laboratory investigations (adverse effects and ketone levels) or radiological/dexa scanning (adverse effects). In contrast, the remaining six outcomes (dietary adherence, tolerability of KD, parents feel supported with KD, quality of life, behaviour, alertness and concentration) are more subjective outcomes. On the rare occasions when these outcomes have been examined in past research, they were generally assessed through parent and clinician reports, limiting their comparability and reliability (Chapter 3). As demonstrated earlier, standardised validated PROMs exist but were rarely used. Further complicating the situation is the fact that the cognitive and functional gains made by children with complex developmental needs may not be meaningfully captured by existing outcome measurement instruments, especially if the measure is norm referenced rather than comparing the child to him/herself over time (Downs *et al.*, 2019; Tangarorang *et al.*, 2019). Therefore, identifying appropriate outcome measurement instruments for behaviour, quality of life, alertness, and concentration is likely to prove the most challenging.

This issue of identifying appropriate outcome measurement instruments is a key focus for The Inchstone Project, a multidisciplinary group who strive to ‘measure better’ for children with developmental and epileptic encephalopathies (The Inchstone Project, 2023). Their goal is to develop new or adapted measures that are sensitive to the small but important changes that children with rare disease may have in response to new therapies. The FDA were supportive of The Inchstone Project adapting or incorporating elements of existing effective

validated instruments rather than inventing new ones. This pragmatic approach is reassuring, as we anticipate that parts of already existing instruments may be suitable, so a combination may be appropriate to meet the needs of this population.

As we move forward, it is important to maintain parental involvement in the future development efforts. Emma Williams, an expert parent and charity coordinator, will continue to represent parents within our expert group. Once appropriate outcome measurement instrument/s have been identified or developed, we will seek feedback from a broader group of parents prior to implementation to determine their acceptability.

Evidence supports the use of KD therapy in adult drug-resistant epilepsy with similar reductions in seizure frequency to those reported in children (McDonald and Cervenka, 2017; Martin-McGill *et al.*, 2020; Cervenka *et al.*, 2021). Although the core outcome set has been developed for children, there is scope to consider its applicability to adults with drug resistant epilepsy using KD therapy. It is plausible that the present core outcome set would only need minor adjustments, however this would need to be explored further with adult users and professionals with experience supporting adults with KD therapy. Although most of the fourteen outcomes would remain relevant to adults, if given the opportunity, they might prioritise different outcomes compared to parents. The adverse effects of KD therapy on adults are similar to those experienced by children (Cervenka *et al.*, 2021), except that concerns regarding growth are less relevant. It is possible that the outcome addressing how supported parents feel with KD therapy would still be relevant if the adult is cared for by parents or

caregivers; however, if the adult is self-managing their KD, it could assess how supported they feel. Behaviour may be less relevant, and quality of life variables might differ to include aspects like work, personal relationships, socialising and eating outside the home. The acceptability of the existing core outcome set could be explored in an initial meeting of adult users and professionals similar to the consensus meeting to gather perspectives from key stakeholders. In the event that agreement could not be reached, or the existing core outcome set needed significant adjustments, then a Delphi survey could be conducted to ensure that the process is conducted in a transparent, trustworthy and equitable way.

In a similar manner, there is potential for the core outcome set to be adapted for use in two metabolic disorders of glucose metabolism; Glucose transporter type 1 deficiency syndrome (Glut1-DS) and pyruvate dehydrogenase deficiency (PDHD) that are typically diagnosed in childhood. Patients with these conditions are likely to experience drug-resistant epilepsy and KD therapy is the only treatment available, supplying ketones to the brain as an alternative fuel source to glucose (Klepper and Leiendecker, 2013; Kossoff *et al.*, 2018). While the existing outcomes in the core outcome set remain relevant, it is uncertain whether parents of children with drug resistant epilepsy together with a metabolic condition will prioritise the same outcomes as parents of children with drug-resistant epilepsy alone. In particular, a core outcome set for GLUT1-DS may require additional outcomes that address motor function symptoms, such as spasticity, hypotonia, and ataxia as these symptoms often feature in GLUT1-DS and are improved or resolved by KD therapy (Klepper *et al.*, 2020). Adapting

the core outcome set for use in this population could be accomplished in a similar manner to that described above for an adult population.

As mentioned previously the potential for a peer mentoring programme for parents requires further exploration. Partnering with Matthews Friends charity, a follow up focus group with parents could help to explore these issues in more depth and set some parameters for what the role might involve. Followed then by a working group of health professionals, parents and charity representatives to explore how this might be best implemented. This would be an excellent dissertation topic and could be offered to interested undergraduate masters or postgraduate students at the University of Plymouth.

Finally, a manuscript is in preparation for submission to Epilepsia entitled *'The highs and lows of drug-resistant epilepsy and ketogenic diet therapy – a qualitative study of families' experiences'.* Parents' involvement in the development of a core outcome set is an innovative concept that is beneficial for professionals to understand, reinforcing the importance of including parents' perspectives when planning and executing research. Based on the findings of this large study, we share parents' perspectives regarding the management of a KD and provide context for the recommendations that arise as a result of their suggestions for optimal support when managing KD therapy. This will help to support the provision of excellent clinical services in this field. If accepted, it is anticipated that this will be the fifth and final publication arising from the research presented in this thesis and it will be published open access in order to reach a broad audience.

7.8 Conclusions

We recommend that all future trials evaluating KD therapy for children with drug resistant epilepsy utilise the CORE-KDT core outcome set as a framework for outcome selection. The core outcome sets 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. By implementing the CORE-KDT set routinely, both settings will benefit from improved consistency in outcome selection and reporting.

References

Abdelmoity, Ayman T., Le Pichon, J. B., Abdelmoity, S. A., Sherman, A. K., Hall, A. S. and Abdelmoity, Ahmed T. (2021) 'Combined use of the ketogenic diet and vagus nerve stimulation in pediatric drug-resistant epilepsy', *Epilepsia Open*, 6(1), pp. 112–119.

Achenbach, T. M. and Ruffle, T. M. (2000) 'The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies.', *Pediatrics in Review*, 21(8), pp. 265–271.

Akman, C. I., Montenegro, M. A., Jacob, S., Eck, K., Chiriboga, C. and Gilliam, F. (2009) 'Seizure frequency in children with epilepsy: Factors influencing accuracy and parental awareness', *Seizure*, 18(7).

Alise, M. A. and Teddlie, C. (2010) 'A continuation of the paradigm wars? Prevalence rates of methodological approaches across the social/behavioral sciences', *Journal of Mixed Methods Research*, 4(2), pp. 103–126.

Alpherts, W. C. and Aldenkamp, A. P. (1990) 'Computerized neuropsychological assessment of cognitive functioning in children with epilepsy', *Epilepsia*, 31(suppl 4), pp. S35-40.

Armeno, M., Verini, A., Caballero, E., Cresta, A., Valenzuela, G. R. and Caraballo, R. (2021) 'Long-term effectiveness and adverse effects of ketogenic diet therapy in infants with drug-resistant epilepsy treated at a single center in Argentina', *Epilepsy Research*, 178 (106793).

Armeno, M., Verini, A., Pino, M. del, Araujo, M. B., Mestre, G., Reyes, G. and Caraballo, R. H. (2019) 'A prospective study on changes in nutritional status and growth following two years of ketogenic diet (KD) therapy in children with refractory epilepsy', *Nutrients*, 11(7).

Arnold, L. M., Crofford, L. J., Mease, P. J., Burgess, S. M., Palmer, S. C., Abetz, L. and Martin, S. A. (2008) 'Patient perspectives on the impact of fibromyalgia', *Patient Education and Counseling*, 73(1), pp. 114–120.

Austin, J. K. and McDermott, N. (1988) 'Parental attitude and coping behaviors in families of children with epilepsy', *The Journal of Neuroscience Nursing* , 20(3), pp. 174–179.

Barwick, K., Parker, T., Murphy, N., Todd, A., Leveritt, M. and Wilkinson, S. A. (2017) 'Development and pilot testing of a parent-reported health-related quality of life measure for children on the ketogenic diet: The KetoQoL', *Nutrition and Dietetics*, 74(5), pp. 521–528.

Bayley, N. (1993) *Bayley Scales of Infant Development, second edition: Manual*. San Antonio: TX: The Psychological Corporation.

Beery, K. E. and Beery, N. A. (2006) *The Beery-Buktenica Developmental Test of Visual-Motor Integration administration, scoring and teaching manual.* 5th edn. Bloomington MN: NCS Pearson.

Beghi, E., Mascio, R. Di and Sasanelli, F. (1986) 'Adverse Reactions to Antiepileptic Drugs: A Multicenter Survey of Clinical Practice', *Epilepsia*, 27(4), pp. 323–330.

Berg, A. T., Langfitt, J. T., Testa, F. M., Levy, S. R., DiMario, F., Westerveld, M. and Kulas, J. (2008) 'Global cognitive function in children with epilepsy: A community-based study', *Epilepsia*, 49(4), pp. 608–614.

Bergqvist, A. G. C., Schall, J. I., Gallagher, P. R., Cnaan, A. and Stallings, V. A. (2005) 'Fasting versus gradual initiation of the ketogenic diet: A prospective, randomized clinical trial of efficacy', *Epilepsia*, 46(11), pp. 1810–1809.

van Berkel, A. A., IJff, D. M. and Verkuyl, J. M. (2018) 'Cognitive benefits of the ketogenic diet in patients with epilepsy: A systematic overview', *Epilepsy and Behavior*, 87, pp.69-77.

Van Berkel, A., Crone, M., Neppelenbroek, S., Spijkers, E., Vellema, M. and Vogels, T. (2006) *Manual for the use of SDQ in youth healthcare*. Zutphen: Congresses.

Boers, M., Kirwan, J. R., Wells, G., Beaton, D., Gossec, L., D'Agostino, M. A., Conaghan, P. G., Bingham, C. O., Brooks, P., Landewé, R., March, L., Simon, L. S., Singh, J. A., Strand, V. and Tugwell, P. (2014) 'Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0', *Journal of Clinical Epidemiology*, 67(7), pp. 745–753.

Bough, K. J. and Rho, J. M. (2007) 'Anticonvulsant mechanisms of the ketogenic diet', *Epilepsia*, 48(1), pp. 43–58.

Braun, V. and Clarke, V. (2006) 'Using thematic analysis in psychology', *Qualitative Research in Psychology*, 3, pp. 77–101.

Brookes, S. T., Macefield, R. C., Williamson, P. R., McNair, A. G., Potter, S., Blencowe, N. S., Strong, S. and Blazeby, J. M. (2016) 'Three nested randomized controlled trials of peer-only or multiple stakeholder group feedback within Delphi surveys during core outcome and information set development', *Trials*, 17, 409.

Bruce, S., Devlin, A., Air, L. and Cook, L. (2017) 'Changes in quality of life as a result of ketogenic diet therapy: A new approach to assessment with the potential for positive therapeutic effects', *Epilepsy and Behavior*, 66, pp. 100–104.

Buetow, S. (2010) 'Thematic analysis and its reconceptualization as "saliency analysis"', *Journal of Health Services Research and Policy*, 15 (2), pp.123-125.

Burnard, P. (1991) 'A method of analysing interview transcripts in qualitative research', *Nurse Education Today*,11(6), pp. 461–466.

Caraballo, R. H., Vaccarezza, M., Cersosimo, R., Rios, V., Soraru, A., Arroyo, H., Agosta, G., Escobal, N., Demartini, M., Maxit, C., Cresta, A., Marchione, D., Carniello, M. and Panico, L. (2011) 'Long-term follow-up of the ketogenic diet for refractory epilepsy: Multicenter Argentinean experience in 216 pediatric patients', *Seizure*, 20(8), pp. 640–645.

Carpay, H. A., Vermeulen, J., Stroink, H., Brouwer, O. F., Peters, A. C., van Donselaar, C. A., Aldenkamp, A. P. and Arts, W. F. (1997) 'Disability due to restrictions in childhood epilepsy', *Developmental Medicine and Child Neurology*, 39(8), pp. 521–526.

Carroll, J. H. (2019) *CORE-KDT*. Available at: https://www.plymouth.ac.uk/core-kdt (Accessed: 30 December 2020).

Carroll, J. H, Cross, J. H., Hickson, M., Williams, E., Aldridge, V. and Collinson, A. (2022a) 'The CORE-KDT study: a mixed methods protocol to establish core outcomes for refractory childhood epilepsy treated with ketogenic diet therapy', *Trials*, 23(1), 675.

Carroll, J.H., Martin-McGill, K. J., Cross, J. H., Hickson, M., Williams, E., Aldridge, V. and Collinson, A. (2022b) 'Core outcome set development for childhood epilepsy treated with ketogenic diet therapy: Results of a scoping review and parent interviews.', *Seizure*, 99, pp. 54–67.

Carroll, J. H., Cross, J. H., Hickson, M., Williams, E., Aldridge, V. and Collinson, A. (2023) 'A core outcome set for childhood epilepsy treated with ketogenic diet therapy (CORE-KDT study): International parent and health professional consensus', *Epilepsia*, 64(4), pp.919-936.

Carroll, J., Martin-McGill, K., Cross, H., Hickson, M. and Collinson, A. (2019) 'Outcome measurement and reporting in childhood epilepsy treated with ketogenic diet therapy: a scoping review protocol', *JBI Database of Systematic Reviews and Implementation Reports*, 17(5), pp. 633–639.

Cervenka, M. C., Wood, S., Bagary, M., Balabanov, A., Bercovici, E., Brown, M.-G., Devinsky, O., Di Lorenzo, C., Doherty, C. P., Felton, E., Healy, L. A., Klein, P., Kverneland, M., Lambrechts, D., Langer, J., Nathan, J., Munn, J., Nguyen, P., Phillips, M., Roehl, K., Tanner, A., Williams, C. and Zupec-Kania, B. (2021) 'International Recommendations for the Management of Adults Treated With Ketogenic Diet Therapies', *Neurology: Clinical Practice*, 11(5), pp. 385–397.

Chen, W. and Kossoff, E. H. (2012) 'Long term follow-up of children treated with the modified Atkins diet', *Journal of Child Neurology*, 27(6), pp. 754–758.

Chisolm, P. F., Warner, J. D., Hale, A. T., Estevez-Ordonez, D., Murdaugh, D., Rozzelle, C. J. and Blount, J. P. (2022) 'Quantifying and reporting outcome measures in pediatric epilepsy surgery: A systematic review', *Epilepsia*, 63(11), pp. 2754–2781.

Cianchetti, C., Messina, P., Pupillo, E., Crichiutti, G., Baglietto, M. G., Veggiotti, P., Zamponi, N., Casellato, S., Margari, L., Erba, G. and Beghi, E. (2015) 'The perceived burden of epilepsy: Impact on the quality of life of children and adolescents and their families', *Seizure*, 24, pp. 93–101.

Cohen, M. Z., Kahn, D. L. and Steeves, R. H. (eds) (2000) *Hermeneutic Phenomenological Research: A Practical Guide for Nurse Researchers*. London: Sage Publications, Inc.

Collins, C. S. and Stockton, C. M. (2018) 'The Central Role of Theory in Qualitative Research', *International Journal of Qualitative Methods*, 17(1), pp. 1–10.

COMET Initiative (2021) *Checklist for public research partners and core outcome set developers involved in designing a COS study*. Available at: https://www.comet-initiative.org/assets/downloads/cos%20study%20development%20-%20ppi%20checklist%2016-03-16.pdf (Accessed: 29.04.23)

Conners, C. K. (1969) 'A teacher rating scale for use in drug studies with children', *American Journal of Psychiatry*, 126, pp. 884–888.

Coppola, G., Veggiotti, P., Cusmai, R., Bertoli, S., Cardinali, S., Dionisi-Vici, C., Elia, M., Lispi, M. L., Sarnelli, C., Tagliabue, A., Toraldo, C. and Pascotto, A. (2002) 'The ketogenic diet in children, adolescents and young adults with refractory epilepsy: An Italian multicentric experience', *Epilepsy Research*, 48(3), pp. 221–227.

Core Outcome Measures in Effectiveness Trials (COMET) Initiative (no date) *CORE-KDT study registration*. Available at: https://www.comet-initiative.org/Studies/Details/1116 (Accessed: 26 June 2021).

Creswell, J. and Plano Clark, V. (2007) *Designing and Conducting Mixed Methods Research*. Thousand Oaks, CA: Sage.

Crudgington, H., Collingwood, A., Bray, L., Lyle, S., Martin, R., Gringras, P., Pal, D. K. and Morris, C. (2020) 'Mapping epilepsy-specific patient-reported outcome measures for children to a proposed core outcome set for childhood epilepsy', *Epilepsy and Behavior*, 112(107372).

Crudgington, H., Rogers, M., Bray, L., Carter, B., Currier, J., Dunkley, C., Gibbon, F. M., Hughes, D., Lyle, S., Roberts, D., Tudur Smith, C., Gringras, P., Pal, D. K. and Morris, C. (2019) 'Core Health Outcomes in Childhood Epilepsy (CHOICE): Development of a core outcome set using systematic review methods and a Delphi survey consensus', *Epilepsia*, 60(5), pp. 857–871.

Cubukcu, D., Guzel, O. and Arslan, N. (2018) 'Effect of ketogenic diet on motor functions and daily living activities of children with multidrug-resistant epilepsy: A prospective study', *Journal of Child Neurology*, 33(11), pp. 718–723.

Davey, J., Turner, R. M., Clarke, M. J. and Higgins, J. P. (2011) 'Characteristics of meta-analyses and their component studies in the Cochrane Database of Systematic Reviews: A cross-sectional, descriptive analysis', *BMC Medical Research Methodology*, 11(160).

Davies, S., Heyman, I. and Goodman, R. (2003) 'A population survey of mental health problems in children with epilepsy', *Developmental Medicine and Child Neurology*, 45(5), pp. 292–295.

Deakin, H. and Wakefield, K. (2014) 'Skype interviewing: reflections of two PhD researchers', *Qualitative Research*, 14(5), pp603-616.

Department of Health (1991) *Dietary reference values for food energy and nutrients for the United Kingdom. Report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy.*, *Reports on health and social subjects*. London: HMSO.

Devinsky, O., Cross, J. H., Laux, L., Marsh, E., Miller, I., Nabbout, R., Scheffer, I. E., Thiele, E. A. and Wright, S. (2017) 'Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome', *New England Journal of Medicine*, 376(21), pp. 2011–2020.

Devinsky, O., Patel, A. D., Cross, J. H., Villanueva, V., Wirrell, E. C., Privitera,

M., Greenwood, S. M., Roberts, C., Checketts, D., VanLandingham, K. E. and Zuberi, S. M. (2018) 'Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome', *New England Journal of Medicine*, 378(20), pp. 1888–1897.

Dodd, S., Clarke, M., Becker, L., Mavergames, C., Fish, R. and Williamson, P. R. (2018) 'A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery', *Journal of Clinical Epidemiology*, 96, pp. 84–92.

Downs, J., Jacoby, P., Leonard, H., Epstein, A., Murphy, N., Davis, E., Reddihough, D., Whitehouse, A. and Williams, K. (2019) 'Psychometric properties of the Quality of Life Inventory-Disability (QI-Disability) measure', *Quality of Life Research*, 28(3), pp. 783–794.

Dressler, A., Stöcklin, B., Reithofer, E., Benninger, F., Freilinger, M., Hauser, E., Reiter-Fink, E., Seidl, R., Trimmel-Schwahofer, P. and Feucht, M. (2010) 'Long-term outcome and tolerability of the ketogenic diet in drug-resistant childhood epilepsy-the austrian experience', *Seizure*, 19(7), pp. 404–408.

Duncan, J. S. and Sander, J. W. (1991) 'The Chalfont Seizure Severity Scale', *Journal of Neurology, Neurosurgery and Psychiatry*, 54(10), pp. 873–876.

Dunn, L. M. and Dunn, D. M. (1997) 'Peabody Picture Vocabulary Test-Third Edition (PPVT-III)'. Circle Pines, MN: American Guidance Service.

Dyson, L. and Fewell, R. R. (1986) 'Stress and Adaptation in Parents of Young Handicapped and Nonhandicapped Children: A Comparative Study', *Journal of Early Intervention*, 10(1), pp. 25–34.

Easter, M. (2019) 'Inside the rise of keto: how an extreme diet went mainstream, *Men's Health*, January. Available at: https://www.menshealth.com/nutrition/a25775330/keto-diet-history/ (accessed on 15/03/21).

El-Rashidy, O.F., Nassar, M. F., Abdel-Hamid, I. A., Shatla, R. H., Abdel-Hamid, M. H., Gabr, S. S., Mohamed, S. G., El-Sayed, W. S. and Shaaban, S. Y. (2013) 'Modified Atkins diet vs classic ketogenic formula in intractable epilepsy', *Acta Neurologica Scandinavica*, 128(6), pp. 402–408.

El-Rashidy, O. F., Nassar, M. F., El Gendy, Y. G., Deifalla, S. M. and Gaballa, S. (2017) 'Experience with MAD on children with epilepsy in Egypt after classic KD failure', *Acta Neurologica Scandinavica*, 137(2), pp. 195–198.

Elger, C. E. and Schmidt, D. (2008) 'Modern management of epilepsy: A

practical approach', *Epilepsy and Behavior*, 12(4), pp. 501–539.

Elo, S. and Kyngäs, H. (2008) 'The qualitative content analysis process', *Journal of Advanced Nursing*, 62(1), pp. 107–115.

Farasat, S., Kossoff, E. H., Pillas, D. J., Rubenstein, J. E., Vining, E. P. and Freeman, J. M. (2006) 'The importance of parental expectations of cognitive improvement for their children with epilepsy prior to starting the ketogenic diet', *Epilepsy and Behavior*, 8(2), pp. 406–410.

Fayed, N., Cameron, S., Fraser, D., Cameron, J. I., Al-Harbi, S., Simpson, R., Wakim, M., Chiu, L. and Choong, K. (2020) 'Priority outcomes in critically ill children: A patient and parent perspective', *American Journal of Critical Care*, 29(5), pp. e94–e103.

Fekkes, M., Theunissen, N. C., Brugman, E., Veen, S., Verrips, E. G., Koopman, H. M., Vogels, T., Wit, J. M. and Verloove-Vanhorick, S. P. (2000) 'Development and psychometric evaluation of the TAPQOL: A health-related quality of life instrument for 1-5 year old children.', *Quality of Life Research*, 9(8), pp. 961–972.

Ferraria, N., Mendes, P., Oliveira, F., Martins, C., Fonseca, M. J. and Monteiro, J. P. (2013) 'Ketogenic diet for refractory epilepsy in children-an institutional experience', *Pediatrics and Therapeutics*, 3(3), pp. 1–4.

Ferraris, C., Guglielmetti, M., Pasca, L., De Giorgis, V., Ferraro, O. E., Brambilla, I., Leone, A., De Amicis, R., Bertoli, S., Veggiotti, P. and Tagliabue, A. (2019) 'Impact of the ketogenic diet on linear growth in children: A single-center retrospective analysis of 34 cases', *Nutrients*, 11(7):1442.

Ferreira, P. L., Baltazar, C. F., Cavalheiro, L., Cabri, J. and Goncalves, R. S. (2014) 'Reliability and validity of PedsQL for Portuguese children aged 5-7 and 8-12 years', *Health and Quality of Life Outcomes*, 12:122.

Ferro, M. A. and Speechley, K. N. (2012) 'What about dads? An exploratory analysis of depressive symptoms in paternal primary caregivers of children with epilepsy', *Epilepsy and Behavior*, 23(1), pp. 90–91.

Finnis, J. (1980) *Natural Law and natural Rights*. Oxford,UK: Clarendon Press.

Fish, R., Sanders, C., Adams, R., Brewer, J., Brookes, S. T., DeNardo, J., Kochhar, R., Saunders, M. P., Sebag-Montefiore, D., Williamson, P. R. and Renehan, A. G. (2018) 'A core outcome set for clinical trials of chemoradiotherapy interventions for anal cancer (CORMAC): a patient and health-care professional consensus', *The Lancet Gastroenterology and*

Hepatology, 3(12), pp. 865–873.

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel, J., Forsgren, L., French, J. A., Glynn, M., Hesdorffer, D. C., Lee, B. I., Mathern, G. W., Moshé, S. L., Perucca, E., Scheffer, I. E., Tomson, T., Watanabe, M. and Wiebe, S. (2014) 'ILAE Official Report: A practical clinical definition of epilepsy', *Epilepsia*, 55(4), pp. 475–482.

Fisher, R. S., Blum, D. E., DiVentura, B., Vannest, J., Hixson, J. D., Moss, R., Herman, S. T., Fureman, B. E. and French, J. A. (2012) 'Seizure diaries for clinical research and practice: limitations and future prospects', *Epilepsy and Behavior*, 24(3), pp. 304–310.

Fisher, R. S., Cross, J. H., French, J. A., Higurashi, N., Hirsch, E., Jansen, F. E., Lagae, L., Moshé, S. L., Peltola, J., Roulet Perez, E., Scheffer, I. E. and Zuberi, S. M. (2017) 'Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology', *Epilepsia*, 58(4), pp. 522–530.

Follansbee-Junger, K. W., Mann, K. A., Guilfoyle, S. M., Morita, D. A., Varni, J. W. and Modi, A. C. (2016) 'Development of the PedsQL™ Epilepsy Module: Focus group and cognitive interviews', *Epilepsy and Behavior*, 62, pp.115-120.

Frankenburg, W. K. and Dodds, J. B. (1967) 'The Denver Developmental Screening Test', *The Journal of Pediatrics*, 71(2), pp. 181–191.

Freeman, J. M., Freeman, J. and Kelly, M. (2000) *The ketogenic diet: a treatment for epilepsy.* 3rd edn. New York: Demos.

Freeman, J. M., Vining, E. P. G., Pillas, D. J., Pyzik, P. L., Casey, J. C. and Kelly, M. T. (1998) 'The efficacy of the ketogenic diet - 1998: A prospective evaluation of intervention in 150 children', *Pediatrics*, 102(6), pp. 1358–1363.

Freitag, H. and Tuxhorn, I. (2005) 'Cognitive Function in Preschool Children after Epilepsy Surgery: Rationale for Early Intervention', *Epilepsia*, 46(4), pp. 561–567.

Gargon, E., Gorst, S. L., Harman, N. L., Smith, V., Matvienko-Sikar, K. and Williamson, P. R. (2018) 'Choosing important health outcomes for comparative effectiveness research: 4th annual update to a systematic review of core outcome sets for research', *PLoS ONE*, 13(12), pp. 1–15.

Gargon, E., Gurung, B., Medley, N., Altman, D. G., Blazeby, J. M., Clarke, M. and Williamson, P. R. (2014) 'Choosing important health outcomes for comparative effectiveness research: A systematic review', *PLoS ONE*, 9(6), p.

e99111.

Gibbon, F. M., Maccormac, E. and Gringras, P. (2019) ‘Sleep and epilepsy: Unfortunate bedfellows’, *Archives of Disease in Childhood*, 104(2), pp. 189–192. doi:

Glauser, T. A., Cnaan, A., Shinnar, S., Hirtz, D. G., Dlugos, D., Masur, D., Clark, P. O., Capparelli, E. V. and Adamson, P. C. (2010) ‘Ethosuximide, Valproic Acid, and Lamotrigine in Childhood Absence Epilepsy’, *New England Journal of Medicine*, 362(9), pp. 790–799.

Goodwin, S. W., Lambrinos, A. I., Ferro, M. A., Sabaz, M. and Speechley, K. N. (2015) ‘Development and assessment of a shortened Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55)’, *Epilepsia*, 56(6), pp. 864–72.

Guba, E. G. and Lincoln, Y. S. (1989) ‘What is this Constructivist Paradigm Anyway?’, in *Fourth Generation Evaluation*. London: SAGE Publications, pp. 79–90.

Guelpa, G. and Marie, A. (1911) ‘La lutte contre l’epilepsie par la desintoxication et par la reeducation alimentaire’, *Revue de Therapie Medico-Chirurgicale*, 78, pp. 8–13.

Hader, W. J., Tellez-Zenteno, J., Metcalfe, A., Hernandez-Ronquillo, L., Wiebe, S., Kwon, C. S. and Jette, N. (2013) ‘Complications of epilepsy surgery - A systematic review of focal surgical resections and invasive EEG monitoring’, *Epilepsia*, 54(5), pp. 840–847.

Halböök, T., Lundgren, J. and Rosen, I. (2007) ‘Ketogenic diet improves sleep quality in children with therapy-resistant epilepsy’, *Epilepsia*, 48(1), pp. 59–65.

Hamiwka, L. D. and Wirrell, E. C. (2009) ‘Comorbidities in pediatric epilepsy: Beyond “just” treating the seizures’, *Journal of Child Neurology*, 24(6), pp. 734-42

Harden, J., Black, R. and Chin, R. F. M. (2016) ‘Families’ experiences of living with pediatric epilepsy: A qualitative systematic review’, *Epilepsy and Behavior*, 60, pp. 225–237.

Harman, N. L., Bruce, I. A., Kirkham, J. J., Tierney, S., Callery, P., O’Brien, K., Bennett, A. M. D., Chorbachi, R., Hall, P. N., Harding-Bell, A., Parfect, V. H., Rumsey, N., Sell, D., Sharma, R. and Williamson, P. R. (2015) ‘The importance of integration of stakeholder views in core outcome set development: Otitis Media with Effusion in children with cleft palate’, *PLoS ONE*, 10(6): e0129514.

Hendriksen, J. G., Poysky, J. T., Schrans, D. G., Schouten, E. G., Aldenkamp, A. P. and Vles, J. S. (2009) 'Psychosocial adjustment in males with Duchenne muscular dystrophy: psychometric properties and clinical utility of a parent-report questionnaire', *Journal of Pediatric Psychology*, 34(1), pp. 69–78.

Hobdell, E. F., Grant, M. L., Valencia, I., Mare, J., Kothare, S. V., Legido, A. and Khurana, D. S. (2007) 'Chronic sorrow and coping in families of children with epilepsy', *Journal of Neuroscience Nursing*, 39(2), pp. 76–82.

Hsieh, H. F. and Shannon, S. E. (2005) 'Three approaches to qualitative content analysis', *Qualitative Health Research*, 15(9), pp. 1277–1288.

Huttenlocher, P. R. (1976) 'Ketonaemia and seizures: metabolic and anticonvulsant effects of two ketogenic diets in childhood epilepsy.', *Pediatric Research*, 10(5), pp. 536–540.

Huttenlocher, P. R., Wilbourn, A. J. and Signore, J. M. (1971) 'Medium-chain triglycerides as a therapy for intractable childhood epilepsy', *Neurology*, 21(11), pp. 1097–1103.

IJff, D M, Postulart, D., Lambrechts, D. A. J. E., Majoie, M. H. J. M., de Kinderen, R. J. A., Hendriksen, J. G. M., Evers, S. M. A. A. and Aldenkamp, A. P. (2016) 'Cognitive and behavioral impact of the ketogenic diet in children and adolescents with refractory epilepsy: A randomized controlled trial', *Epilepsy and Behavior*, 60, pp. 153–157.

Information and Data Management Advisory Group (DMAG) (2019) *University of Plymouth Research Data Policy*.

INVOLVE. (2012) Briefing notes for researchers: public involvement in NHS, public health and social care research. INVOLVE, Eastleigh. Available at: https://www.invo.org.uk/wp-content/uploads/2012/04/INVOLVEBriefingNotesApr2012.pdf (Accessed on 29.07.23).

Jennum, P., Pickering, L., Christensen, J., Ibsen, R. and Kjellberg, J. (2017) 'Morbidity and mortality of childhood- and adolescent-onset epilepsy: A controlled national study', *Epilepsy and Behavior*, 66, pp. 80–85.

Jensen, M. P., Liljenquist, K. S., Bocell, F., Gammaitoni, A. R., Aron, C. R., Galer, B. S. and Amtmann, D. (2017) 'Life impact of caregiving for severe childhood epilepsy: Results of expert panels and caregiver focus groups', *Epilepsy and Behavior*. 74, pp. 135–143.

Johnson, R. B. and Onwuegbuzie, A. J. (2007) 'Toward a Definition of Mixed

Methods Research', *Journal of Mixed Methods Research*. Sage: Los Angeles, CA, pp. 112–133.

Joint Epilepsy Council (2011) 'Epilepsy prevalence, incidence and other statistics', *Joint Epilepsy Council of the UK and Ireland*.

Jones, C., Atkinson, P., Memon, A., Dabydeen, L., Das, K. B., Cross, J. H., Gillberg, C., Neville, B. G. R., Scott, R. C. and Reilly, C. (2019) 'Experiences and needs of parents of young children with active epilepsy: A population-based study', *Epilepsy and Behavior*, 90, pp. 37–44.

Kang, H.C., Lee, Y. J., Lee, J. S., Lee, E. J., Eom, S., You, S. J. and Kim, H. D. (2011) 'Comparison of short- versus long-term ketogenic diet for intractable infantile spasms', *Epilepsia*, 52(4), pp. 781–787.

Kaushik, S., Chopra, D., Sharma, S. and Aneja, S. (2019) 'Adverse drug reactions of anti-epileptic drugs in children with epilepsy: a cross-sectional study', *Current Drug Safety*, 14(3), pp. 217–224.

Keeley, T., Williamson, P., Callery, P., Jones, L. L., Mathers, J., Jones, J., Young, B. and Calvert, M. (2016) 'The use of qualitative methods to inform Delphi surveys in core outcome set development', *Trials*, 17, 230.

Keene, D. L. (2006) 'A Systematic Review of the Use of the Ketogenic Diet in Childhood Epilepsy', *Pediatric Neurology*, 35(1), pp. 1–5.

Kerr, C., Nixon, A. and Angalakuditi, M. (2011) 'The impact of epilepsy on children and adult patients' lives: Development of a conceptual model from qualitative literature', *Seizure*, 20(10), pp. 764–774.

Khoo, T. B., Tukimin, S. M. B., Syed Zainal Abidin, S. M. B., Lai, J. J. and Yusoof, N. A. B. (2016) 'Long-term outcome and tolerability of ketogenic diet treatment for refractory epilepsies in children – A tertiary centre Malaysian experience', *Neurology Asia*, 21(1), pp. 17–21.

Kim, J A, Yoon, J. R., Lee, E. J., Lee, J. S., Kim, J. T., Kim, H. D. and Kang, H. C. (2016) 'Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy', *Epilepsia*, 57(1), pp. 51–58.

de Kinderen, R. J. A., Lambrechts, D. A. J. E., Wijnen, B. F. M., Postulart, D., Aldenkamp, A. P., Majoie, M. H. J. M. and Evers, S. M. A. A. (2016) 'An economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy: An interim analysis', *Epilepsia*, 57(1), pp. 41–50.

Kirkham, J. J., Davis, K., Altman, D. G., Blazeby, J. M., Clarke, M., Tunis, S. and Williamson, P. R. (2017) 'Core Outcome Set-STAndards for Development: The COS-STAD recommendations', *PLoS Medicine*, 14(11):e1002447.

Kirkham, J. J., Gorst, S., Altman, D. G., Blazeby, J. M., Clarke, M., Devane, D., Gargon, E., Moher, D., Schmitt, J., Tugwell, P., Tunis, S. and Williamson, P. R. (2016) 'Core Outcome Set–STAndards for Reporting: The COS-STAR Statement', *PLoS Medicine*, 13(10):e1002148. d: 10.1371/journal.pmed.1002148.

Kirkham, J. J., Gorst, S., Altman, D. G., Blazeby, J. M., Clarke, M., Tunis, S. and Williamson, P. R. (2019) 'Core Outcome Set-STAndardised Protocol Items: The COS-STAP Statement', *Trials*, 20(1), 116.

Kirwan, J., Heiberg, T., Hewlett, S., Hughes, R., Kvien, T., Ahlmèn, M., Boers, M., Minnock, P., Saag, K., Shea, B., Almazor, M. S. and Taal, E. (2003) 'Outcomes from the Patient Perspective Workshop at OMERACT 6', *Journal of Rheumatology*, 30(4), pp. 868–872.

Kivunja, C. and Kuyini, A. B. (2017) 'Understanding and Applying Research Paradigms in Educational Contexts', *International Journal of Higher Education*, 6(5), pp.26-41.

Klepper, J., Akman, C., Armeno, M., Auvin, S., Cervenka, M., Cross, H. J., De Giorgis, V., Della Marina, A., Engelstad, K., Heussinger, N., Kossoff, E. H., Leen, W. G., Leiendecker, B., Monani, U. R., Oguni, H., Neal, E., Pascual, J. M., Pearson, T. S., Pons, R., Scheffer, I. E., Veggiotti, P., Willemsen, M., Zuberi, S. M. and De Vivo, D. C. (2020) 'Glut1 Deficiency Syndrome (Glut1DS): State of the art in 2020 and recommendations of the international Glut1DS study group', *Epilepsia Open*, 5(3), pp. 354–365.

Klepper, J. and Leiendecker, B. (2013) 'Glut1 deficiency syndrome and novel ketogenic diets', *Journal of Child Neurology*, 28(8), pp. 1045-1048.

Kossoff, E. H., Cervenka, M. C., Henry, B. J., Haney, C. A. and Turner, Z. (2013) 'A decade of the modified Atkins diet (2003-2013): Results, insights, and future directions', *Epilepsy and Behavior*, 29(3), pp. 437–442.

Kossoff, E. H., Krauss, G. L., McGrogan, J. R. and Freeman, J. M. (2003) 'Efficacy of the Atkins diet as therapy for intractable epilepsy', *Neurology*, 61(12), pp. 1789–1791.

Kossoff, E. H., Pyzik, P. L., Rubenstein, J. E., Christina Bergqvist, A. G., Buchhalter, J. R., Donner, E. J., Nordli, D. R. and Wheless, J. W. (2007a)

‘Combined ketogenic diet and vagus nerve stimulation: Rational polytherapy?’, *Epilepsia*, 48, pp. 77–81.

Kossoff, E. H., Turner, Z., Bluml, R. M., Pyzik, P. L. and Vining, E. P. G. (2007b) ‘A randomized, crossover comparison of daily carbohydrate limits using the modified Atkins diet’, *Epilepsy and Behavior*, 10(3), pp. 432–436.

Kossoff, E. H., Zupec-Kania, B. A., Amark, P. E., Ballaban-Gil, K. R., Christina Bergqvist, A. G., Blackford, R., Buchhalter, J. R., Caraballo, R. H., Cross, J. H., Dahlin, M. G., Donner, E. J., Klepper, J., Jehle, R. S., Kim, H. D., Christiana Liu, Y. M., Nation, J., Nordli Jr, D. R., Pfeifer, H. H., Rho, J. M., Stafstrom, C. E., Thiele, E. A., Turner, Z., Wirrell, E. C., Wheless, J. W., Veggiotti, P., Vining, E. P. G., Anderson, A., Cohen, B., Currey, M., Donley, D., Dure, L., Garg, B., Goldstein, M., Grabert, B., Griesemer, D., Kovnar, E., Larson, R., Legido, A., Morrison, L. A., Parker, C., Renfroe, J. B., Schreck, J., Shinnar, S., Snyder, R., Tardo, C., Timmons, G. D. and Yim, G. (2009) ‘Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group’, *Epilepsia*, 50(2), pp. 304–317.

Kossoff, E. H., Zupec-Kania, B. A., Auvin, S., Ballaban-Gil, K. R., Christina Bergqvist, A. G., Blackford, R., Buchhalter, J. R., Caraballo, R. H., Cross, J. H., Dahlin, M. G., Donner, E. J., Guzel, O., Jehle, R. S., Klepper, J., Kang, H. C., Lambrechts, D. A., Liu, Y. M. C., Nathan, J. K., Nordli, D. R., Pfeifer, H. H., Rho, J. M., Scheffer, I. E., Sharma, S., Stafstrom, C. E., Thiele, E. A., Turner, Z., Vaccarezza, M. M., van der Louw, E. J. T. M., Veggiotti, P., Wheless, J. W. and Wirrell, E. C. (2018) ‘Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group’, *Epilepsia Open*, 3(2), pp. 175–192.

Kotagal, P. and Yardi, N. (2008) ‘The relationship between sleep and epilepsy’, *Seminars in Pediatric Neurology*, 15(2), pp. 42–49.

Kverneland, M., Molteberg, E., Iversen, P. O., Veierød, M. B., Taubøll, E., Selmer, K. K. and Nakken, K. O. (2018) ‘Effect of modified Atkins diet in adults with drug-resistant focal epilepsy: A randomized clinical trial’, *Epilepsia*, 59(8), pp. 1567–1576.

Kwan, P., Arzimanoglou, A., Berg, A. T., Brodie, M. J., Hauser, W. A., Mathern, G., Moshé, S. L., Perucca, E., Wiebe, S. and French, J. (2010) ‘Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies’, *Epilepsia*, 51(6), pp. 1069–1077.

Kwan, P. and Brodie, M. J. (2000) ‘Early Identification of Refractory Epilepsy’, *New England Journal of Medicine*, 342(5), pp. 314–319.

Kwan, P., Schachter, S. C. and Brodie, M. J. (2011) ‘Drug-resistant epilepsy’, *The New England Journal of Medicine*, 365(10), pp. 919–926.

Lambrechts, D. A. J. E., Bovens, M. J. M., de la Parra, N. M., Hendriksen, J. G. M., Aldenkamp, A. P. and Majoie, M. J. M. (2013) ‘Ketogenic diet effects on cognition, mood, and psychosocial adjustment in children’, *Acta Neurologica Scandinavica*, 127(2), pp. 103–108.

Lambrechts, D. A. J. E., de Kinderen, R. J. A., Vles, H. S. H., de Louw, A. J., Aldenkamp, A. P. and Majoie, M. J. M. (2015) ‘The MCT-ketogenic diet as a treatment option in refractory childhood epilepsy: A prospective study with 2-year follow-up’, *Epilepsy and Behavior*, 51, pp. 261–266.

Lambrechts, D. A., de Kinderen, R. J., Vles, J. S., de Louw, A. J., Aldenkamp, A. P. and Majoie, H. J. (2017) ‘A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy’, *Acta Neurologica Scandinavica*, 135(2), pp. 231–239.

Larson, A. M., Ryther, R. C. C., Jennesson, M., Geffrey, A. L., Bruno, P. L., Anagnos, C. J., Shoeb, A. H., Thibert, R. L. and Thiele, E. A. (2012) ‘Impact of pediatric epilepsy on sleep patterns and behaviors in children and parents’, *Epilepsia*, 53(7), pp. 1162–1169.

Lefevre, F. and Aronson, N. (2000) ‘Ketogenic diet for the treatment of refractory epilepsy in children: A systematic review of efficacy.’, *Pediatrics*, 105(4):E46.

Lincoln, Y. S. and Guba, E. G. (1985) *Naturalistic Enquiry*. Beverly Hills, CA: Sage.

Lindgren, C. L., Burke, M. L., Hainsworth, M. A. and Eakes, G. G. (1992) ‘Chronic sorrow: a lifespan concept.’, *Scholarly Inquiry for Nursing Practice*, 6(1), pp. 27–40.

Liu, X., Carney, P. R., Bussing, R., Segal, R., Cottler, L. B. and Winterstein, A. G. (2017) ‘Trends in antiepileptic drug use in children and adolescents with epilepsy’, *Pediatric Neurology*, 74, pp. 32–40.

Lo Lacono, V., Symonds, P. and Brown, D. H. K. (2016) ‘Skype as a tool for qualitative research interviews’, *Sociological Research Online*, 21(2), pp.103-117.

Lord, K. and Magrath, G. (2010) ‘Use of the ketogenic diet and dietary practices in the UK’, *Journal of Human Nutrition and Dietetics*, 23(2), pp. 126–132.

Löscher, W. and Schmidt, D. (2011) ‘Modern antiepileptic drug development has failed to deliver: Ways out of the current dilemma’, *Epilepsia*, 52(4), pp. 657–678.

St. Louis, E. (2009) ‘Minimizing AED Adverse Effects: Improving Quality of Life in the Interictal State in Epilepsy Care’, *Current Neuropharmacology*, 7(2), pp. 1-6–114.

van der Louw, E., Aldaz, V., Harvey, J., Roan, M., van den Hurk, D., Cross, J. H., Auvin, S., Forbes, E., van de Bor, B., Olieman, J., Simchowitz, V., Storme, T., Klepper, J. and Dressler, A. (2020) ‘Optimal clinical management of children receiving ketogenic parenteral nutrition: a clinical practice guide’, *Developmental Medicine and Child Neurology*, 62(1), pp. 48–56.

van der Louw, E., van den Hurk, D., Neal, E., Leiendecker, B., Fitzsimmon, G., Dority, L., Thompson, L., Marchió, M., Dudzińska, M., Dressler, A., Klepper, J., Auvin, S. and Cross, J. H. (2016) ‘Ketogenic diet guidelines for infants with refractory epilepsy’, *European Journal of Paediatric Neurology*, 20(6), pp.798-809.

Lundman, B. and Graneheim, U. H. (2004) ‘Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness’, *Nurse Education Today*, 24(2), pp. 105–112.

Macbeth, D. (2001) ‘On “Reflexivity” in Qualitative Research: Two Readings, and a Third’, *Qualitative Inquiry*, 7(1), pp. 35–68.

Macdonald, R. L. and Kelly, K. M. (1995) ‘Antiepileptic drug mechanisms of action’, *Epilepsia*, 36(Suppl 2), pp. S2-12.

Mack, N., Woodsong, C., MacQueen, K., Guest, G. and Namey, E. (2005) *Qualitative research methods: a data collectors field guide. Family Health International.*

Maclennan, Steven, Williamson, P. R., Bekema, H., Campbell, M., Ramsay, C., N’dow, J., Maclennan, Sara, Vale, L., Dahm, P., Mottet, N., Lam, T., Abel, P., Ahmed, H. U., Akehurst, G., Almquist, R., Beck, K., Budd, D., Canfield, S., Catto, J., Cornford, P., Cross, W., Ewen, A., Grant, J., Heer, R., Hurst, D., Jones, R., Kockelbergh, R., Mackie, A., Macdonald, G., Mcneill, A., Mason, M., Mcclinton, S., Mclaren, D., Mostafid, H., Pearce, I., Pennet, L., Royle, J., Schreuder, H., Stewart, G. D., Van Der Poel, H., Wardlaw, K. and Wiegel, T. (2017) ‘A core outcome set for localised prostate cancer effectiveness trials’, *BJU International*, 120(5), pp. 64–79.

Magrath, G., MacDonald, A. and Whitehouse, W. (2000) ‘Dietary practices and

use of the ketogenic diet in the UK', *Seizure*, 9(2), pp. 128–130.

Marson, A. G., Appleton, R., Baker, G. A., Chadwick, D. W., Doughty, J., Eaton, B., Gamble, C., Jacoby, A., Shackley, P., Smith, D. F., Tudur-Smith, C., Vanoli, A. and Williamson, P. R. (2007) 'A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial', *Health Technology Assessment*, 369(9566), pp. 1016–1026.

Martin-McGill, K. J., Bresnahan, R., Levy, R. G. and Cooper, P. N. (2020) 'Ketogenic diets for drug-resistant epilepsy', *Cochrane Database of Systematic Reviews*, 6, CD001903.pub5.

Martin-Mcgill, K. J., Jackson, C. F., Breshnahan, R., Levy, R. G. and Cooper, P. N. (2018) 'Ketogenic diets for drug-resistant epilepsy', *Cochrane Database of Systematic Reviews*, 11, CD001903.pub4.

Martin-McGill, K. J., Lambert, B., Whiteley, V. J., Wood, S., Neal, E. G., Simpson, Z. R. and Schoeler, N. E. (2019) 'Understanding the core principles of a "modified ketogenic diet": a UK and Ireland perspective', *Journal of Human Nutrition and Dietetics*, 32(3), pp. 385–390.

Martin, K., Jackson, C. F., Levy, R. G. and Cooper, P. N. (2016) 'Ketogenic diet and other dietary treatments for epilepsy', (2), *Cochrane Database of Systematic Reviews*, 2, CD001903.

Martinez, C. C., Pyzik, P. L. and Kossoff, E. H. (2007) 'Discontinuing the ketogenic diet in seizure-free children: Recurrence and risk factors', *Epilepsia*, 48(1), pp. 187–190.

Mastriani, K. S., Williams, V. C., Hulsey, T. C., Wheless, J. W. and Maria, B. L. (2008) 'Evidence-based versus reported epilepsy management practices', *Journal of Child Neurology*, 23(5), pp. 507–514.

Mazzucato, M. (2018) *Mission-oriented research & innovation in the European Union : a problem-solving approach to fuel innovation-led growth*.

McDonald, T. J. W. and Cervenka, M. C. (2017) 'Ketogenic diets for adults with highly refractory epilepsy', *Epilepsy Currents*, 17(6), pp. 346–350.

McNair, D. M., Lorr, M. and Droppleman, L. F. (1992) *Revised Manual for the Profile of Mood States*. SanDiego: Educational and Industrial Testing Services.

Meloy, J. M. (1994) *Writing the qualitative dissertation: Understanding by doing.* Hillsdale, NJ: Lawrence Erlbaum Associates.

Mendez, M. and Radtke, R. A. (2001) ‘Interactions between sleep and epilepsy’, *Journal of Clinical Neurophysiology*, 18(2), pp. 106–127.

Miller, A. C., Gordon, R. M., Daniele, R. J. and Diller, L. (1992) ‘Stress, appraisal, and coping in mothers of disabled and nondisabled children’, *Journal of Pediatric Psychology*, 17(5), pp. 587–605.

Mills, C. (2000) *The Sociological Imagination*. Oxford,UK: Oxford University Press.

Mohanraj, R. and Brodie, M. J. (2006) ‘Diagnosing refractory epilepsy: Response to sequential treatment schedules’, *European Journal of Neurology*, 13, pp. 277–282.

Morris, C., Dunkley, C., Gibbon, F. M., Currier, J., Roberts, D., Rogers, M., Crudgington, H., Bray, L., Carter, B., Hughes, D., Tudur Smith, C., Williamson, P. R., Gringras, P. and Pal, D. K. (2017) ‘Core Health Outcomes In Childhood Epilepsy (CHOICE): Protocol for the selection of a core outcome set’, *Trials*, 18(1):572.

Msall, M. E., DiGaudio, K., Rogers, B. T., LaForest, S., Catanzaro, N. L., Campbell, J., Wilczenski, F. and Duffy, L. C. (1994) ‘The Functional Independence Measure for Children (WeeFIM). Conceptual basis and pilot use in children with developmental disabilities’, *Clinical Pediatrics*, 33(7), pp. 421–430.

Mu, P. F. (2008) ‘Transition experience of parents caring of children with epilepsy: A phenomenological study’, *International Journal of Nursing Studies*, 45(4), pp. 543–551.

Murakami, M. and Tognini, P. (2022) ‘Molecular Mechanisms Underlying the Bioactive Properties of a Ketogenic Diet’, *Nutrients*, 14(4), 782.

Murugupillai, R., Ranganathan, S. S., Wanigasinghe, J., Muniyandi, R. and Arambepola, C. (2018) ‘Development of outcome criteria to measure effectiveness of antiepileptic therapy in children’, *Epilepsy and Behavior*, 80, pp. 56–60.

Nabbout, R., Copioli, C., Chipaux, M., Chemaly, N., Desguerre, I., Dulac, O. and Chiron, C. (2011) ‘Ketogenic diet also benefits Dravet syndrome patients receiving stiripentol: A prospective pilot study’, *Epilepsia*, 52(7), pp. 54–57.

National Institute for Health and Care Excellence (NICE) (2012) *Epilepsies: diagnosis and management clinical guideline [CG137]*. (updated 2016 & 2020).

National Institute for Health and Care Excellence (NICE) (2019a) *Cannabidiol with clobazam for treating seizures associated with Dravet syndrome (TA614).*

National Institute for Health and Care Excellence (NICE) (2019b) *Cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome*.

National Institute for Health and Care Excellence (NICE) (2022a) *Epilepsies in children, young people and adults [NG217]*.

National Institute for Health and Care Excellence (NICE) (2022b) *Epilepsies in children, young people and adults: diagnosis and management. Evidence review: Ketogenic diets for drug resistant epilepsy*.

National Institute of Health Research (NIHR) UK Standards of Public Involvement. (2019) Available at https://drive.google.com/file/d/1U-lJNJCfFepaAOruEhzz1TdLvAcHTt2Q/view?pli=1 (Accessed on 29.07.23)

National Institute of Health Research (NIHR) Briefing notes for researchers. April 2021. Available at https://www.nihr.ac.uk/documents/briefing-notes-for-researchers-public-involvement-in-nhs-health-and-social-care-research/27371 (Accessed on 29.07.23)

Neal, E. G., Chaffe, H., Schwartz, R. H., Lawson, M. S., Edwards, N., Fitzsimmons, G., Whitney, A. and Cross, J. H. (2008a) 'The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial', *The Lancet Neurology*, 7(6), pp. 500–506.

Neal, E. G., Chaffe, H. M., Edwards, N., Lawson, M. S., Schwartz, R. H. and Cross, J. H. (2008b) 'Growth of children on classical and medium-chain triglyceride ketogenic diets', *Pediatrics*, 122(2), pp. 334–340.

Neal, E. G., Chaffe, H., Schwartz, R. H., Lawson, M. S., Edwards, N., Fitzsimmons, G., Whitney, A. and Cross, J. H. (2009) 'A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy', *Epilepsia*, 50(5), pp. 1109–1117.

Ngugi, A. K., Kariuki, S. M., Bottomley, C., Kleinschmidt, I., Sander, J. W. and Newton, C. R. (2011) 'Incidence of epilepsy: A systematic review and meta-analysis', *Neurology*, 77, pp. 1005–1012.

Nordli, D. R., Kuroda, M. M., Carroll, J., Koenigsberger, D. Y., Hirsch, L. J., Bruner, H. J., Seidal, W. T. and De Vivo, D. C. (2001) 'Experience with the ketogenic diet in infants', *Pediatrics*, 108(1), pp. 129–33.

O'Brien, J., Gray, V. and Woolfall, K. (2020) 'Child and parent experiences of

childhood epilepsy surgery and adjustment to life following surgery: A qualitative study', *Seizure*, 83, pp. 83–88.

O'Donoghue, M. F., Duncan, J. S. and Sander, J. W. A. S. (1996) 'The National Hospital Seizure Severity Scale: A Further Development of the Chalfont Seizure Severity Scale', *Epilepsia*, 37(6), pp. 563-571.

Olshansky, S. (1962) 'Chronic sorrow: A response to having a mentally defective child', *Social Casework*, 51, pp. 190–193.

Orosz, I., McCormick, D., Zamponi, N., Varadkar, S., Feucht, M., Parain, D., Griens, R., Vallée, L., Boon, P., Rittey, C., Jayewardene, A. K., Bunker, M., Arzimanoglou, A. and Lagae, L. (2014) 'Vagus nerve stimulation for drug-resistant epilepsy: A European long-term study up to 24 months in 347 children', *Epilepsia*, 55(10), pp. 1576–1584.

Palisano, R., Rosenbaum, P., Walter, S., Russell, D., Wood, E. and Galuppi, B. (1997) 'Development and reliability of a system to classify gross motor function in children with cerebral palsy', *Developental Medicine and Child Neurology*, 39(4), pp. 214–223.

Panebianco, M., Zavanone, C., Dupont, S., Restivo, D. A. and Pavone, A. (2016) 'Vagus nerve stimulation therapy in partial epilepsy: a review', *Acta Neurologica Belgica*, 116(3), pp. 241–8.

Patel, A., Pyzik, P. L., Turner, Z., Rubenstein, J. E. and Kossoff, E. H. (2010) 'Long-term outcomes of children treated with the ketogenic diet in the past', *Epilepsia*, 51(7), pp. 1277–1282.

Pereira, A. M., Bruni, O., Ferri, R. and Nunes, M. L. (2012) 'Sleep instability and cognitive status in drug-resistant epilepsies', *Sleep Medicine*, 13(5), pp. 536–541.

Perucca, P., Carter, J., Vahle, V. and Gilliam, F. G. (2009) 'Adverse antiepileptic drug effects: Toward a clinically and neurobiologically relevant taxonomy', *Neurology*, 72(14), pp. 1223–1229.

Perucca, P. and Gilliam, F. G. (2012) 'Adverse effects of antiepileptic drugs', *The Lancet Neurology*, 11(9), pp. 792–802.

Peterman, M. G. (1925) 'The ketogenic diet in epilepsy', *Journal of the American Medical Association*, 84, pp. 1979–1983.

Pfeifer, H. H. and Thiele, E. A. (2005) 'Low-glycemic-index treatment: A liberalized ketogenic diet for treatment of intractable epilepsy', *Neurology*,

65(11), pp.1810-1812.

Pires, M. E., Ilea, A., Bourel, E., Bellavoine, V., Merdariu, D., Berquin, P. and Auvin, S. (2013) 'Ketogenic diet for infantile spasms refractory to first-line treatments: An open prospective study', *Epilepsy Research*, 105(1–2), pp. 189–194.

Poelzer, K., Mannion, C., Ortiz, M. M., Bang, R. and Woods, P. (2019) 'A systematic review of the quality of life for families supporting a child consuming the ketogenic diet for seizure reduction', *Current Developments in Nutrition*, 3(5), nzz079 (e collection)

Polit D.F. and Beck C.T. (2004) *Nursing Research. Principles and Methods.* Philadelphia: Lippincott Williams & Wilkins.

Price, A., Albarqouni, L., Kirkpatrick, J., Clarke, M., May Liew, S., Roberts, N. and Burls, A. (2018) Patient and public involvement in the design of clinical trials: An overview of systematic reviews. *Journal of Evaluation in Clinical Practice,* 24(1), pp. 240– 253.

Prinsen, C. A. C., Vohra, S., Rose, M. R., Boers, M., Tugwell, P., Clarke, M., Williamson, P. R. and Terwee, C. B. (2016) 'How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" - a practical guideline', *Trials*, 17(1), 449.

Puka, K. and Smith, M. Lou (2016) 'Where are they now? Psychosocial, educational, and vocational outcomes after epilepsy surgery in childhood', *Epilepsia*, 57(4), pp. 574–581.

Pyett, P. M. (2003) 'Validation of qualitative research in the "real world"', *Qualitative Health Research*, 13(8), pp. 1170–1179.

Raju, K. N., Gulati, S., Kabra, M., Agarwala, A., Sharma, S., Pandey, R. M. and Kalra, V. (2011) 'Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open labeled study', *Epilepsy Research*, 96(1–2), pp. 96–100.

Ramaglia, G., Romeo, A., Viri, M., Lodi, M., Sacchi, S. and Cioffi, G. (2007) 'Impact of idiopathic epilepsy on mothers and fathers: Strain, burden of care, worries and perception of vulnerability', *Epilepsia*, 48(9), pp. 1810–1813.

Rantanen, K., Eriksson, K. and Nieminen, P. (2011) 'Cognitive impairment in preschool children with epilepsy', *Epilepsia*, 52(8), pp. 1499–1505.

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F. M. C., Aylett, S. E., Burch, V., Gillberg, C., Scott, R. C. and Neville, B. G. R. (2014) 'Neurobehavioral comorbidities in children with active epilepsy: A population-based study', *Pediatrics*, 133(6), pp. e1586-1593.

Reilly, C., Atkinson, P., Memon, A., Jones, C., Dabydeen, L., Cross, J. H., Das, K. B., Gillberg, C., Neville, B. G. R. and Scott, R. C. (2018a) 'Child and parental sleep in young children with epilepsy: A population-based case-control study', *Epilepsia Open*, 3(3), pp. 383–391.

Reilly, C., Atkinson, P., Memon, A., Jones, C., Dabydeen, L., Das, K. B., Gillberg, C., Neville, B. G. R. and Scott, R. C. (2018b) 'Symptoms of depression, anxiety, and stress in parents of young children with epilepsy: A case controlled population-based study', *Epilepsy and Behavior*, 80, pp. 1773–1783.

Reilly, C., Atkinson, P., Memon, A., Jones, C., Dabydeen, L., Das, K. B., Gillberg, C., Neville, B. G. R., Mahoney, J. M. and Scott, R. C. (2019) 'Global development and adaptive behaviour in children with early-onset epilepsy: a population-based case–control study', *Developmental Medicine and Child Neurology*, 61(2), pp. 145–151.

Ronen, G. M., Streiner, D. L. and Rosenbaum, P. (2003) 'Health-related quality of life in children with epilepsy: development and validation of self-report and parent proxy measures.', *Epilepsia*, 44(4), pp. 598–612.

Rosenbaum, P. (2011) 'Family-centred research: What does it mean and can we do it?', *Developmental Medicine and Child Neurology*, 53(2), pp. 99–100.

Rosenbaum, S. E., Glenton, C., Nylund, H. K. and Oxman, A. D. (2010) 'User testing and stakeholder feedback contributed to the development of understandable and useful summary of findings tables for Cochrane reviews', *Journal of Clinical Epidemiology*, 63(6), pp. 607–619.

Russ, S. A., Larson, K. and Halfon, N. (2012) 'A national profile of childhood epilepsy and seizure disorder', *Pediatrics*, 129(2), pp. 256–264.

Sabaz, M., Cairns, D. R., Lawson, J. A., Nheu, N., Bleasel, A. F. and Bye, A. M. E. (2000) 'Validation of a new quality of life measure for children with epilepsy', *Epilepsia*, 41(6), pp. 765–744.

Sahnan, K., Tozer, P. J., Adegbola, S. O., Lee, M. J., Heywood, N., McNair, A. G. K., Hind, D., Yassin, N., Lobo, A. J., Brown, S. R., Sebastian, S., Phillips, R. K. S., Lung, P. F. C., Faiz, O. D., Crook, K., Blackwell, S., Verjee, A., Hart, A. L. and Fearnhead, N. S. (2019) 'Developing a core outcome set for fistulising

perianal Crohn's disease', *Gut*, 68(2), pp. 226–238.

Sandelowski, M. (2000) 'Focus on research methods: Whatever happened to qualitative description?', *Research in Nursing and Health*, 23(4), pp. 334–340.

Sandelowski, M. and Barroso, J. (2003) 'Classifying the findings in qualitative studies', *Qualitative Health Research*. 13(7), pp. 905–923.

Sarlo, G. L. and Holton, K. F. (2021) 'Caregiver perspectives on dietary therapies for epilepsy', *Epilepsy Research*, 178, 106803.

Saxena, A., Jones, L., Shankar, R., McLean, B., Newman, C. G. J. and Hamandi, K. (2018) 'Sudden unexpected death in epilepsy in children: A focused review of incidence and risk factors', *Journal of Neurology, Neurosurgery and Psychiatry*, 89(10), pp. 1064–1070.

Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., French, J., Guilhoto, L., Hirsch, E., Jain, S., Mathern, G. W., Moshé, S. L., Nordli, D. R., Perucca, E., Tomson, T., Wiebe, S., Zhang, Y. H. and Zuberi, S. M. (2017) 'ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology', *Epilepsia*, 58(4), pp. 512–521.

Schlichting, L. (2005) 'Peabody picture vocabulary test-III-NL'. Amsterdam, the Netherlands.: Harcourt Assessment BV.

Schmitt, J., Apfelbacher, C., Spuls, P. I., Thomas, K. S., Simpson, E. L., Furue, M., Chalmers, J. and Williams, H. C. (2015) 'The Harmonizing Outcome Measures for Eczema (HOME) Roadmap: A Methodological Framework to Develop Core Sets of Outcome Measurements in Dermatology', *Journal of Investigative Dermatology*, 135(1), pp. 337–345.

Schoeler, N. E., MacDonald, L., Champion, H., Helen Cross, J., Sander, J. W., Sisodiya, S. M. and Horne, R. (2014) 'Assessing parents' attitudes towards ketogenic dietary therapies', *Epilepsy and Behavior*. 39, pp. 1–5.

Scholte, E. M. and Van der Ploeg, J. D. (2007) *Social Emotional Questionnaire (SEV) manual*. Bohn Stafleu from Loghum: Wood.

Schon von, H., Lippach, I. and Gelpke, W. (1959) *Metabolic studies with a mixed glyceride of medium-chain fatty acids. II. Invesitgations on the changes of ketone-body content of blood and urine after administration of the mixed glycerides, Gastroenterologica,* 91(3), pp. 199–213.

Van Schooneveld, M. M. J. and Braun, K. P. J. (2013) 'Cognitive outcome after epilepsy surgery in children', *Brain and Development*, 35(8), pp. 721–29.

Schwartz, R. H., Eaton, J., Bower, B. and Aynsley-Green, A. (1989) 'Ketogenic diets in the treatment of epilepsy: short term clinical effects.', *Developmental Medicine and Child Neurology*, 31(2), pp. 145–151.

Scottish Intercollegiate Guidelines Network, (SIGN) (2020) *Epilepsies in children and young people: investigative procedures and management (SIGN Publication no.159)*. Edinburgh.

Selassie, G. R. H., Viggedal, G., Olsson, I. and Jennische, M. (2008) 'Speech, language, and cognition in preschool children with epilepsy', *Developmental Medicine and Child Neurology*, 50(6), pp. 432–438.

Seo, J. H., Lee, Y. M., Lee, J. S., Kang, H. C. and Kim, H. D. (2007) 'Efficacy and tolerability of the ketogenic diet according to lipid:nonlipid ratios-comparison of 3:1 with 4:1 diet', *Epilepsia*, 48(4), pp. 801–805.

Shah, L. M., Turner, Z., Bessone, S. K., Winesett, S. P., Stanfield, A. and Kossoff, E. H. (2019) 'How often is antiseizure drug-free ketogenic diet therapy achieved?', *Epilepsy and Behavior*, 93, pp. 29–31.

Sharma, S., Goel, S., Jain, P., Agarwala, A. and Aneja, S. (2016) 'Evaluation of a simplified modified Atkins diet for use by parents with low levels of literacy in children with refractory epilepsy: A randomized controlled trial', *Epilepsy Research*, 127, pp. 152–159.

Sharma, S., Sankhyan, N., Gulati, S. and Agarwala, A. (2013) 'Use of the modified Atkins diet for treatment of refractory childhood epilepsy: A randomized controlled trial', *Epilepsia*, 54(3), pp. 481–486.

Shaw, J. W., Johnson, J. A. and Coons, S. J. (2005) 'US Valuation of the EQ-5D Health States: Development and Testing of the D1 Valuation Model', *Medical Care*, 43(3), pp. 203–220.

Shore, C. P., Austin, J. K., Huster, G. A. and Dunn, D. W. (2002) 'Identifying risk factors for maternal depression in families of adolescents with epilepsy.', *Journal for specialists in pediatric nursing,* 7(2), pp. 71–80.

Shorvon, S. D. (2009) 'Drug treatment of epilepsy in the century of the ILAE: The first 50 years, 1909-1958', *Epilepsia*, 50(3), pp. 69–92.

Shorvon, S. and Tomson, T. (2011) 'Sudden unexpected death in epilepsy', *The Lancet*, 378(9808) pp. 2028-2038.

Shoshan, H. N. and Wehrt, W. (2022) 'Understanding "Zoom fatigue": A mixed-

method approach', *Applied Psychology*, 71(3), pp. 827–852.

Sinha, I. P., Gallagher, R., Williamson, P. R. and Smyth, R. L. (2012) 'Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people', *Trials*, 13, 103.

Skivington, K., Matthews, L., Simpson, S. A., Craig, P., Baird, J., Blazeby, J. M., Boyd, K. A., Craig, N., French, D. P., McIntosh, E., Petticrew, M., Rycroft-Malone, J., White, M. and Moore, L. (2021) 'A new framework for developing and evaluating complex interventions: Update of Medical Research Council guidance', *The British Medical Journal,* 374, n2061.

Smith, G., Wagner, J., Andrews, J., Austin, J., Mueller, M., Carter, E. and Griesemer, K. (2014) 'Caregiving in pediatric epilepsy: Results of focus groups and implications for research and practice', *Epilepsy and Behavior*, 34(5), pp. 34–41.

Smith, V., Clarke, M., Williamson, P. and Gargon, E. (2015) 'Survey of new 2007 and 2011 Cochrane reviews found 37% of prespecified outcomes not reported', *Journal of Clinical Epidemiology*, 68(3), pp. 237–45.

Sondhi, V., Agarwala, A., Pandey, R. M., Chakrabarty, B., Jauhari, P., Lodha, R., Toteja, G. S., Sharma, S., Paul, V. K., Kossoff, E. and Gulati, S. (2020) 'Efficacy of ketogenic diet, modified Atkins diet, and low glycemic index therapy diet among children with drug-resistant epilepsy: a randomized clinical trial', *Journal of the Americal Medical Association Pediatrics*, 174(10), pp.944-951.

Sparrow, S., Cicchetti, D. and Balla, D. (2005) *Vineland adaptive behavior scale- II*. Circle Pines, MN: American Guidance Service.

Staniszewska, S., Brett, J., Mockford, C. and Barber, R. (2011). The GRIPP checklist: strengthening the quality of patient and public involvement reporting in research. *The International Journal of Technology Assessment in Health Care,* 27 (4), 391-399.

Staniszewska, S., Brett, J., Simera, I., Seers, K., Mockford, C., Goodlad, S., Altman, D. G., Moher, D., Barber, R., Denegri, S., Entwistle, A., Littlejohns, P., Morris, C., Suleman, R., Thomas, V. and Tysall, C. (2017). GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *British Medical Journal*, 358:j3453

Sveinsson, O., Andersson, T., Carlsson, S. and Tomson, T. (2017) 'The incidence of SUDEP: A nationwide population-based cohort study', *Neurology*, 89(2), pp. 170–177.

Symonds, J. D., Elliott, K. S., Shetty, J., Armstrong, M., Brunklaus, A., Cutcutache, I., Diver, L. A., Dorris, L., Gardiner, S., Jollands, A., Joss, S., Kirkpatrick, M., McLellan, A., MacLeod, S., O'Regan, M., Page, M., Pilley, E., Pilz, D. T., Stephen, E., Stewart, K., Ashrafian, H., Knight, J. C. and Zuberi, S. M. (2021) 'Early childhood epilepsies: Epidemiology, classification, aetiology, and socio-economic determinants', *Brain*, 144(9), pp. 2879–2891.

Talbot, F., Metcalf, K. and Moriarty, M. (1927) 'A clinical study of epileptic children treated by ketogenic diet', *Boston Medical and Surgical Journal*, 196(3), pp. 89–96.

Tangarorang, J., Leonard, H., Epstein, A. and Downs, J. (2019) 'A framework for understanding quality of life domains in individuals with the CDKL5 deficiency disorder', *American Journal of Medical Genetics, Part A*, 179(2), pp. 249–256.

Tebo, C. C., Evins, A. I., Christos, P. J., Kwon, J. and Schwartz, T. H. (2014) 'Evolution of cranial epilepsy surgery complication rates: A 32-year systematic review and meta-analysis: a review', *Journal of Neurosurgery*, 120(6), pp. 1415–27.

The Inchstone Project (2023) *The Instone Project results*. Available at: https://deepconnections.net/inchstone-project/inchstone-results/ (Accessed: 15 April 2023).

The NHS Health Research Authority (no date) *The NHS Health Research Authority online guidance for researchers and ethics committees on consent and how to prepare materials to support the process*. Available at: http://www.hra-decisiontools.org.uk/consent/ (Accessed: 3 March 2019).

Thiele, E. A., Marsh, E. D., French, J. A., Mazurkiewicz, M. B., Benbadis, S. R., Joshi, C., Lyons, P. D., Taylor, A., Roberts, C., Sommerville, K., Gunning, B., Gawlowicz, J., Lisewski, P., Mitosek Szewczyk, K., Steinborn, B., Zolnowska, M., Hughes, E., McLellan, A., Benbadis, S., Ciliberto, M., Clark, G., Dlugos, D., Filloux, F., Flamini, R., French, J., Frost, M., Haut, S., Joshi, C., Kapoor, S., Kessler, S., Laux, L., Lyons, P., Marsh, E., Moore, D., Morse, R., Nagaraddi, V., Rosenfeld, W., Seltzer, L., Shellhaas, R., Thiele, E., Thio, L. L., Wang, D. and Wilfong, A. (2018) 'Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial', *The Lancet*, 391(10125), pp. 1085–1096.

Thorne, S. (2008) *Interpretive Description*. Walnut Creek, CA: Left Coast Press.

Thorne, S., Kirkham, S. R. and O'Flynn-Magee, K. (2004) 'The Analytic Challenge in Interpretive Description', *International Journal of Qualitative*

Methods. SAGE Publications, 3(1), pp. 1–11.

Titre-Johnson, S., Schoeler, N., Eltze, C., Williams, R., Vezyroglou, K., McCullagh, H., Freemantle, N., Heales, S., Kneen, R., Marston, L., Martland, T., Nazareth, I., Neal, E., Lux, A., Parker, A., Agrawal, S., Fallon, P. and Cross, J. H. (2017) 'Ketogenic diet in the treatment of epilepsy in children under the age of 2 years: Study protocol for a randomised controlled trial', *Trials*, 18, 195).

Toffa, D. H., Touma, L., El Meskine, T., Bouthillier, A. and Nguyen, D. K. (2020) 'Learnings from 30 years of reported efficacy and safety of vagus nerve stimulation (VNS) for epilepsy treatment: A critical review', *Seizure*, 83, pp. 104–123.

Tong, A., Sainsbury, P. and Craig, J. (2007) 'Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups', *International Journal for Quality in Health Care*, 19(6), pp.349-357.

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., Lewin, S., Godfrey, C. M., Macdonald, M. T., Langlois, E. V, Soares-Weiser, K., Moriarty, J., Clifford, T., Tuncalp, O. and Straus, S. E. (2018) 'PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation', *Annals of Internal Medicine*, 169(7), pp. 467–473.

Tugwell, P., Boers, M., Brooks, P., Simon, L., Strand, V. and Idzerda, L. (2007) 'OMERACT: An international initiative to improve outcome measurement in rheumatology', *Trials*, 8, 38.

Turk, D. C., Dworkin, R. H., Allen, R. R., Bellamy, N., Brandenburg, N., Carr, D. B., Cleeland, C., Dionne, R., Farrar, J. T., Galer, B. S., Hewitt, D. J., Jadad, A. R., Katz, N. P., Kramer, L. D., Manning, D. C., McCormick, C. G., McDermott, M. P., McGrath, P., Quessy, S., Rappaport, B. A., Robinson, J. P., Royal, M. A., Simon, L., Stauffer, J. W., Stein, W., Tollett, J. and Witter, J. (2003) 'Core outcome domains for chronic pain clinical trials: IMMPACT recommendations', *Pain*, 106(3), pp. 24–30.

Uijl, S. G., Uiterwaal, C. S. M. P., Aldenkamp, A. P., Carpay, J. A., Doelman, J. C., Keizer, K., Vecht, C. J., de Krom, M. C. and van Donselaar, C. A. (2006) 'A cross-sectional study of subjective complaints in patients with epilepsy who seem to be well-controlled with anti-epileptic drugs', *Seizure*, 15(4), pp. 242–248.

UK Epilepsy Priority Setting Partnership (2022) *Top ten priorities*. Available at: https://epilepsyresearch.org.uk/uk-epilepsy-psp/.

Ünalp, A., Baysal, B. T., Sarıtaş, S., Güzin, Y., Edizer, S., Akışın, Z. and Yılmaz, Ü. (2021) 'Evaluation of the effects of ketogenic diet therapy on sleep quality in children with drug-resistant epilepsy and their mothers', *Epilepsy and Behavior*, 124, 108327.

Varni, J. W., Seid, M. and Rode, C. A. (1999) 'The PedsQL: measurement model for the pediatric quality of life inventory', *Medical Care*, 37(2), pp. 126–139.

Verrips, G. H., Vogels, A. G. C., Verloove-Vanhorick, S. P., Fekkes, M., Koopman, H. M., Kamphuis, R. P., Theunissen, N. C. M. and Wit, J. M. (1997) 'Health-related quality of life measure for children-the TACQOL+', *Journal of Applied Therapeutics*, 1(4), pp.357-360.

Vining, E. P. G., Freeman, J. M., Ballaban-Gil, K., Camfield, C. S., Camfield, P. R., Holmes, G. L., Shinnar, S., Shuman, R., Trevathan, E. and Wheless, J. W. (1998) 'A multicenter study of the efficacy of the ketogenic diet', *Archives of Neurology*, 55(11), pp. 1433–1437.

Vining, E. P., Pyzik, P., McGrogan, J., Hladky, H., Anand, A., Kriegler, S. and Freeman, J. M. (2002) 'Growth of children on the ketogenic diet', *Developmental Medicine & Child Neurology*, 44(12), pp. 796–802.

Wang, H. S. and Lin, K. L. (2013) 'Ketogenic diet: An early option for epilepsy treatment, instead of a last choice only', *Biomedical Journal*, 36, pp. 16–17.

Washington, A. E. and Lipstein, S. H. (2011) 'The Patient-Centered Outcomes Research Institute — Promoting Better Information, Decisions, and Health', *New England Journal of Medicine*, 365(15), pp. 436–445.

Al Wattar, B. H., Tamilselvan, K., Khan, R., Kelso, A., Sinha, A., Pirie, A. M., McCorry, D., Khan, K. S. and Thangaratinam, S. (2017) 'Development of a core outcome set for epilepsy in pregnancy (E-CORE): a national multi-stakeholder modified Delphi consensus study', *BJOG: An International Journal of Obstetrics and Gynaecology*, 124(4), pp. 661-667.

Webster, M. (2018) 'Siblings' caring roles in families with a child with epilepsy', *Sociology of Health and Illness*, 40(1), pp. 204–217.

Webster, M. (2019a) 'The cycle of uncertainty: parents' experiences of childhood epilepsy', *Sociology of Health and Illness*. 41(2), pp. 205–218.

Webster, M. (2019b) 'When intesive mothering becomes a necessity', in Harman, V., Cappellini, B., and Faircloth, C. (eds) *Feeding Children Inside and*

Outside the Home. London: Routledge, pp. 191–206.

Webster, M. and Gabe, J. (2016) 'Diet and identity: being a good parent in the face of contradictions presented by the ketogenic diet', *Sociology of Health and Illness*, 38(1), pp. 123–136.

Whiteley, V. J., Martin-McGill, K. J., Carroll, J. H., Taylor, H. and Schoeler, N. E. (2020) 'Nice to know: impact of NICE guidelines on ketogenic diet services nationwide', *Journal of Human Nutrition and Dietetics*, 33(1), pp. 98–105.

Wijnen, B. F. M., de Kinderen, R. J. A., Lambrechts, D. A. J. E., Postulart, D., Aldenkamp, A. P., Majoie, M. H. J. M. and Evers, S. M. A. A. (2017) 'Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy', *Epilepsy Research*, 132, pp. 91–99.

Wilder, R. M. (1921) 'The effects of ketonemia on the course of epilepsy', *Mayo Clinical Bulletin*, 2, 308.

Wille, N., Badia, X., Bonsel, G., Burstrom, K., Cavrini, G., Devlin, N., Egmar, A. C., Greiner, W., Gusi, N., Herdman, M., Jelsma, J., Kind, P., Scalone, L. and Ravens-Sieberer, U. (2010) 'Development of the EQ-5D-Y: a child-friendly version of the EQ-5D', *Quality of Life Research*, 19(6), pp. 875–886.

Williams, E., Abrahams, J., Maguire, A. and Harris, G. (2012) 'A parent's perspective on dietary treatments for epilepsy', *Epilepsy Research*. 100(3), pp. 338–343.

Williamson, P., Altman, D. G., Blazeby, J., Clarke, M. and Gargon, E. (2012a) 'Driving up the quality and relevance of research through the use of agreed core outcomes', *Journal of Health Services Research and Policy*, 17(1), pp. 1–2.

Williamson, PR., Altman, D. G., Blazeby, J. M., Clarke, M., Devane, D., Gargon, E. and Tugwell, P. (2012b) 'Developing core outcome sets for clinical trials: Issues to consider', *Trials*, 13, 132.

Williamson, P. R., Altman, D. G., Bagley, H., Barnes, K. L., Blazeby, J. M., Brookes, S. T., Clarke, M., Gargon, E., Gorst, S., Harman, N., Kirkham, J. J., McNair, A., Prinsen, C. A. C., Schmitt, J., Terwee, C. B. and Young, B. (2017) 'The COMET Handbook: version 1.0', *Trials*, 18, 280.

Winsor, A. A., Richards, C., Bissell, S., Seri, S., Liew, A. and Bagshaw, A. P. (2021) 'Sleep disruption in children and adolescents with epilepsy: A systematic review and meta-analysis', *Sleep Medicine Reviews*, 57,101416.

Wirrell, E., Wong-Kisiel, L., Mandrekar, J. and Nickels, K. (2012) 'Predictors and course of medically intractable epilepsy in young children presenting before 36 months of age: A retrospective, population-based study', *Epilepsia*, 53(9), pp. 1563–1569.

Woodgate, R. L., Edwards, M., Ripat, J. D., Borton, B. and Rempel, G. (2015) 'Intense parenting: A qualitative study detailing the experiences of parenting children with complex care needs', *BMC Pediatrics*, 15, 197.

World Health Organisation (2007) *Position Paper. Paediatric age categories to be used in differentiating between listing on a model essential medicines list for children*.

World Health Organization (1998) *WHOQOL user manual.* Geneva, Switzerland.

World Health Organization (2001) *International classification of functioning, disability and health.* Geneva, Switzerland.

Wu, Q., Wang, H., Fan, Y. Y., Zhang, J. M., Liu, X. Y., Fang, X. Y., Yang, F. H., Cao, Q. J. and Qi, Y. (2018) 'Ketogenic diet effects on 52 children with pharmacoresistant epileptic encephalopathy: A clinical prospective study', *Brain and Behavior*, 8(5), pp. 1–8.

Wylde, V., Mackichan, F., Bruce, J. and Gooberman-Hill, R. (2015) 'Assessment of chronic post-surgical pain after knee replacement: Development of a core outcome set', *European Journal of Pain*, 19(5), pp. 611–620.

Yardley, L. (2000) 'Dilemmas in qualitative health research', *Psychology and Health*. Routledge, 15(2), pp. 215–228.

Youn, S. E., Park, S., Kim, S. H., Lee, J. S., Kim, H. D. and Kang, H. C. (2020) 'Long-term outcomes of ketogenic diet in patients with tuberous sclerosis complex-derived epilepsy', *Epilepsy Research*, 164, 106348.

Young, B. and Bagley, H. (2016) 'Including patients in core outcome set development: Issues to consider based on three workshops with around 100 international delegates', *Research Involvement and Engagement*, 2, 25.

Appendix A. Paper 1: Scoping review protocol
Accepted Manuscript *(Carroll et al., 2019)*

Outcome measurement and reporting in childhood epilepsy treated with ketogenic diet therapy: a scoping review protocol

Authors

Jennifer Carroll[1] Kirsty Martin-McGill [2] Helen Cross[3] Mary Hickson[1] Avril Collinson[1]

1. The University of Plymouth Centre for Innovations in Health and Social Care: A Joanna Briggs Institute Centre of Excellence, Institute of Health and Community, Plymouth, Devon, UK

2. The Walton Centre NHS Foundation Trust, University of Liverpool, Lower Lane, Liverpool, UK

5. Clinical Neurosciences, UCL-Institute of Child Health, 30 Guilford St. London, UK

Correspondence: Jennifer Carroll, jennifer.carroll@plymouth.ac.uk

Acknowledgements

This review will contribute to a Doctor of Philosophy degree for the lead author.

With thanks to Dr Elizabeth Neal RD: Expert in field. Matthews Friends Charity and Clinics, Lingfield, UK.

Title

Outcome measurement and reporting in childhood epilepsy treated with ketogenic diet therapy: a scoping review protocol

Introduction

Epilepsy is a condition where individuals are prone to recurrent epileptic seizures. This may result from a number of different causes, although initial treatment will remain consistently antiepileptic medications. Although two thirds will respond or enter spontaneous remission, up to one third of children with epilepsy will be refractory to standard antiepileptic medication.[1] The International League Against Epilepsy (ILAE) describe refractory epilepsy as failure to achieve sustained seizure freedom with two appropriate and tolerated anti-epileptic drugs.[2] When resective epilepsy surgery is not feasible, other non-pharmacological treatments including ketogenic diet therapy are considered.[3] The ketogenic diet (KD) is a high fat, restricted carbohydrate regimen that has been used as a treatment for refractory epilepsy since its first reported use in 1921.[4] There are many types of KD in use with varying degrees of dietary restriction. The classical KD is based on a ratio of fat to carbohydrate, usually 3:1 or 4:1.[5] Long chain triglycerides are the predominant fat source, carbohydrate is heavily restricted and protein is limited to that required for growth. The medium chain triglyceride (MCT) KD [6] allows a slightly higher carbohydrate and protein intake than classical KD as medium chain triglyceride fat is absorbed and transported more efficiently than long chain triglyceride fat with greater ketone production per unit of dietary energy.[7] In addition to the traditional ketogenic diets, modified versions are frequently used and include the modified Atkins diet,[8] modified ketogenic diet used in the UK with similar principles to modified Atkins Diet and finally the low glycaemic index treatment.[9] These modified versions take a less restrictive approach than the more traditional classical and MCT KDs but the principles of high fat and low carbohydrate remain and require significant dietary adjustment for the child.

Ketogenic diet therapy is a well-established treatment for refractory epilepsy with more than 50% of treated children achieving greater than 50% seizure reduction in retrospective and prospective observational studies.[10-13] Three key randomised controlled trials (RCTs) assessing the efficacy of KD have been published: Neal et al.[5] using the classical and MCT KD, Sharma et al.[14] the modified Atkins diet and Lambrechts et al.[15] the MCT KD. In all three studies, significantly more children treated with KDT experienced seizure reduction of at least 50% than those in the care as usual (CAU) control group; (38% KD vs 6% CAU),[5] (52% KD vs 11.5% CAU)[14] and (50% KD vs 18% CAU).[15] Neal et al.[5] demonstrated that the classical and MCT diet were comparable in efficacy and tolerability.

Typically, seizure reduction or seizure freedom are the primary outcomes of choice with attrition, tolerability and adverse effects often considered secondary outcomes. A more holistic approach might also consider health related quality of life outcomes such as reduced

hospitalisation,[16] reduced medication load and cost[17] and improved behaviour and cognition.[18] In a recent Cochrane review[19] authors concluded that there are no published RCTs which examine the effect of KD on cognition and quality of life. They suggest that a validated tool be used in future trials. Standardised and validated tools such as the PedsQol,[20] Child Health questionnaire (CHQ)[21] and the epilepsy specific Quality of Life in Childhood Epilepsy Questionnaire (QOLCE)[22] aim to assess the impact of chronic disease on childhood quality of life. However, shortcomings and challenges exist when applying these tools to populations with disability. In clinical practice, ketogenic teams try to address these shortcomings by developing alternative questionnaires tailored for parents or caregivers of children with chronic epilepsy.[23]

There is no general consensus on which outcomes should be reported in clinical trials for most clinical areas including childhood epilepsy treated with KD therapy. Reaching consensus on a core set of outcomes would reduce outcome reporting bias, drive up quality and relevance of research, improve reporting consistency, and support meta-analysis leading to better informed healthcare decisions.[24] The authors have chosen to conduct a scoping review to provide a descriptive overview of the outcomes currently measured and reported in childhood epilepsy. Prior to developing the present review protocol, preliminary searches were undertaken to identify any existing scoping or systematic reviews published or underway on a similar or identical topic. The Joanna Briggs Institute (JBI) Database of Systematic Reviews and Implementation Reports, PROSPERO, Cochrane Database of Systematic Reviews, CINAHL and PubMed were searched and no relevant reviews located. This proposed scoping review will follow the approach recommended by the JBI.[25-26] The scoping review methodology was chosen for its suitability for addressing the proposed aim; namely to identify a comprehensive list of outcomes measured and reported in childhood epilepsy treated with KD therapy. Furthermore, the definitions of outcomes will be explored, the tools or methods employed to measure the outcome, the time to measurement of the outcome after KD therapy commenced and finally the reporting of the outcomes. Collating and mapping this information will inform the process of developing a core outcome set for use in clinical practice and future research trials, using methodology recommended by the Core Outcome Measures in Effective Trials (COMET) Initiative.[24]

Review Question

The objective of this scoping review is to investigate the outcomes measured and reported in trials of children with refractory epilepsy treated with ketogenic diet therapy. The scoping review will aim to list the outcomes and map the associated components including, intervention (type of KD therapy), definition (if used) of the outcome, the tool or indicators used to measure the outcome, validity of tool used, the time to measurement of the outcome after the intervention commenced and the reporting of the outcome.

Specifically, the review question is: What outcomes are measured and reported in studies of childhood epilepsy treated with ketogenic diet therapy?

Keywords

Childhood; core outcome set; epilepsy; ketogenic diet; outcomes

Inclusion Criteria

Participants

The scoping review will consider studies that include male and female children with epilepsy aged 18 years or below treated with KD therapy for at least 1 month. Studies undertaken with adults will be excluded. Children treated with KD therapy for diagnosis' other than childhood epilepsy will be excluded (for example; neuro-oncology and metabolic disorders).

Concept

This review will consider the outcomes measured and reported in studies that assess the use of ketogenic diet therapy to treat childhood epilepsy. The following components will be investigated; intervention (type of KD therapy), outcomes, definition (if used) of the outcome, the tool or indicators used to measure the outcome, validity of tool used, the time to measurement of the outcome after the intervention commenced and the reporting of the outcome. Participants may be treated with other medical therapies including but not limited to anti-epileptic medications or surgery in conjunction with KD therapy.

Context

The context of this review will be settings with paediatric patients undertaking KD therapy for refractory epilepsy.

Types of Sources

This scoping review will consider both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. There are only 7 randomised controlled trials [19] examining KD therapy so analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies will be considered for inclusion. In 2008, the first RCT assessing the effectiveness of KD for childhood epilepsy was published [5] and the first internationally agreed guidelines on the management of children treated with KD therapy [3.] Two key publications that would guide subsequent research and the clinical management of children treated with KD. Therefore, studies published from 2008 onwards will be included. Inclusion of a variety of study designs will ensure a large number of relevant studies will be reviewed, in which repetition of measured and reported outcomes is

expected. Studies published in English will be included. Studies published in the last 10 years (2008 to present) will be included as the wide scoping nature of this review is likely to identify a large number of studies for inclusion within which repetition of measured and reported outcomes is expected. Systematic reviews will be excluded at the title and abstract screening phase. However, the reference lists will be reviewed to ensure all primary studies have been identified in the searches. The reference list of all studies selected for inclusion will be screened for additional studies.

Methods

The proposed systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews.[25]

Search Strategy

The search strategy will aim to find both published and unpublished studies. An initial limited search of PubMed and CINAHL was undertaken, followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe articles. This informed the development of a search strategy tailored for each information source. A full search strategy for PubMed is detailed in Appendix I.

Information Sources

The databases to be searched will include: Cochrane Database of Systematic Reviews, Cochrane CENTRAL, CINAHL, PubMed, Scopus, Embase, AMED and The Joanna Briggs Institute (JBI) Database of Systematic reviews and Implementation Reports. The trial registers to be searched will include: International Standard Randomised Controlled Trials Number (ISRCTN) Registry and ClinicalTrials.gov. The search for unpublished studies will include: the British Library e-these online services (EThOS) database, OAIster and OpenGrey (System for Information on Grey Literature in Europe SIGLE). An expert in the field will be consulted to ensure no studies are missed.

Study Selection

Following the search, all identified citations will be collated and uploaded into EndNote V8 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. The reference list of systematic reviews will be reviewed to ensure all primary studies have been identified in the searches. The reference list of all studies selected for inclusion will be screened for additional studies.

Studies that meet the inclusion criteria will be retrieved in full and their details imported into JBI SUMARI. The full text of selected studies will be retrieved and assessed in detail against the inclusion criteria. Only those that can be retrieved in full will be included. Authors will be contacted to request full text access where necessary. Study protocols will be requested from authors of included studies to compare outcomes of interest. Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final scoping review report. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram.

Data Extraction

Data will be extracted from papers included in the review using the standardised data extraction tool available in JBI SUMARI by two independent reviewers (JC & KMM). As a minimum the following data will be extracted; study type, author details, journal of publication and year, participant characteristics, intervention (type of KDT), each outcome reported, definition (if used) of outcome, the tool or indicators used to measure the outcome, validity of tool used, the time to measurement of the outcome after the intervention commenced and the reporting of the outcome. A draft data extraction tool is provided (Appendix II). This will be modified and revised as necessary during the process of extracting data from each included study. Modifications will be detailed in the full scoping review report. Any disagreements that arise between the reviewers (JC & KMM) will be resolved through discussion or with a third reviewer (HC). Authors of papers will be contacted to request missing or additional data where required.

Data Presentation

The extracted data will be presented in a diagrammatic or tabular form in a manner that is most relevant to the objective and questions of this scoping review. The tables and charts will report on the outcomes measured and reported by researchers, the definitions used to describe these outcomes and the method of measurement. A narrative summary will accompany the tabulated and/or charted results and will describe how the results relate to the reviews objective and questions. This scoping review is phase one of a larger project in which the overall aim is to develop a core outcome set for refractory childhood epilepsy treated with KD therapy. The study will identify the outcomes to be measured in clinical effectiveness trials but will also guide audit or service evaluation in clinical practice. Parents, health care professionals, researchers and relevant charities will be consulted to ensure the final core outcome set reflects the interests of all and facilitates future decision making. The study is registered as 1116 on the COMET database of core outcome set studies. (http://www.comet-initiative.org/studies/details/1116)

Funding

Supported by The University of Plymouth

Conflicts of Interest

KMM receives a PhD studentship from Vitaflo (International) Ltd. JC, HC, MH and AC declare no conflict of interest.

References

1. Krauss GL and Sperling MR. Treating patients with medically resistant epilepsy. Neurol Clin Pract 2011;1(1):14–23.

2. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51: 1069-1077.

3. Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Bergvist AG, Blackford R, et al. Optimal Clinical Management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. Epilepsia 2009;50(2):304-17.

4. Wilder RM. The effects of ketonemia on the course of epilepsy. May CLin Proc 1921;2:307-08.

5. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7:500-506.

6. Huttenlocher PR, Wilbourn AJ, Signore JM. Medium-chain triglycerides as a therapy for intractable child epilepsy. Neurology 1971;21:1097–1103.

7. Schön von H, Lippach I, Gelpke W. Metabolic studies with a mixed glyceride of medium-chain fatty acids. 2. Changes in the ketone body content of blood and urine after administration of the mixed glyceride. Gastroenterologia 1959;91:199–213.

8. Kossoff EH, Cervenka MC, Henry BJ, Haney CA, Turner Z. A decade of the modified Atkins diet (2003–2013): Results, insights, and future directions. Epilepsy Behav 2013;9:437-442.

9. Pfeifer HH & Thiele EA. Low-glycemic index treatment: A liberalized ketogenic diet for treatment of intractable epilepsy. Neurology 2005;65:1810-1812.

10. Freeman JM, Vining EP, Kossoff EH, Pyzik PL, Ye X, Goodman SE. A blinded, crossover study of the efficacy of the ketogenic diet. Epilepsia 2009;50:322-325.

11. Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM. The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. Pediatrics 1998;102:1358-1363

12. Keene DL. A systematic review of the use of the ketogenic diet in childhood epilepsy. Pediatr Neurol. 2006;35:1-5.

13. Lefevre F, Aronson N. Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy. Pediatrics. 2000;105:E46.

14. Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: A randomized controlled trial. Epilepsia 2013;54(3):481-486.

15. Lambrechts DAJE, de Kinderen RJA, Vles JSH, de Louw AJA, Aldenkamp AP, MAjoie HJM. A randomised controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scan 2017;135:231-239.

16. Joshi M, Kearns J, Wilford E, Hussain N, Khan A. Effectiveness of ketogenic diet to reduce seizure related acute paediatric admission in children with Epilepsy. Dev Med Child Neurol 2016;58(S1):64.

17. Gilbert DL, Pyzik PL, Vining EP, Freeman JM. Medication Cost Reduction in Children on the Ketogenic Diet: Data From a Prospective Study. J Child Neurol 1999; 14(7):469-471.

18. Hallböök T, Ji S, Maudsley S, Martin B. The effects of the ketogenic diet on behavior and cognition. Epilepsy Res 2012;100(3):304-309.

19. Martin K, Jackson CF, Levy RG, Cooper PN. Ketogenic diet and other dietary treatments for Epilepsy. Cochrane Database Sys Rev 2016, Issue 2. Art.No.:CD001903

20. Varni JW, Limbers CA. The Pediatric Quality of Life Inventory: measuring pediatric health-related quality of life from the perspective of children and their parents. Pediatr Clin N Am 2009;56:843–63.

21. Landgraf JM, Ware JE, The CHQ. User's Manual. First Edition. Boston MA: The Health Institute. New England Medical Centre; 1999.

22. Sabaz M, Cairns DR, Lawson JA, Nheu N, Bleasel AF, Bye AM. Validation of a new quality of life measure for children with epilepsy. Epilepsia 2000;41(6):765–74.

23. Bruce S, Devlin A, Air L, Cook L. Changes in quality of life as a result of ketogenic diet therapy: A new approach to assessment with the potential for positive therapeutic effects. Epilepsy Behav 1017;66:100-104.

24. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, Clarke M, Gargon E, Gorst S, Harman N, Kirkham JJ, McNair A, Prinsen CAC, Schmitt J, Terwee CB, Young B. The Comet Handbook: version 1.0. Trials, 2017;18(3):1.

25. Peters MDJ, Godfrey CM, McInerney, Khalil H, Parker D, and Baldini Soares C. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc. 2015;13(3):141 - 146.

26. Khalil H, Peters M, Godfrey CM, Mcinerney P, Parker D, Baldini Soares C. An evidence based approach to scoping reviews. Worldviews Evid Based Nurs 2016;13(2)118-223.

Appendices

Appendix I: 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 p*ediatric [tiab] OR child [tiab] Or infant [tiab] OR adolescen* [tiab] OR teen [tiab]

Limits: 10 years. Search returned 461 records

Appendix II: Data Extraction Form

Author	Journal	Country	Year	Study design	# of subjects	Attrition	Duration	Age range	Primary epilepsy related diagnosis	Type of KD	Outcome	Definition of outcome	Is this stated to be the primary outcome?	Is this stated to be a secondary outcome?	Outcome not stated a priori	Responder (parent or clinician)	Measurement tool

Continued

Validity of measurement tool	Time points at which outcome measured	Protocol obtained?	Outcome reported in results	Outcomes stated in protocol reported in paper?	General Comments

Carroll *et al. Trials* (2022) 23:675
https://doi.org/10.1186/s13063-022-06629-7

Trials

STUDY PROTOCOL Open Access

The CORE-KDT study: a mixed methods protocol to establish core outcomes for refractory childhood epilepsy treated with ketogenic diet therapy

Jennifer H. Carroll[1], J. Helen Cross[2*], Mary Hickson[1], Emma Williams[3], Valerie Aldridge[3] and Avril Collinson[1]

Abstract

Background: A core outcome set defines the minimum outcomes that should be included in clinical trials, audit or practice. The aim being to increase the quality and relevance of research by ensuring consistency in the measurement and reporting of outcomes. Core outcome sets have been developed for a variety of disease states and treatments. However, there is no established set of core outcomes for refractory childhood epilepsy treated with ketogenic diet therapy. This should be developed using a patient-centred approach to ensure the outcomes measured are relevant to patients and clinical practice.

Methods: This is a mixed methods study of four phases to develop a core outcome set for refractory childhood epilepsy treated with ketogenic diet therapy. In phase 1, a systematic scoping review of the literature will establish which outcomes are measured in trials of refractory epilepsy treated with ketogenic diet therapy. In phase 2, qualitative interviews with parents and carers will aim to identify the outcomes of importance to these stakeholders. Phase 3 will see a comprehensive list of outcomes collated from the first two phases, grouped into domains according to an outcome taxonomy. Phase 4 will invite parents, health care professionals and researchers to participate in a two-round Delphi study to rate the importance of the presented outcomes. Following which, the core outcome set will be ratified at a face to face consensus meeting.

Discussion: This study will guide outcome measurement in future studies of childhood epilepsy treated with ketogenic diet therapy and clinical practice through audit and service evaluation.

Keywords: Core outcome set, Delphi survey, Epilepsy, Ketogenic diet, Outcomes, Paediatric, Systematic scoping review, Semi-structured interview, Consensus method

Background

Epilepsy is a common neurological disorder where up to one third of children become drug resistant or refractory [1], experiencing regular debilitating seizures, despite treatment with multiple antiepileptic medications. When medication fails to control seizure activity, non-pharmacological treatments such as ketogenic diet (KD) therapy are considered.

The KD is a very low carbohydrate and high fat regimen, used to treat refractory epilepsy since the 1920s [2]. It mimics a starvation state whereby the bodies main energy source switches from that of glucose to ketones produced through lipolysis of high levels of dietary fat. KD therapy is a well-established treatment for refractory

*Correspondence: H.cross@ucl.ac.uk

[2] UCL Developmental Neurosciences, UCL - NIHR BRC Great Ormond Street Institute of Child Health, London, UK
Full list of author information is available at the end of the article

epilepsy with a growing number of randomised controlled trials demonstrating efficacy [3–10]. Yet the exact anticonvulsant mechanism is not clear [11]. When treating epilepsy, National Institute for Health and Care Excellence (NICE) guidance suggests seizure freedom as a primary outcome and secondary outcomes should include seizure reduction, quality of life and cognitive function [12]. Yet in published clinical effectiveness trials, seizure reduction and/or freedom are typically the primary outcomes with side effects of treatment often assessed as secondary outcomes [13]. Less frequently considered are health-related quality of life outcomes such as reduced hospitalisation [14], medication load and cost [15], improved behaviour and cognition [16, 17].

KD therapy is a resource-intensive treatment requiring regular input and monitoring from a team of specialists, including a ketogenic dietitian and paediatric neurologist. For the family, it is often a labour-intensive regimen that requires significant dietary adjustment for the child. Whilst more recently developed KDs offer improved palatability and reduced potential for adverse side effects, adherence to the dietary regimen may not always be easy. When successful it can have a significant impact on functioning and quality of life [16] for the child and wider family, yet such outcomes are inconsistently measured and reported between trials. The development of a core outcome set is one method proposed to address these problems.

A core outcome set defines the minimum outcomes that should be consistently measured and reported in future clinical trials in a specific area of healthcare [18]. A core outcome set would reduce outcome reporting bias, drive up quality and relevance of research, improve reporting consistency and support meta-analysis leading to better informed healthcare decision making [19]. It would also serve to guide outcome assessment in clinical practice through audit and service evaluation. Successful examples of core outcome sets include Outcome Measures in Rheumatology (OMERACT) [20]; the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) [21]; and Harmonising Outcome Measures in Eczema (HOME) [22].

The most recent Cochrane review [23] concluded that a core outcome set would help to improve consistency in outcomes for drug resistant epilepsy treated with ketogenic diet. Core outcome sets are developed using consensus methods in partnership with major stakeholders, including experts in the clinical area, patients and parents where appropriate [18]. This patient-centred approach will ensure outcomes are clinically relevant and reflect the views of parents and carers. Previous studies have examined parental expectations [24, 25] and attitudes [26] towards KD therapy via questionnaires, but no attempts have been made to establish parental opinion on outcomes of importance.

Aims and objectives

Aim

The overall aim of this project is to develop a core outcome set for refractory childhood epilepsy treated with KD therapy. The study will identify the outcomes to be measured in clinical effectiveness trials but will also guide audit or service evaluation in clinical practice. Parents[1], health care professionals, researchers, relevant charities and industry will be consulted to ensure the final core outcome set reflects the interests of all and facilitates future decision making.

Objectives

The key objectives are as follows: (1) to identify a list of outcomes from published studies using KD therapy to treat childhood epilepsy, (2) to identify the tools or methods used to measure the reported outcomes, (3) to determine a list of potentially important outcomes to parents of a child with epilepsy treated with KD therapy and (4) to collate the outcomes identified in (1) and (3) and reach consensus on a core outcome set from the perspective of parents and healthcare professionals.

Methods

The study is registered with The Core Outcome Measures in Effectiveness Trials (COMET) Initiative (#1116) [27] and will follow its procedures and guidance [18]. Ethical approval was granted by the National Health Service (NHS) Health Research Authority (London-Surrey Research Ethics Committee, reference 19/LO/1680). Written informed consent will be gathered from participants. The study will be divided into four distinct phases. Phase 1 will identify a list of all possible relevant outcomes and the tools used to measure these, via a systematic scoping review of studies involving children with epilepsy treated with KD therapy. Phase 2 will undertake semi-structured interviews with up to 20 parents who have a child with epilepsy treated with KD therapy, in order to identify potential additional outcomes important to them. Phase 3 will define outcome domains into which outcomes, identified in the scoping review and qualitative interviews, will be grouped according to the COMET taxonomy [28]. Phase 4 will prioritise the most important outcomes from two stakeholder groups via a two-arm anonymous remote Delphi survey. Stakeholder group 1 will include health professionals and researchers

[1] The term 'parent' will be used throughout and includes carers and legal guardians.

and group 2 will include parents. Few children would have the understanding or capacity to participate in this study so the researchers have elected to interview parents only. The findings of this work will be integrated into a core outcome set at a consensus group meeting with representation from both stakeholder groups.

Public involvement

The importance of involving families in research is well documented [29, 30]. From the outset, we have recognised the value and importance of parents and carers as stakeholders and worked closely with our lay research partners (EW and VA) 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 with recruitment supported by Young Epilepsy, a charity for children and young people with epilepsy, and Matthew's Friends. Two parents with children with epilepsy on KD therapy were interviewed. They felt this study of outcomes was worthwhile research and welcomed the inclusion of parents as participants in each phase. The findings informed the design of the semi-structured interview schedule for use in phase 2 and highlighted that the main considerations when undertaking interviews with parents are likely to be time and competing demands. It was felt parents are more likely to choose a telephone or video call for ease and convenience instead of a face-to-face meeting.

A study advisory group will be convened involving both health professionals and parents of children with epilepsy. Representatives from relevant UK charities will be consulted (Young Epilepsy and Matthew's Friends), the latter playing a particular role in supporting families to undertake KD therapy. This group will provide oversight for the study and review key documentation such as, but not limited to, participant information and the semi-structured interview script. In addition, they will participate in the phase 3 consultation process to ratify the list of outcomes arising from phases 1 and 2 and associated lay descriptors in preparation for the 2-round Delphi study.

Phase 1: Systematic scoping review of outcomes measured and reported for childhood epilepsy treated with ketogenic diet therapy

Research question: what outcomes are measured and reported in studies of childhood epilepsy treated with ketogenic diet therapy?

Search strategy

The proposed scoping review is registered on the Joanna Briggs Institute Systematic Review Register [31] and the detailed protocol agreed a priori and published [32]. In summary, the proposed review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [33]. An initial limited search of CINAHL and PubMed will be undertaken to identify key search terms and inform the development of a tailored search strategy for each information source. The extensive search strategy will aim to identify both published and unpublished studies. Reference lists of systematic reviews will be reviewed to ensure all primary studies have been identified. Reference lists of included full-text articles will be hand searched for additional studies. CINAHL, MEDLINE, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, Embase, AMED, Scopus and Joanna Briggs Institute Evidence Synthesis will be searched. Trial registers including ClinicalTrials.gov and International Standard Randomised Controlled Trials Number (ISRCTN) Registry will be checked. Unpublished grey literature will sought via OpenGrey (System for Information on Grey Literature in Europe SIGLE) OAIster and British Library e-theses (EThOS). Search results will be catalogued in Endnote V8 (Clarivate Analytics, PA, USA) reference manager.

Types of studies

There are a limited number of randomised controlled trials examining KD therapy so clinical trials and observational studies published in English will be included. Searches will be undertaken over a 10 year period, as the wide scoping nature of this review is likely to identify a large number of studies for inclusion within which repetition of measured and reported outcomes is expected. The potential for omission of outcomes of importance will be ameliorated by offering participants the opportunity to identify other outcomes of importance in the semi-structured qualitative interviews (parents) and Delphi study (parents, health professionals and researchers).

Type of intervention

A single intervention: KD therapy is under investigation. Ketogenic diets are high fat, very low carbohydrate and adequate protein diets. KD therapy encompasses all types of ketogenic diet used in clinical trials and practice namely, classical KD, medium chain triglyceride (MCT) KD, the Modified Atkins diet, modified ketogenic diet therapy and low glycaemic index treatment. Participants may be treated with other medical therapies or surgery in conjunction with KD therapy.

Types of participants

Studies of male or female children under the age of 18 years old with refractory epilepsy treated with KD therapy for at least 1 month.

Exclusion criteria

Studies of children treated with KD therapy for a diagnosis other than epilepsy (for example metabolic disease and neuro-oncology) and studies of adult participants.

Eligibility of studies

Two reviewers (JC and a researcher with significant experience in systematic review methods) will independently assess the title and abstracts returned from searches to assess whether the papers meet the inclusion criteria. Where it is unclear from the abstract then the full text will be retrieved and assessed. Authors will be contacted to request full-text access where necessary. Full-text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion stated. If agreement regarding eligibility cannot be reached, a third reviewer within the research team will be consulted. Study protocols will be requested from authors of included studies to compare reporting of outcomes in study protocol with those reported in the final publication.

Data extraction

Data will be extracted by one reviewer from the full text of original studies using a pre-defined and piloted spreadsheet. A second reviewer will independently extract data from 10% of included studies, chosen at random, to check for consistency. As a minimum, the following data will be extracted; journal of publication and year, study type, author details, participant characteristics, intervention (variant of KD), outcomes reported, definition of outcome, the tool or indicators used to measure the outcome, the validity of assessment tools used and the frequency of outcome measurement.

Data analysis and presentation

The scoping review protocol and subsequent report will follow the PRISMA-ScR process [33]. A PRISMA [34] flowchart will outline the stages of the systematic search. The extracted data will be presented using tables and figures to best meet the objectives of the scoping review. A narrative summary will follow with discussion of the key findings. The final list of identified outcomes will be used in phase 3 of this study.

Phase 2: Semi-structured interviews with parents of a child with epilepsy treated with ketogenic diet therapy

Research question: What outcomes do parents regard as potentially important when undertaking ketogenic diet therapy for the treatment of refractory childhood epilepsy?

Overview and method

The objective of this qualitative description study is to establish which outcomes are valued by parents and carers. It is recommended that patients and the public be consulted when developing a core outcome set, preserving the perspective of these stakeholders and improving the accessibility of the later consensus process for participants [18, 35]. Parent proxy reporting is an accepted approach when the child is unable to respond independently, for example, due to age, cognitive impairment or illness [36]. Few children would have the understanding or capacity to participate in this study so the researchers have elected to interview parents only. Data generated through qualitative research is accepted to be contextually rich and meaningful, enabling an in-depth exploration of issues that cannot be achieved through quantitative methods alone [37]. Interestingly, core outcome set studies which sought patient or public opinion highlighted further outcomes of importance that were not previously identified through systematic review of published studies [38–40]. Stratified purposeful sampling will be used to assess a range of perspectives on the topic under investigation. A sampling frame will be used to monitor the clinical and socio-demographic characteristics of participants to ensure diversity in terms of the following characteristics: age of child, diagnosis, type of KD, duration of treatment with KD therapy and response to treatment. Parental experiences of a recently diagnosed infant who has just commenced KD therapy will likely differ from those whose adolescent child is diagnosed many years and stable on KD therapy. It is plausible that these differing experiences may influence the identification and perceived importance of outcomes. Therefore, a range of ages will be included from infant (0–2 years), young child (2–6 years), child (6–12 years) to adolescent (12–18 years) [41], within which there is expected to be variety in the duration of treatment and response to KD therapy. This will be broadly defined as recently commenced KD therapy ($\leq$ 3 months of treatment with KD therapy), established on KD therapy (4 months or longer) or weaned from KD therapy (in the previous 12 months). The sampling frame will be assessed iteratively as recruitment proceeds and advertising materials refocussed to seek under-represented groups if necessary. We aim to recruit 20 parents, although this may change depending on early analyses. Other notable studies [42, 43] reached saturation at between 15 and 16 participants where no new outcomes were being identified and further interviews would provide no new additional insights [37]. A semi-structured interview script will be prepared and

piloted with lay patient research partners. All interviews will be audio recorded and conducted by the primary researcher (JC).

Participants

Parent participants will be invited through clinical partners at NHS Trusts, relevant UK charities (Matthew's Friends, Young Epilepsy and Epilepsy Action), and 'Epilepsy – The Ketogenic Way' Facebook group. International participants will be reached via the aforementioned charities and Facebook group. Participants can register their interest on our study webpage [44] and access participant information regarding the details of the study. Informed written consent will be sought prior to the interview.

Inclusion criteria

Parents of a child aged 0–18 years with refractory epilepsy who is currently being treated with KD therapy or has weaned from KD in the past year and is able to participate in an interview in the English language.

Exclusion criteria

Parents of a child being treated with KD therapy for a condition other than epilepsy (for example metabolic disease and neuro-oncology). Parents of a child previously treated with KD therapy but who weaned from the diet over 1 year ago. Inability to understand the English language.

Interview format and data collection

Interviews will be undertaken by JC, a registered dietitian and researcher with approximately 12 years' experience with KD therapy. A semi-structured interview format will be used. A conversational style of interviewing using open questions will encourage a naturalistic account of parent's experiences and perspectives on topics such as epilepsy diagnosis, treatment with KD and the effect of these on their child and family (semi-structured interview schedule available in the Table 2 in Appendix). Outcomes will be identified by asking participants to identify in their opinion, the important outcomes for children with epilepsy treated with KD therapy. Participants who list multiple outcomes will be asked to prioritise, to help us to understand the outcomes they value most. Alone, this approach might result in a narrow view on outcomes, identifying only those outcomes that parents understand to be results or outcomes. To mitigate this, outcomes will also be identified indirectly via a content analysis of the full interview transcripts. Together, this will enable all possible outcomes to be identified.

Interviews with UK participants will be undertaken in a convenient location such as the family home, video or audio call. Interviews with international participants will be undertaken via video or audio call. There is a possibility that this method may reduce rapport and recognition of non-verbal cues [45] but others [46] argue it is comparable to in person face to face interviews. Despite these potential challenges, video conferencing technology enables the inclusion of otherwise inaccessible international participants to this study. Written consent will be taken prior to the interviews and participants were reminded that they can stop the interview or withdraw from the study at any point.

Analysis of semi-structured interviews

A reflective research diary will be used to document reflections and findings post interview to support later analysis. Audio recordings of the interviews will be fully transcribed, stored and analysed using NVivo software (QSR International, Burlington, MA, USA). A content analysis will be undertaken to identify new outcomes, not previously identified in the systematic scoping review of literature. A further thematic analysis will explore parent's experiences of epilepsy and KD therapy [47, 48]. The aim being to identify the outcomes in the narrative materials and to identify common threads that extend across the set of interviews. The analytical process will begin during data collection with the first two interviews being transcribed and analysed to enable iterative changes to the interview schedule and ongoing data collection. Codes will be generated from the data and modified to accommodate new data and insights. The study team can then refine questions, develop hypotheses and pursue emerging avenues of inquiry further in subsequent interviews. Coding and identification of themes will be conducted by the lead researcher JC in collaboration with a senior researcher experienced in qualitative research methods, who will independently review 10% of the coded transcripts. The final themes and newly identified outcomes will be agreed by all authors through discussion. Newly identified outcomes will be added to the database derived from the scoping review.

Phase 3: Consultation process

Research question: What outcomes should be entered into a Delphi process for further study?

Overview and method

The combined list of potential outcomes derived from the systematic review in phase 1 and semi-structured interviews with parents in phase 2 will be grouped into outcome domains according to an outcome taxonomy (Table 1) [28]. This is an updated version of Williamson & Clarks original taxonomy [18] which was developed following review of two cohorts of Cochrane systematic reviews [49,

Table 1 Outcome Taxonomy adapted from Dodd et al. [28]

Outcome taxonomy
1. Mortality
2. 2–24: **Physiological/clinical**
2: Blood and lymphatic system outcomes
3: Cardiac outcomes
4: Congenital, familial and genetic outcomes
5: Endocrine outcomes
6: Ear and labyrinth outcomes
7: Eye outcomes
8: Gastrointestinal outcomes
9: General outcomes
10: Hepatobiliary outcomes
11: Immune system outcomes
12: Infection and infestation outcomes
13: Injury and poisoning outcomes
14: Metabolism and nutrition outcomes
15: Musculoskeletal and connective tissue outcomes
16: Outcomes relating to neoplasms: benign, malignant and unspecified
17: Nervous system outcomes
18: Pregnancy, puerperium and perinatal outcomes
19: Renal and urinary outcomes
20: Reproductive system and breast outcomes
21: Psychiatric outcomes
22: Respiratory, thoracic and mediastinal outcomes
23: Skin and subcutaneous tissue outcomes
24: Vascular outcomes
Functioning
25: Physical functioning
26: Social functioning
27: Role functioning
28: Emotional functioning/well-being
29: Cognitive functioning
31: Perceived health status
32: Delivery of care, including;
- Satisfaction/patient preference
- Acceptability and availability
- Adherence/compliance
- Withdrawal from treatment
- Appropriateness of treatment
- Process, implementation, and service outcomes
33: Personal circumstances
Resource use
34: Economic
35: Hospital
36: Need for further intervention
37: Societal/carer burden
38: Adverse events/effects

50] and the outcomes recommended in 198 core outcome sets [51]. The findings will be presented to the research team and advisory panel for review. Any disagreement will be discussed and resolved. The purpose being to ratify the list of outcomes, ensuring consistent, accessible language and definitions, whilst avoiding duplication.

Phase 4: Prioritisation of outcomes according to stakeholder group and integration of outcomes into a core outcome set

Research question: What are the most important outcomes to include in a core outcome set for refractory childhood epilepsy treated with ketogenic diet therapy?

Overview and method

A survey of key stakeholders will be undertaken using Delphi survey methodology following recommended practices in the development of core outcome sets [18]. An online questionnaire will rate the importance of the outcomes identified in phase three. This questionnaire will be developed and administered using DelphiManager software. Representatives from two stakeholder groups will be asked to pilot the survey prior to dissemination to all participants (group one, health professionals and researchers; group two, parents). Participants will be invited to rate each outcome in two Delphi rounds, with high scores indicating the importance of inclusion in the final core outcome set.

Stakeholders

Parent participants will be invited through clinical partners at NHS Trusts, relevant UK charities (Matthew's Friends, Young Epilepsy and Epilepsy Action), and 'Epilepsy – The Ketogenic Way' Facebook group. International participants will be reached via the aforementioned charities and Facebook group. Health and neurology professionals (e.g. paediatric neurologists, paediatricians, ketogenic dietitians, epilepsy specialist nurses, clinical and educational psychologists) will be invited to participate through specialist interest groups and professional societies (e.g. British Paediatric Neurology Association, Ketogenic Professional Advisory Group, Ketogenic Dietitians Research Network, Epilepsy Nurses Association, Neurological and Neuropsychology special interest groups of the British Psychology Society, NHS regional Paediatric Epilepsy Network and Cochrane Epilepsy). Industry representatives with relevant experience with ketogenic diet therapy will also be invited. International colleagues will be invited through professional networks. The study will be presented at relevant conferences and meetings to raise awareness and aid recruitment. Participants can register their interest by contacting the research team or visiting the study website [44] to access the appropriate participant information for each stakeholder group.

Survey administration

There are no recommendations for appropriate sample sizes for Delphi surveys. We will therefore be guided by other relevant Delphi surveys [43, 52, 53] and aim to recruit between 20–50 participants in each stakeholder group within the available timeframe. Potential participants will be asked to register through an online platform or by contacting the research team. Whilst the use of KD therapy has grown exponentially over the past decade, there are estimated to be only 750 patients in the UK on KD therapy with 250 waiting to commence therapy [54]. We will aim for representation across a range of age groups, epilepsy diagnosis, duration of treatment with KD therapy and type of KD therapy. Informed consent will be assumed if participants register online for the Delphi survey and submit their answers. The age of the child undertaking KD therapy will be recorded, time on KD, diagnosis, ethnicity and the country of residence.

There are approximately 100 paediatric neurologists nationally in the UK [52] not all of whom will have experience with KD therapy and approximately 90 ketogenic dietitians. The small size of the UK health professional group means that international recruitment is essential. The inclusion of international health professionals and researchers will also ensure that the outcome core set is acceptable worldwide. We will aim for optimal diversity through representation of as many of the aforementioned health professionals in the professional stakeholder group. Profession, experience with KD therapy and country in which they practice will be recorded. Informed consent will be assumed if participants register online for the Delphi survey and submit their answers. Each participant will be assigned a unique identifier to ensure anonymity, yet enable the research team to monitor their participation and send invitation and reminder emails. The COMET initiative DelphiManager software will be used to administer the survey. Two Delphi rounds will be undertaken in line with other core outcome set studies [55–57] as three rounds may be overly burdensome on participants. Equally, two rounds are expected to be sufficient given the focussed nature of the single intervention (KD therapy) under investigation.

Delphi survey round one

Participants will be asked to identify which stakeholder group they belong to using a dropdown menu and to complete additional demographic questions. Health professionals and researchers will identify their profession, country of work and experience with KD therapy. Parents will identify their child's diagnosis, age, duration of treatment with KD therapy and type of KD. All participants will be asked to complete the round one survey within 3 weeks. They will be prompted at the end of week two with a reminder email if the survey has not yet been completed. The survey will be identical for both stakeholder groups. Prior to commencing the Delphi survey and rating each presented outcome individually, participants will be asked to blindly list five outcomes that are most important to them. They will then proceed to the Delphi survey and rate the importance of each outcome identified in phase three. A 9-point Likert scoring system will be used in line with other core outcome set studies [43, 53, 57] where 1–3 signifies an outcome is of limited importance, 4–6 important but not critical and 7–9 is of critical importance. An 'unable to score' option will be included for stakeholders who may not have the expertise to score all outcomes. Partial responses will be included. A final free text section will encourage participants to list any other outcomes they feel are not represented in the survey but are of importance. These will be considered for inclusion in round 2.

Delphi survey round one analysis

Descriptive statistics will summarise the aggregate results of round one for each stakeholder group. Differences between health professional responses (e.g. ketogenic dietitians compared to paediatric neurologists) will be assessed. The feasibility of which depends on the number of respondents from each health profession represented.

Delphi survey round two

Respondents to the round one survey will be invited to participate in round two. All outcomes will be carried forward from round one and any new outcomes potentially identified through the free text question in round one. Participants will be reminded of their own individual score for each outcome and see the aggregate scores of both stakeholder groups. Participants will be asked to reflect on their answer and re-score again the importance of each outcome. They will be encouraged to explain their rationale for any changes via a free text box. Presenting the aggregate scores for each stakeholder group has been shown to improve consensus between groups in what is important to retain in the final core outcome set [58]. A final question will ask the respondent if they would like to attend the face to face consensus meeting.

Delphi survey round 2 analysis and defining consensus

Descriptive statistics will summarise the aggregate results of round 2 for each stakeholder group. To define consensus, the survey responses will be analysed separately for each stakeholder group. A 70/15% consensus definition is proposed [18, 59, 60] whereby an outcome is included in the core outcome set if >70% of each stakeholder group rated it 7–9 and <15% considered it of little importance by scoring it 1–3. Finally, there may be outcomes where there is only partial or no agreement between stakeholder groups that warrant further discussion at the final consensus group meeting.

Consensus group meeting

A face to face meeting will be convened at a relevant conference to improve accessibility and attendance. An equal number of each stakeholder group will be randomly chosen from those who identified a willingness to attend the meeting. Participants will be supported to attend. Results for all outcomes will be presented along with the draft core outcome set. Stakeholders will take part in facilitated small group discussion to consider outcomes that did not reach consensus in the Delphi survey. Anonymous remote voting will be utilised. Outcomes will be included in the final set if 70% of voters score the outcome between 7 and 9.

Dissemination

Ultimately our goal is to develop a core set of outcomes that will aid consistency in outcome measurement and reporting in future trials and clinical practice. However, its use will likely be limited if too many outcomes are included. A working group including members of the research team and expert stakeholders will be formed to explore ways to measure the agreed outcomes and support dissemination. If the resultant core outcome set is too large, the working group will aim to refine it further, ensuring it is practical for use, whilst still preserving the views and insights of the wider stakeholders identified during the interviews, Delphi study and consensus meeting. The final core outcome set will be reported following the Core Outcome Set - Standards for Reporting (COS-STAR) statement and checklist [61]. Dissemination will occur via engagement with trialists, Cochrane, COMET, and publication in relevant journals. Study participants who opted to receive study updates will be sent a newsletter and links to relevant publications.

Discussion

Summarised here is the protocol of a mixed methods study to develop a core outcome set. This will guide outcome measurement and reporting in future trials of refractory childhood epilepsy treated with KD therapy. Professional networks regularly highlight the lack of consensus in outcome collection as an area for development. The findings will therefore inform and support clinicians undertaking audit and service evaluation. It might be argued that KD therapy as a treatment for refractory epilepsy is a niche area affecting a relatively small group of patients and the need for a core outcome set questioned. However, a core outcome set is indicated when considering the complexity of refractory epilepsy, the difficulties in achieving seizure control, the unique and intensive nature of KD therapy and the challenges families face when caring for a child with significant health needs. A core outcome set for self limited epilepsy with centro temporal spikes, an epilepsy limited to childhood, was recently published [62] and whilst there are likely to be some shared outcomes when both are compared, it is expected that our proposed set may capture different or additional outcomes relevant to the complexity of refractory epilepsy and severity of associated co-morbidities. These might include epilepsy-related hospital admissions, antiepileptic drug reduction, financial burden and adverse effects of KD therapy. The collaborative and patient-centred approach, with parent involvement throughout will ensure the agreed core outcomes reflect the views of all major stakeholders. Two key challenges for core outcome set developers include achieving global consensus and implementation of the finalised core outcome set in future clinical trials [59]. To address these, the researchers will engage with international partners early in the study to foster participation and engagement. Expert panels at key conferences and engagement in professional networks will support this. Finally, the researchers will actively engage with trialists, regulators and funding bodies to ensure the finalised core outcome set is recognised and used.

Trial status

Version 1.4 protocol November 2020. This study is not a trial. Participant recruitment for the qualitative interviews and Delphi study will begin in January 2020.

Appendix

Table 2

Table 2 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?

Abbreviations
COMET: Core Outcome Measures in Effectiveness Trials; COS-STAR: Core Outcome Set - Standards for Reporting; HOME: Harmonising Outcome Measures in Eczema; IMMPACT: The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials; ISRCTN: International Standard Randomised Controlled Trials Number Registry; JBI: Joanna Briggs Institute; KD: Ketogenic diet; MCT: Medium chain triglyceride; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OMERACT: Outcome Measures in Rheumatology; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT: Randomised controlled trail; SIGLE: System for Information on Grey Literature in Europe.

Acknowledgements
The authors would like to thank Kirsty Martin-McGill for her collaboration on the scoping review.

Authors' contributions
All authors (JC, HC, MH, EW, VA and AC) made substantive intellectual contributions to the development of the protocol. JC drafted the manuscript; all co-authors reviewed and revised it critically for important intellectual content and the authors approved the final version.

Funding
Funding was received from University of Plymouth and the British Dietetic Association General Education Trust Fund. JHC is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital. Funders did not influence study design.

Availability of data and materials
The dataset generated during this study will be available from the University of Plymouth on reasonable request.

Declarations

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

Consent for publication
Not applicable.

Competing interests
This study will contribute to a Doctor of Philosophy for JC which AC, MH and JHC are supervisors. This work is partly funded by the University of Plymouth. JHC is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital. She has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo and Marinius. She has been a speaker and on advisory boards for GW Pharma, Zogenix, and Nutricia; all remuneration has been paid to her department.

Author details
[1]Faculty of Health, University of Plymouth, Plymouth, Devon, UK. [2]UCL Developmental Neurosciences, UCL - NIHR BRC Great Ormond Street Institute of Child Health, London, UK. [3]Matthew's Friends, Lingfield, Surrey, UK.

Received: 20 August 2020 Accepted: 4 August 2022
Published online: 17 August 2022

References

1. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med. 2011;365(10):919–26.
2. Wilder RM. The effects of ketonemia on the course of epilepsy. Mayo Clin Proc. 1921;2:2.
3. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008;7(6):500–6.
4. Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: a randomized controlled trial. Epilepsia. 2013;54(3):481–6.
5. Lambrechts DA, de Kinderen RJ, Vles JS, de Louw AJ, Aldenkamp AP, Majoie HJ. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand. 2017;135(2):231–9.
6. Raju KN, Gulati S, Kabra M, Agarwala A, Sharma S, Pandey RM, et al. Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open labeled study. Epilepsy Res. 2011;96:96–100.
7. Kim JA, Yoon JR, Lee EJ, Lee JS, Kim JT, Kim HD, et al. Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy. Epilepsia. 2016;57(1):51–8.
8. Sharma S, Goel S, Jain P, Agarwala A, Aneja S. Evaluation of a simplified modified Atkins diet for use by parents with low levels of literacy in children with refractory epilepsy: a randomized controlled trial. Epilepsy Res. 2016;127:152–9.
9. El-Rashidy OF, Nassar MF, Abdel-Hamid IA, Shatla RH, Abdel-Hamid MH, Gabr SS, et al. Modified Atkins diet vs classic ketogenic formula in intractable epilepsy. Acta Neurol Scand. 2013;128(6):402–8.
10. Seo JH, Lee YM, Lee JS, Kang HC, Kim HD. Efficacy and tolerability of the ketogenic diet according to lipid:nonlipid ratios-comparison of 3:1 with 4:1 diet. Epilepsia. 2007;48(4):801–5.
11. Freeman J, Veggiotti P, Lanzi G, Tagliabue A, Perucca E. The ketogenic diet: from molecular mechanisms to clinical effects. Epilepsy Res. 2006;68(2):145–80.
12. National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. Clinical Guideline [CG137]. 2016.
13. Martin-Mcgill KJ, Jackson CF, Breshnahan R, Levy RG, Cooper PN. Ketogenic diet for drug-resistant epilepsy. Cochrane Database Syst Rev. 2018;11:CD001903.
14. Joshi M, Kearns J, Wilford E, Hussain N, Khan A. Effectiveness of ketogenic diet to reduce seizure related acute paediatric admission in children with Epilepsy. Dev Med Child Neurol. 2016;58(Supplement 1):43–4.
15. Gilbert DL, Pyzik PL, Vining EPG, Freeman JM. Medication cost reduction in children on the ketogenic diet: data from a prospective study. J Child Neurol. 1999;14(7):469–71.
16. IJff DM, Postulart D, Lambrechts DAJE, Majoie MHJM, de Kinderen RJA, Hendriksen JGM, et al. Cognitive and behavioral impact of the ketogenic diet in children and adolescents with refractory epilepsy: a randomized controlled trial. Epilepsy Behav. 2016;60:153–7.
17. Hallböök T, Ji S, Maudsley S, Martin B. The effects of the ketogenic diet on behavior and cognition. Epilepsy Res. 2012;100(3):304–9.
18. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. Trials. 2017;18(suppl 3):280.
19. Williamson P, Altman D, Blazeby J, Clarke M, Gargon E. Driving up the quality and relevance of research through the use of agreed core outcomes. J Health Serv Res Policy. 2012;17(1):2.
20. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT Filter 2.0. J Clin Epidemiol. 2014;67(7):745–53.
21. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003;106(3):337–45.
22. Schmitt J, Apfelbacher C, Spuls PI, Thomas KS, Simpson EL, Furue M, et al. The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome measurements in dermatology. J Invest Dermatol. 2015;135(1):24–30.
23. Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy (Review). Cochrane Database Syst Rev. 2020;6:Art. No.: CD001903.
24. Farasat S, Kossoff EH, Pillas DJ, Rubenstein JE, Vining EP, Freeman JM. The importance of parental expectations of cognitive improvement for their children with epilepsy prior to starting the ketogenic diet. Epilepsy Behav. 2006;8(2):406–10.
25. Bruce S, Devlin A, Air L, Cook L. Changes in quality of life as a result of ketogenic diet therapy: a new approach to assessment with the potential for positive therapeutic effects. Epilepsy Behav. 2017;66:100–4.
26. Schoeler NE, MacDonald L, Champion H, Cross JH, Sander JW, Sisodiya SM, et al. Assessing parents' attitudes towards ketogenic dietary therapies. Epilepsy Behav. 2014;39:1–5.
27. COMET. 2019 [Available from: http://www.comet-initiative.org/].
28. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. J Clin Epidemiol. 2018;96:84–92.

29. INVOLVE. Briefing notes for researchers: involving the public in NHS, public health and social care research. Eastleigh INVOLVE; 2012.
30. Rosenbaum P. Family-centered research: what does it mean and how do we do it? Dev Med Child Neurol. 2011;53:769–71.
31. Joanna Briggs Institute. Systematic Review Register 2020. Available from: https://joannabriggs.org/systematic-review-register. (Accessed on 23 June 2020)
32. Carroll J, Martin-McGill K, Cross H, Hickson M, Collinson A. Outcome measurement and reporting in childhood epilepsy treated with ketogenic diet therapy: a scoping review protocol. JBI Database System Rev Implement Rep. 2019;17(5):633–9.
33. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467–73.
34. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336–41.
35. Young B, Bagley H. Including patients in core outcome set development: issues to consider based on three workshops with around 100 international delegates. Res Involv Engagem. 2016;2(1):25.
36. Ronen GM, Streiner DL, Rosenbaum P. Health-related quality of life in children with epilepsy: development and validation of self-report and parent proxy measures. Epilepsia. 2003;44(4):598–612.
37. Mack N, Woodsong C, MacQueen K, Guest G, Namey E. Qualitative research methods: a data collectors field guide. North Carolina: Family Health International; 2005.
38. Rosenbaum SE, Glenton C, Nylund HK, Oxman AD. User testing and stakeholder feedback contributed to the development of understandable and useful Summary of Findings tables for Cochrane reviews. J Clin Epidemiol. 2010;63(6):607–19.
39. Arnold LM, Crofford LJ, Mease PJ, Burgess SM, Palmer SC, Abetz L, et al. Patient perspectives on the impact of fibromyalgia. Patient Educ Couns. 2008;73(1):114–20.
40. Kirwan J, Heiberg T, Hewlett S, Hughes R, Kvien T, Ahlmen M, et al. Outcomes from the patient perspective workshop at OMERACT 6. J Rheumatol. 2003;30(4):868–72.
41. World Health Organisation. Paediatric age categories to be used in differentiating between listing on a model essential medicines list for children. Position Paper. USA; 2007.
42. MacLennan S, Williamson PR, Bekema H, Campbell M, Ramsay C, N'Dow J, et al. A core outcome set for localised prostate cancer effectiveness trials. BJU Int. 2017;120(5b):E64–79.
43. Murugupillai R, Wanigasinghe J, Muniyandi R, Arambepola C. Parental concerns towards children and adolescents with epilepsy in Sri Lanka-Qualitative study. Seizure. 2016;34:6–11.
44. Carroll J. Core outcomes for refractory childhood epilepsy treated with ketogenic diet therapy. The Core-KDT study. 2019 Available from: https://www.plymouth.ac.uk/schools/school-of-health-professions/core-outcomes-for-refractory-childhood-epilepsy-treated-with-ketogenic-diet-therapy. (Accessed on 23 June 20)
45. Iacono VL, Symonds P, Brown DHK. Skype as a tool for qualitative research interviews; 2016. https://doi.org/10.5153/sro3952. (Accessed on 23 June 2020)
46. Deakin H, Wakefield K. Skype interviewing: reflections of two PhD researchers; 2013. https://doi.org/10.1177/1468794113488126. (Accessed on 23 June 2020)
47. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77–101.
48. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. Nurs Health Sci. 2013;15(3):398–405.
49. Smith V, Clarke M, Williamson P, Gargon E. Survey of new 2007 and 2011 Cochrane reviews found 37% of prespecified outcomes not reported. J Clin Epidemiol. 2015;68(3):237–45.
50. Davey J, Turner RM, Clarke MJ, Higgins JP. Characteristics of meta-analyses and their component studies in the Cochrane Database of Systematic Reviews: a cross-sectional, descriptive analysis. BMC Med Res Methodol. 2011;11:160.
51. Gargon E, Gurung B, Medley N, Altman D, Blazeby J, Clarke M, et al. Choosing important health outcomes for comparative effectiveness research: a systematic review. PLoS One. 2014;17(7):A435.
52. Morris C, Dunkley C, Gibbon FM, Currier J, Roberts D, Rogers M, et al. Core Health Outcomes In Childhood Epilepsy (CHOICE): protocol for the selection of a core outcome set. Trials. 2017;18(1):572.
53. Murugupillai R, Ranganathan SS, Wanigasinghe J, Muniyandi R, Arambepola C. Development of outcome criteria to measure effectiveness of antiepileptic therapy in children. Epilepsy Behav. 2018;80:56–60.
54. Whitely VJ, Martin-McGill KJ, Carroll JH, Taylor H, Schoeler N. on behalf of the Ketogenic Dietitians Research Network (KDRN). Nice to know: impact of NICE guidelines on ketogenic diet services nationwide. J Hum Nutr Diet. 2020;33:98–105.
55. Sinha IP, Gallagher R, Williamson PR, Smyth RL. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. Trials. 2012;13:103.
56. Blazeby JM, Macefield R, Blencowe NS, Jacobs M, McNair AGK, Sprangers M, et al. Core information set for oesophageal cancer surgery. Br J Surg. 2015;102(8):936–43.
57. Harman NL, Bruce IA, Kirkham JJ, Tierney S, Callery P, O'Brien K, et al. The importance of integration of stakeholder views in core outcome set development: otitis media with effusion in children with cleft palate. PLoS One. 2015;10(6):e0129514.
58. Brookes ST, Macefield RC, Williamson PR, McNair AG, Potter S, Blencowe NS, et al. Three nested randomized controlled trials of peer-only or multiple stakeholder group feedback within Delphi surveys during core outcome and information set development. Trials. 2016;17:409.
59. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13(132):919–26.
60. Wylde V, MacKichan F, Bruce J, Gooberman-Hill R. Assessment of chronic post-surgical pain after knee replacement: development of a core outcome set. Eur J Pain. 2015;19(5):611–20.
61. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Devane D, et al. Core Outcome Set-STAndards for Reporting: the COS-STAR statement. PLoS Med. 2016;13(10):e1002148.
62. Crudgington H, Rogers M, Bray L, Carter B, Currier J, Dunkley C, et al. Core Health Outcomes in Childhood Epilepsy (CHOICE): Development of a core outcome set using systematic review methods and a Delphi survey consensus. Epilepsia. 2019;60(5):857–71.

Publisher's Note

CORE-KDT
Core Outcomes in Refractory Epilepsy with Ketogenic Diet Therapy

PARENT INFORMATION SHEET
Interview and/or Delphi Survey

Project title: Core Outcomes in Refractory childhood Epilepsy treated with Ketogenic Diet Therapy (The CORE-KDT study)

Thank you for expressing an interest in our research study**.** We are recruiting parents of children with refractory (difficult to manage) epilepsy currently treated with ketogenic diet therapy or who have been in the past year. Please read the following information carefully to help guide your decision to take part or not. We will be happy to answer any questions you may have.

What is the purpose of the study?

Research often uses seizure control and the side effects of a ketogenic diet as the main way of assessing ketogenic diet therapy (these are known as 'outcomes'). However, we think it is important to also consider other outcomes that address physical health, mental health and quality of life to name a few. It is essential we involve parents and carers in this research to identify the outcomes of importance to them. We will also seek the views of healthcare professionals' (for example paediatric neurologists, ketogenic dietitians and epilepsy nurses). Together this will guide the development of an agreed list of outcomes (also known as a 'core outcome set') that should be measured for children who are following a ketogenic diet. The Chief investigator (Jen Carroll) is undertaking this research as part of her PhD studies.

Why have I been invited?

You have been invited to participate because you are a parent or carer to a child aged 18 or under with epilepsy who is being treated with a ketogenic diet or has weaned from the diet in the past year. Your views are very important to us, particularly in relation to managing the ketogenic diet and the outcomes you feel we should be assessing for children with epilepsy treated with ketogenic diet.

Do I have to take part?

Taking part in the study is completely voluntary; you don't have to take part if you don't want to. Your choice to take part or not will not impact on your child's care. If you decide to take part and change your mind you are free to withdraw at any time, without giving a reason.

Can my child take part?

No, this study is assessing parents and carers views.

What will taking part involve?

This study has two phases where we would welcome your involvement and you may choose to take part in one or both phases.

Phase 1 Interview: One interview with a researcher (Jen Carroll) to explore the outcomes of importance to you and your child's experiences of epilepsy and the ketogenic diet. The interview will take approximately 60 minutes. This can be done in person, via telephone or audio/video call using Skype; whichever you prefer**.** If you would prefer to meet in person, Jen will arrange to meet you at a time that is convenient for you which might be a forthcoming hospital appointment or your own home if preferred. The interviews will be audio recorded.

Phase 2 online Delphi survey: Completion of an online survey called a 'Delphi Survey' in which you will be asked to score the importance of a range of outcomes. Delphi surveys are used to reach consensus on a topic of interest. Parents, healthcare professionals and researchers will all be invited to score the same list of outcomes over two rounds. Each round of the survey will take approximately 20 minutes to complete. The online link to the survey will be sent to your email address.

Round 1: you will be presented with a list of outcomes that have been identified from past research studies of childhood epilepsy treated with ketogenic therapy and the interviews undertaken with parents in phase 1. You will be asked to rate how important you think the outcomes are on a scale of 1 (not important) to 9 (critically important). You will have an opportunity to add comments or any outcomes you think are missing.

Round 2: approximately 3 weeks after completing round 1, you will receive an email asking you to complete round 2 of the Delphi survey. The questions will be identical to round 1 and you will again be asked to rate the outcomes on a scale of 1-9. However, you will be able to see your round 1 answer and the anonymous scores of the other groups involved in round 1; parents, healthcare professionals and researchers. You can amend any of your scores in light of this information or keep it the same. This method helps us achieve consensus on the core outcomes of importance.

If you volunteer to take part in the Delphi survey, it is important that you complete both rounds to enable us to gather meaningful data.

How will we use information about you?

We will need to use information from you for this research project. This information will include your:

- name
- contact details.

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.
Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our (University of Plymouth) website www.plymouth.ac.uk/students-and-family/governance/information-governance
- by asking one of the research team
- by sending an email to our Data Protection Officer dpo@plymouth.ac.uk
- by ringing us on 01752 588826

What will happen to the information that I give?

After the interviews, we will listen to the recordings to help understand parents and carers experiences of living with childhood epilepsy, the ketogenic diet and their views on outcomes. The interviews will be typed and anonymised. Your personal details will be kept confidential and will not be shared. Once the results of the interviews are analysed, we will make them available to interview participants to review and welcome any further feedback. The research team may present the data at relevant conferences or in journals read by health care professionals. We may use some direct quotes from the interview. If we do this, we will be very careful to make sure that neither you nor anyone you talk about can be identified. The results of the Delphi survey will be analysed with the aim of reaching consensus on the most important outcomes to measure in future. Your results will be completely anonymous.

What are the advantages of taking part?

There will be no direct benefits to you, but you may find completing the interview and/or Delphi survey interesting and even enjoyable. It is hoped the information you provide will guide and influence the way children on a ketogenic diet are monitored.

What are the possible disadvantages and risks of taking part?

You will not be exposed to any risk of physical harm associated with the interview or completion of the Delphi survey and you don't have to answer any questions that you don't want to. Understandably, it is possible that talking about your experiences might be upsetting, if this happens you can stop at any time.

Will my taking part in the study be kept confidential?

We will protect the confidentiality and anonymity of all participants and their data at all times. We will anonymise anything you say that might identify you or others when we write up the results. All the data from the study will be stored on the University of Plymouth secure network drives. Ethical approval has been granted by London-Surrey REC (19/LO/1680, date: 14/11/19) and supported by the University of Plymouth Faculty Research Ethics and Integrity Committee (FREIC ref 19/20-1197, date: 05/12/19).
It is possible that some of the data collected will be looked at by authorised persons from the University of Plymouth to check that the study is being carried out correctly. Anyone who has access to the records will also be governed by the same rules of confidentiality.

How long will the data be kept for?

The University of Plymouth is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Plymouth will keep identifiable information about you for 10 years after the study has finished.

What happens next?

If you wish to take part and haven't already registered your interest, then please do so via the study website ***https://www.plymouth.ac.uk/core-kdt*** where you will be asked to provide your contact details. If preferred, please contact the researchers directly using the contact details below. They will be more than happy to answer any further questions you might have. Parents and carers are encouraged to take part individually of each other as they may have differing opinions. Please feel free to share information about the study with other parents or carers of a child with epilepsy treated with ketogenic diet therapy. If they would like to take part, they will need to register separately from you**.**

What happens after the survey?

When the two rounds of Delphi survey are complete, you will be asked if you would be interested in attending a consensus group meeting with representatives from all groups. Again, this is voluntary and travel expenses will be reimbursed**.**

Questions?

If you have any questions about the study, interviews or Delphi survey, please don't hesitate to contact one of our research team.

Jen Carroll 01752 588826 (University Lecturer, Dietitian, PhD student and Chief Investigator) Jennifer.carroll@plymouth.ac.uk **Avril Collinson 01752588848** (University Lecturer, Dietitian and Director of Studies) Avril.collinson@plymouth.ac.uk	**Our address:** Institute of Health and Community, School of Health Professions, University of Plymouth, Plymouth, PL6 8BH.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to someone from the research team (Jen Carroll or Avril Collinson) who will do their best to answer your questions. If you have a minor complaint or concern then you need to contact the researchers in the first instance.

Formal Complaints

If you wish to make a formal complaint or if you are not satisfied with the response you have gained from the researcher(s) in the first instance then please contact:

Administrator to Faculty Research Ethics and Integrity Committee
Faculty of Health and Human Sciences,
University of Plymouth,
4th Floor Rolle Building, Drake Circus,
Plymouth, PL4 8AA
Tel: 01752 586992

Who is funding the research?

This study is sponsored by the University of Plymouth and The British Dietetic Association General and Education Trust Fund.

Who has reviewed the study?

This study has been reviewed and approved by London-Surrey Research Ethics Committee (19/LO/1680, date: 14/11/19) and supported by University of Plymouth Faculty Research Ethics and Integrity Committee (FREIC ref 19/20-1197, date: 05/12/19)

Thank you for taking the time to read the information sheet. If you decide to participate you will be given a copy of the information sheet to keep and your consent will be sought.

Appendix D. CORE-KDT study participant information sheet: professionals

V1.5.1 21/01/20-IRAS Project ID: 251380

CORE-KDT

Core Outcomes in Refractory Epilepsy with Ketogenic Diet Therapy

PROFESSIONAL INFORMATION SHEET
Delphi Survey

Project title: Core Outcomes in Refractory childhood Epilepsy treated with Ketogenic Diet Therapy (The CORE-KDT study)

Thank you for expressing an interest in our research study. We are recruiting health care professionals and researchers who have experience working with refractory childhood epilepsy treated with ketogenic diet (KD) therapy. Please read the following information carefully to help guide your decision to take part or not. We will be happy to answer any questions you may have.

What is the purpose of the study?

Our aim is to establish consensus among parents, carers, healthcare professionals and researchers on a core set of outcomes for refractory childhood epilepsy treated with KD therapy. The primary outcomes in clinical effectiveness trials tend to address seizure control and the side effects of KD therapy. However, we think it is important to also consider other outcomes that address physical health, mental health and quality of life to name a few. It is essential we involve parents, healthcare professionals and researchers working with this patient group to identify the outcomes of importance to them. Together this will guide the development of a core set of outcomes that should be measured in future clinical trials and may benefit clinical practice too. The chief investigator (Jen Carroll) is undertaking this study as part of her PhD studies.

What healthcare professionals can take part?

We are seeking the opinions of healthcare professionals and researchers who work with children with refractory epilepsy treated with KD therapy. For example, but not limited to; paediatric neurologists, ketogenic dietitians and epilepsy specialist nurses. If your profession isn't listed but you work with this patient group, please do get in contact with the researchers. Please feel free to share the study information with any other relevant professionals within your team that might like to take part.

What will taking part involve?

You are invited to take part in an online survey called a 'Delphi Survey' in which you will be asked to score the importance of a range of outcomes. Delphi surveys are used to reach consensus on a topic of interest. Parents, healthcare professionals and

researchers will all be invited to anonymously score the same list of outcomes over two rounds. Each round of the survey will take approximately 20 minutes to complete. The online link to the survey will be sent to your email address.

Round 1: you will be presented with a list of outcomes that have been identified from a scoping review of research studies (from 2008 to 2018) of childhood epilepsy treated with KD therapy and interviews undertaken with parents earlier in this study. You will be asked to rate how important you think the outcomes are on a scale of 1 (not important) to 9 (critically important). You will have an opportunity to add comments or any outcomes you think are missing.

Round 2: approximately 3 weeks after completing round 1, you will receive an email asking you to complete round two of the Delphi survey. The questions will be identical to round 1 and you will again be asked to rate the outcomes on a scale of 1-9. However, you will be able to see your round 1 answer and the anonymous scores of the other groups involved in round 1; parents, healthcare professionals and researchers. You can amend any of your scores in light of this information or keep it the same. This method helps us achieve consensus on the core outcomes of importance.

If you volunteer to take part in the Delphi survey, it is important that you complete both rounds to enable us to gather meaningful data.

Do I have to take part?

Taking part in the study is completely voluntary; you don't have to take part if you don't want to. If you decide to take part and change your mind you are free to withdraw at any time, without giving a reason. Completing the survey will be regarded as your implied consent to take part, that is the assumption that a person has knowingly agreed to participate in the research by performing a research activity or task.

What are the risks and benefits of taking part?

The survey is very low risk. There will be no direct benefits to you but the information you give may guide future research into childhood epilepsy treated with KD therapy and influence the routine monitoring of this patient group.

How will we use information about you?

We will need to use information from you for this research project. This information will include your

- name
- contact details.

People will use this information to do the research or to check your records to make sure that the research is being done properly.
People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.
Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our (University of Plymouth) website www.plymouth.ac.uk/students-and-family/governance/information-governance
- by asking one of the research team
- by sending an email to our Data Protection Officer dpo@plymouth.ac.uk
- by ringing us on 01752 588826

Will my taking part in the study be kept confidential?

We will protect the confidentiality and anonymity of all participants and their data at all times. We will anonymise anything you say that might identify you or others when we write up the results. All the data from the study will be stored on the University of Plymouth secure network drives. Ethical approval has been granted by London-Surrey Research ethics committee (19/LO/1680, date 14/11/19) and supported by the Faculty Research Ethics and Integrity Committee on FREIC ref 19/20-1197, date: 05/12/19).
It is possible that some of the data collected will be looked at by authorised persons from the University of Plymouth to check that the study is being carried out correctly. Anyone who has access to the records will also be governed by the same rules of confidentiality.

How long will the data be kept for?

The University of Plymouth is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Plymouth will keep identifiable information about you for 10 years after the study has finished.

What happens next?

If you wish to take part and haven't already registered your interest, then please do so via the study website ***https://www.plymouth.ac.uk/core-kdt*** where you will be asked to provide your contact details. If preferred, please contact the researchers directly using the contact details below. They will be more than happy to answer any further questions you might have. Please feel free to share information about the study with other professionals. If they would like to take part, they will need to register separately from you.

What happens after the survey?

When the two rounds of Delphi survey are complete, you will be asked if you would be interested in attending a consensus group meeting with representatives from all groups.

Again, this is entirely voluntary and will be held at a meeting or conference where healthcare professionals are in attendance. More information about this meeting will be sent to you after round 2 of the survey.

Questions?

If you have any questions, please don't hesitate to contact one of our research team.

Jen Carroll 01752 588826 (University Lecturer, Dietitian, PhD student and Chief Investigator) Jennifer.carroll@plymouth.ac.uk **Avril Collinson 01752588848** (University Lecturer, Dietitian and Director of Studies) Avril.collinson@plymouth.ac.uk	**Our address:** Institute of Health and Community, School of Health Professions, University of Plymouth, Plymouth, PL6 8BH.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to someone from the research team (Jen Carroll or Avril Collinson) who will do their best to answer your questions. If you have a minor complaint or concern then you need to contact the researchers in the first instance.

Formal Complaints

If you wish to make a formal complaint or if you are not satisfied with the response you have gained from the researcher(s) in the first instance then please contact:

Administrator to the Faculty Research Ethics and Integrity Committee
Faculty of Health and Human Sciences, University of Plymouth,
4th Floor Rolle Building, Drake Circus,
Plymouth, PL4 8AA. Tel: 01752 586992

Who is funding the research?

This study is sponsored by the University of Plymouth and The British Dietetic Association General and Education Trust Fund.

Who has reviewed the study?

This study has been reviewed and approved
Ethical approval has been granted by London-Surrey Research ethics committee (19/LO/1680, date 14/11/19) and supported by the Faculty Research Ethics and Integrity Committee on FREIC ref 19/20-1197, date: 05/12/19)

Thank you for taking the time to read the information sheet. If you decide to participate you will be given a copy of the information sheet to keep and your consent will be sought.

Appendix E. Consent form

CORE-KDT
Core Outcomes in Refractory Epilepsy with Ketogenic Diet Therapy

CONSENT FORM

IRAS ID: 251380 REC: 19/LO/1680

Title of Project: Core Outcomes in Refractory childhood Epilepsy treated with Ketogenic Diet Therapy (The CORE-KDT study)

Please refer to Participant Information Sheet V1.5.1 (21/01/20) for further information regarding this study

Participant Identification Number for this study:

Name of Researcher: Jen Carroll Please initial box

1. I confirm that I have read the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that the information collected about me may be used to support other research in the future and may be shared anonymously with other researchers. ☐
4. I understand that the information held and maintained by the University of Plymouth may be used to help contact me. ☐
5. I agree to take part in the above study and that the general results will be made available to the medical community through poster presentations at conferences and publication in a reputable clinical journal. ☐
6. I am willing to be contacted again in the future with regard to potentially taking part (without any obligation) in further related research studies. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

If returning electronically, please type your initials in the boxes, your name and date and return to the researcher from the email address you provided on registering your interest for the study.

Appendix F. CORE-KDT study logo

Appendix G. Advertising leaflet

CORE-KDT

Core Outcomes in Refractory Epilepsy with Ketogenic Diet Therapy

What would you consider to be successful results for your child using the ketogenic diet?

Contact us:

For more information or to take part:
Website: www.plymouth.ac.uk/core-kdt
(e) core-kdt@plymouth.ac.uk
(t) 01752 588826

SCAN ME

UNIVERSITY OF PLYMOUTH

V1.1. Ethical approval REC reference 19/LO/1680

Are you?

A parent or carer of a child aged 18 years or under with refractory (difficult to treat) epilepsy, treated with the ketogenic diet or weaned from the diet in the last year?

Why is this research important?

The impact or results of treatment are often described as 'outcomes'.

With your help we can develop a list of the most important outcomes to measure when monitoring children with epilepsy treated with the ketogenic diet.

What's involved?

1.An interview to share your views on experiences of epilepsy and results with ketogenic diet
and/or
2. Complete an online survey to rate the importance of a list of outcomes.

Appendix H. Sample social media posts

Jen Carroll @JenCarrollRD · 10/07/2021

Are you using #ketogenicdiet to treat #epilepsy in children, as a parent or professional? Share your views on important outcomes to measure in research & clinics. Watch 👉youtu.be/vIj8KM03nXg to learn more about our study & 👇 to take part by July 12th delphimanager.liv.ac.uk/CORE-KDT/Delphi

You Retweeted

Matthew's Friends @mat... · 18/01/2020

Is your child's epilepsy treated with the ketogenic diet?

Researchers at the University of Plymouth Core-KDT are working with us - share your experiences and views through an interview and/or online survey plymouth.ac.uk/core-kdt (e) core-kdt@plymouth.ac.uk

#ketogenicdiet

5 5

Jen Carroll @JenCarrollRD · 06/07/2021

Thanks for sharing @youngepilepsy 🙌🏻

Young Epilepsy @... · 06/07/2021

Do you have experience with ketogenic diet therapies? We're working with @PlymUni to understand the most important outcomes for parents of children with epilepsy treated with KDT.

More info: bit.ly/KDT_Video
Take part: bit.ly/KDT_Survey

#EpilepsyResearch 💜

You Retweeted

You Retweeted

Young Epilepsy @youn... · 17/02/2020

Can you help researchers at University of Plymouth understand your family goals for the ketogenic diet?

👉 More information here - bit.ly/2RpiWds

5 5

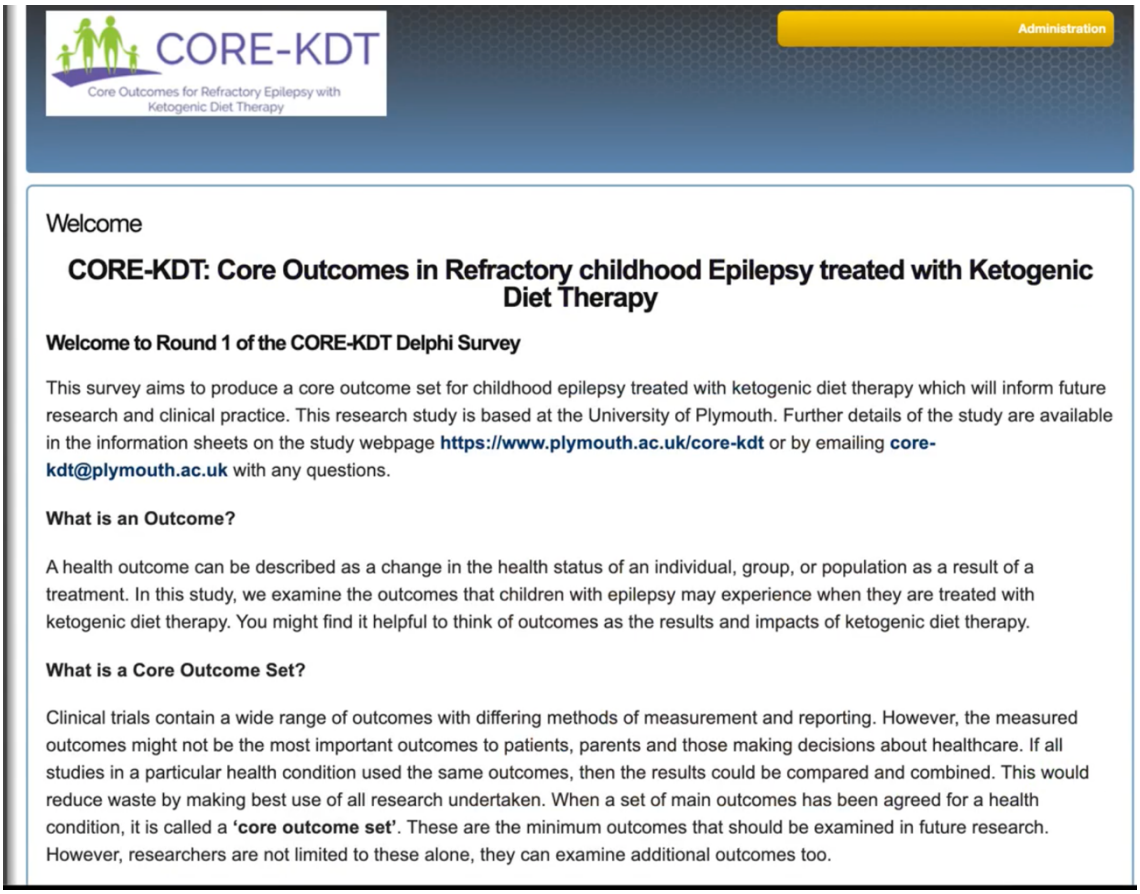
Appendix I. Sample search strategy

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]

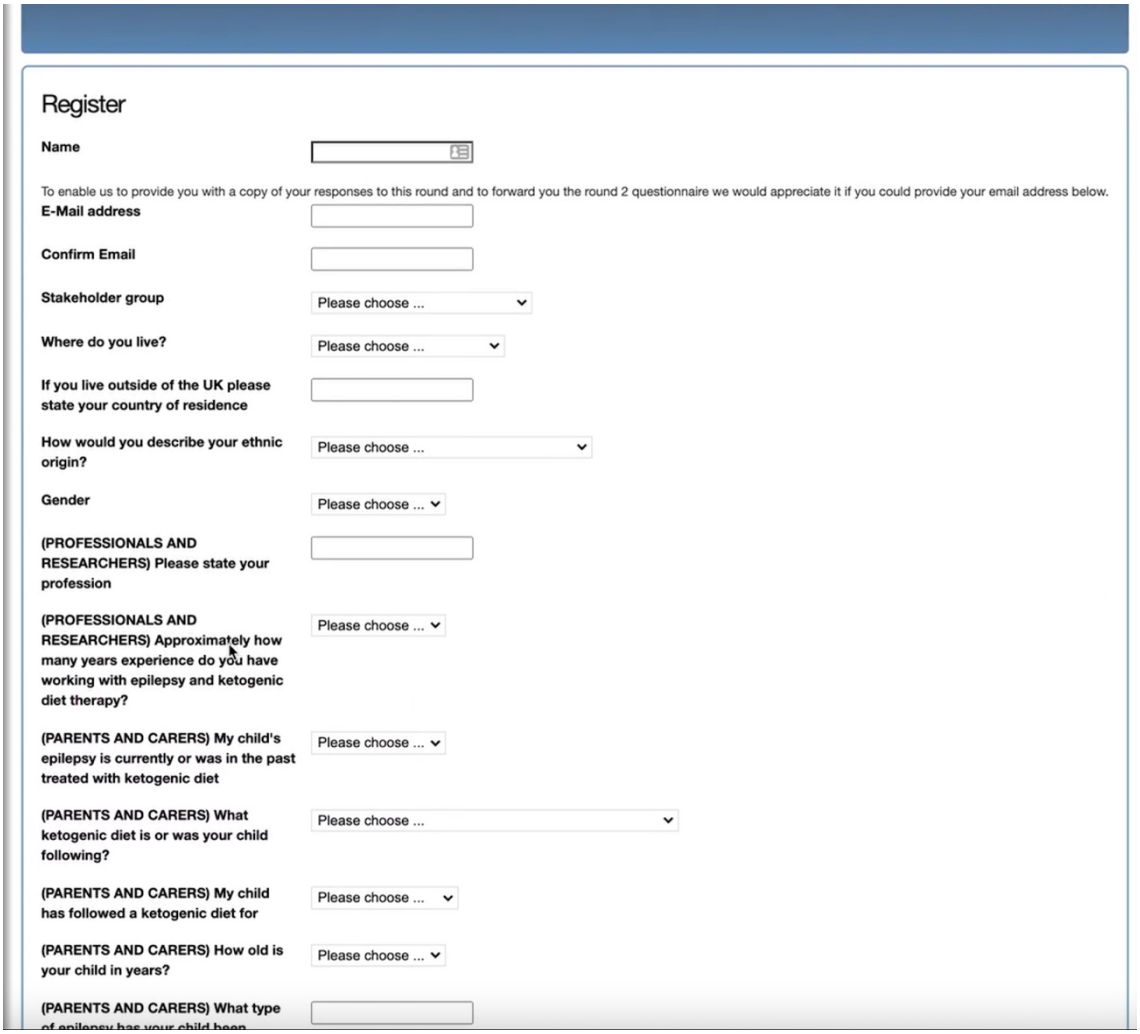
AND
child*[MeSH] OR adolescen* [MeSH] OR infant [MeSH] OR p*ediatric [tiab] OR child [tiab] Or infant [tiab] OR adolescen* [tiab] OR teen [tiab]
Limits: 10 years. Search returned 461 records.

Appendix J. DelphiManager content

Sample text from the CORE-KDT Delphi survey welcome page



Sample text from the CORE-KDT Delphi survey registration page



Register

Name

To enable us to provide you with a copy of your responses to this round and to forward you the round 2 questionnaire we would appreciate it if you could provide your email address below.

E-Mail address

Confirm Email

Stakeholder group — Please choose ...

Where do you live? — Please choose ...

If you live outside of the UK please state your country of residence

How would you describe your ethnic origin? — Please choose ...

Gender — Please choose ...

(PROFESSIONALS AND RESEARCHERS) Please state your profession

(PROFESSIONALS AND RESEARCHERS) Approximately how many years experience do you have working with epilepsy and ketogenic diet therapy? — Please choose ...

(PARENTS AND CARERS) My child's epilepsy is currently or was in the past treated with ketogenic diet — Please choose ...

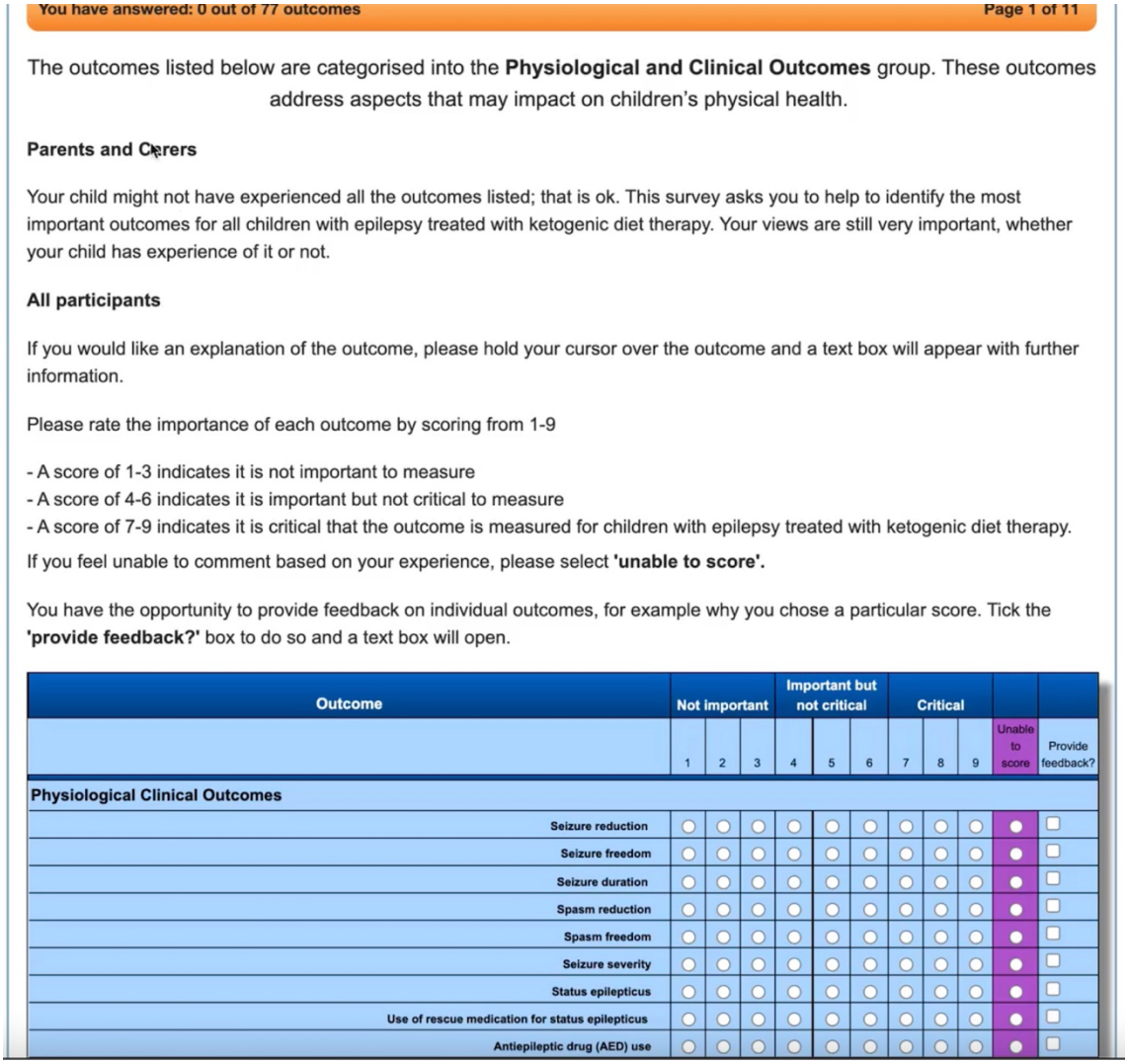
(PARENTS AND CARERS) What ketogenic diet is or was your child following? — Please choose ...

(PARENTS AND CARERS) My child has followed a ketogenic diet for — Please choose ...

(PARENTS AND CARERS) How old is your child in years? — Please choose ...

(PARENTS AND CARERS) What type of epilepsy has your child been

Sample section of page 1 of the Delphi survey, including instructions and layout of the outcomes list



You have answered: 0 out of 77 outcomes — Page 1 of 11

The outcomes listed below are categorised into the **Physiological and Clinical Outcomes** group. These outcomes address aspects that may impact on children's physical health.

Parents and Carers

Your child might not have experienced all the outcomes listed; that is ok. This survey asks you to help to identify the most important outcomes for all children with epilepsy treated with ketogenic diet therapy. Your views are still very important, whether your child has experience of it or not.

All participants

If you would like an explanation of the outcome, please hold your cursor over the outcome and a text box will appear with further information.

Please rate the importance of each outcome by scoring from 1-9

- A score of 1-3 indicates it is not important to measure
- A score of 4-6 indicates it is important but not critical to measure
- A score of 7-9 indicates it is critical that the outcome is measured for children with epilepsy treated with ketogenic diet therapy.

If you feel unable to comment based on your experience, please select **'unable to score'.**

You have the opportunity to provide feedback on individual outcomes, for example why you chose a particular score. Tick the **'provide feedback?'** box to do so and a text box will open.

Outcome	Not important			Important but not critical			Critical				
	1	2	3	4	5	6	7	8	9	Unable to score	Provide feedback?
Physiological Clinical Outcomes											
Seizure reduction	○	○	○	○	○	○	○	○	○	●	☐
Seizure freedom	○	○	○	○	○	○	○	○	○	●	☐
Seizure duration	○	○	○	○	○	○	○	○	○	●	☐
Spasm reduction	○	○	○	○	○	○	○	○	○	●	☐
Spasm freedom	○	○	○	○	○	○	○	○	○	●	☐
Seizure severity	○	○	○	○	○	○	○	○	○	●	☐
Status epilepticus	○	○	○	○	○	○	○	○	○	●	☐
Use of rescue medication for status epilepticus	○	○	○	○	○	○	○	○	○	●	☐
Antiepileptic drug (AED) use	○	○	○	○	○	○	○	○	○	●	☐

Appendix K. Consensus meeting invitation and information sheet

Professional invitation

Subject: Invitation to CORE-KDT outcomes consensus group meeting February 23rd 2022

Dear XXXX,

Thank you for taking part in our recent online Delphi survey and sharing your views on the importance of outcomes relating to childhood epilepsy treated with KD therapy.

We would like to invite you to join the CORE-KDT virtual consensus meeting on **February 23rd 2022, 10:30-14:00 London UK time** (calculate your time zone here https://www.timeanddate.com/worldclock/). This is the final stage of the CORE-KDT project, where we will finalise the list of the most important outcomes to measure for children with epilepsy treated with KD therapy.

We really hope you can join us.

The meeting will be hosted on Zoom and attended by parents, health professionals, industry and charity representatives. All with shared experience (personal or professional) in epilepsy and KD therapy. You have expertise in supporting families with their child's epilepsy and ketogenic diet and hence we would really value your input and expertise.

Next Steps

1) please find attached information sheet to outline what to expect at the meeting. If you have any concerns or questions re the virtual nature, use of Zoom or anything else, then please get in touch and we can work through them together.

2) If you are willing to attend the consensus meeting, please complete the consent form attached and return via email. This can be completed electronically, (rather than printing and handwriting) by typing your initials in the boxes and adding an electronic or typed signature and date. We would appreciate you confirming your attendance as soon as possible as we need to balance the number of parents and healthcare professionals.

Thank you for your ongoing support for this project, we are almost there!

Parent invitation

Subject: Invitation to CORE-KDT outcomes consensus group meeting February 23rd 2022

Dear XXX ,

Thank you for taking part in our recent online Delphi survey and sharing your views on the importance of outcomes relating to childhood epilepsy treated with KD therapy.

We would like to invite you to join the CORE-KDT virtual consensus meeting on **February 23rd 2022 (10:30-14:00).** This is the final stage of the CORE-KDT project, where we will finalise the list of the most important outcomes to measure for children with epilepsy treated with KD therapy.

We really hope you can join us, we tried to avoid school times to ensure as many parents can attend as possible to share their views.

The meeting will be hosted on Zoom and attended by parents, dietitians, nurses, consultants, charity and industry representatives. All with shared experience (personal or professional) in epilepsy and KD therapy. You are an expert in living with epilepsy and managing the ketogenic diet and hence we really value your input and expertise.

Next Steps

1) please confirm your attendance at the consensus meeting via return email

2) If you have any concerns re the virtual nature, use of Zoom or anything else, then please do let me know and we can work through them together

3) it would be really helpful to have an informal chat via Zoom in the weeks before the meeting to;

- discuss what will happen during the consensus meeting
- answer any questions you might have
- test Zoom to minimise any technical issues on the day of the consensus meeting

This will take no more than 20-30 minutes. You can book a date and time that works best for you by following this link https://calendly.com/core-kdt or emailing with your availability

A consent form and information pack will follow closer to the meeting. Thank you for your ongoing support for this project, we are almost there!

CORE-KDT

Core Outcomes in Refractory Epilepsy with Ketogenic Diet Therapy

Consensus Meeting

Wednesday 23rd February 2022

10:30 -14:00

What to expect

Project title: Core Outcomes in Refractory childhood Epilepsy treated with Ketogenic Diet Therapy (The CORE-KDT study)

Thank you for taking part in the earlier phases of the CORE-KDT study (interviews and/or the online Delphi survey). The consensus group meeting is the final phase of the project. This information sheet tells you why the meeting is being held and what it will involve. We will meet online using Zoom to reduce the upheaval for participants and enable international participation.

We hope you find this information helpful and agree to join the meeting to help us achieve consensus on the most important outcomes to measure for children with epilepsy treated with ketogenic diet therapy. We are happy to answer any questions you may have.

What is the purpose of the CORE-KDT study?

Research often uses seizure control and the side effects of a ketogenic diet as the main way of assessing ketogenic diet therapy (these are known as 'outcomes'). However, we think it is important to also consider other outcomes that address physical health, mental health and quality of life to name a few. It is essential we involve parents, carers and health professionals, in this research to identify the most outcomes. Together their views will guide the development of an agreed list of outcomes. This is called a 'core outcome set' and it should represent the 'essential' things that all researchers should measure when investigating the impact of ketogenic diet therapy.

Having a core outcome set will ensure outcomes which are relevant to parents, carers and health professionals are included in future trials and improve the quality of evidence used for making decisions about treatment. The chief investigator (Jen Carroll) is undertaking this research as part of her PhD studies.

Why have I been invited to attend the consensus meeting?

You have been invited to participate because you have participated in the interview and or the survey phase. Your views are very important to us, particularly in relation to managing the ketogenic diet and the outcomes you feel we should be assessing for children with epilepsy treated with ketogenic diet.

Do I have to take part?

Taking part in the consensus meeting is completely voluntary; you don't have to take part if you don't want to. If you are a parent or carer, your choice to take part or not will not impact on your child's care. If you decide to take part and change your mind you are free to withdraw at any time, without giving a reason.

Can my child attend the meeting?

No, this meeting will assess parents, carers and health professionals views.

Do I need to do anything to prepare for the consensus meeting?

In the weeks before the meeting we will send you a 'pre meeting information pack'. This will contain the list of outcomes which will be discussed at the meeting. If you took part

in the Delphi process, you will also be sent a summary of how you rated each outcome in the survey. This is provided simply to help you remember what was in the survey and how you rated each outcome at the time. You may find it helpful to have it to refer to on the day of the meeting. If you did not take part in the Delphi process, we will send you the list of the outcomes that people were asked to rate in the survey. We have provided you with this to help you understand the kind of things we will be discussing on the day of the meeting. Otherwise, you do not need to do anything to prepare for the meeting.

Who will attend the consensus meeting?

Approximately 30 people will attend the CORE-KDT consensus meeting. This will include a facilitator (chairperson), the research team, parents, carers, health professionals including dietitians, consultant neurologists, epilepsy specialist nurses and neuropsychologists.

What will happen at the consensus meeting?

The meeting will start with an informal introduction to the team and a brief presentation outlining the agenda for the meeting, the background to the Core-KDT project and the findings to date. We will then share the outcomes for which uncertainty exists over their importance for inclusion in the final core outcome set. We will discuss and vote upon these outcomes which did not achieve consensus in the earlier Delphi survey.

We will hold a series of discussions facilitated by an independent chairperson. The aim being to allow people to express their opinions on the outcome and to hear the opinions of others. We will encourage active participation; however, this doesn't mean everyone is expected to speak. You might feel more comfortable sharing your opinions in the chat box that will be available. Either way, all participants are sharing their opinions when they vote. The meeting will be recorded so the research team can revisit discussions to remind them of what was said. This will be treated in confidence. When writing up the results of the meeting, individual comments or votes will not be identifiable.

How will voting take place?

After each discussion, you will be asked to vote on how important it is that the outcome is included in the core outcome set. A vote box will pop up on your screen with clear instructions. Voting will be on a scale from 1-9; not particularly important to critically important. We will do a practise vote during the meeting to ensure everyone understands and is able to vote. The 'pre meeting information pack' (electronic and printed version) will include a form on which you can record your scores manually in case of any technical difficulties on the day.

How will the voting results influence what outcomes are included in the core outcome set?

An outcome will be included in the core outcome set if 70% or more of each group (parents and health professionals) score the outcome between 7-9. It is important to note that the core outcomes agreed will be the minimum set of outcomes to be measured. It's not to say that the excluded outcomes will never be measured again, they can still be measured and included if trials or clinical teams feel they're important to the question they are trying to answer.

How long will the meeting last?

The meeting will start at 10:30 and finish at 14:00 (UK time). Two breaks will be scheduled. Please join the Zoom meeting link from 10:15 to ensure a prompt start.

What is a core outcome set and why do we need it?

To help patients, doctors and other health professionals make decisions about treatments, we need evidence about what works best. Treatments are developed and tested by researchers to make sure they work and are safe. To do this, researchers need to look at the effects those treatments have on patients. Researchers do this by measuring an 'outcome'.

For example, in a study of how well a new asthma treatment works, 'outcomes' might include:

- A measure of how fast you can blow air out of your lungs
- Night time wheeze
- Asthma quality of life measure

What are the challenges in measuring outcomes?

Currently, different studies looking at treatments for the same condition often measure different outcomes. For instance, imagine two studies of how to treat asthma

- Study A - researchers measure night time wheeze
- Study B - researchers measure how fast participants can blow air out of their lungs

When the two studies are finished, we cannot compare or combine their results because they have used different outcomes. We would not be comparing like with like.

How can we solve this problem?

If all studies in a particular health condition used the same outcomes, they could all be compared and combined. This would reduce waste by making best use of all the research.

When a set of main outcomes has been agreed for a health condition, it's called a 'core outcome set'. If all studies in a particular condition, such as epilepsy treated with ketogenic diet therapy, then measured and reported these core outcomes, we could bring together all the studies to get a better understanding of the impact of ketogenic diet therapy.

What makes an outcome 'core'?

There are many different outcomes that can be measured to test how well a treatment works. Some outcomes will be more important to some people than others. For example, one parent whose child has asthma might be very interested in whether a new treatment reduces their night time wheeze. Another parent may be interested in whether the treatment improves their child's quality of life. Parents, carers, patients and health professionals might have different priorities.

For an outcome to be considered critical and 'core', it needs to be relevant and important to parents, carers and health professionals. This is the reason why consensus methods such as the Delphi survey and the consensus meeting are so important. They offer all key stakeholders the opportunity to share their views. The final core outcome set lists all the 'essential' outcomes to be measured, in this case for children with epilepsy treated with ketogenic diet therapy.

Why is it so important to involve parents and carers?

Core outcome sets need to include outcomes that are most relevant to parents and carers, and the best way to do this is to involve them in the development. Interviews with parents during the CORE-KDT study identified 7 new outcomes that had not before been considered in past research studies. These would likely have been missed if parents were not involved in the process.

Will my participation in the meeting be confidential?

Yes, we will always protect the confidentiality and anonymity of all participants and their data. We will anonymise anything you say that might identify you or others when we write up the results. All data from the study will be stored on the University of Plymouth secure network drives. Ethical approval has been granted by London-Surrey REC (19/LO/1680, date: 14/11/19) and supported by the University of Plymouth Faculty Research Ethics and Integrity Committee (FREIC ref 19/20-1197, date: 05/12/19). It is possible that some of the data collected will be looked at by authorised persons from the University of Plymouth to check that the study is being carried out correctly. Anyone who has access to the records will also be governed by the same rules of confidentiality.

It is increasingly common for medical journals to ask for a list of people who contributed to the research to accompany the results. We will ask in the meeting if you would like your name to be included in the list of contributors. If you decide you do not want your name included, you can still take part in the meeting. We will not include the names of anyone who does not give their permission.

How long will the data be kept for?

The University of Plymouth is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Plymouth will keep identifiable information about you for 10 years after the study has finished.

Who has reviewed the study?

This study has been reviewed and approved by London-Surrey Research Ethics Committee (19/LO/1680, date: 14/11/19) and supported by University of Plymouth Faculty Research Ethics and Integrity Committee (FREIC ref 19/20-1197, date: 05/12/19)

Questions?

If you have any questions about the consensus meeting, please don't hesitate to contact one of our research team.

Jen Carroll (University Lecturer, Dietitian, PhD student and Chief Investigator) Jennifer.carroll@plymouth.ac.uk Core-kdt@plymouth.ac.uk **Avril Collinson** (University Lecturer, Dietitian & Director of Studies) Avril.collinson@plymouth.ac.uk	**Our address:** Institute of Health and Community, School of Health Professions, University of Plymouth, Plymouth, PL6 8BH.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to someone from the research team (Jen Carroll or Avril Collinson) who will do their best to answer your questions. If you have a minor complaint or concern then you need to contact the researchers in the first instance.

Formal Complaints

If you wish to make a formal complaint or if you are not satisfied with the response you have gained from the researcher(s) then please contact:
Administrator to Faculty Research Ethics and Integrity Committee
Faculty of Health and Human Sciences,
University of Plymouth,
4th Floor Rolle Building, Drake Circus,
Plymouth, PL4 8AA
Tel: 01752 586992

Who is funding the research?

This study is sponsored by the University of Plymouth, The British Dietetic Association General and Education Trust Fund and Danone Nutricia.

Thank you for taking the time to read the information sheet. If you decide to participate, your consent will be sought.

Acknowledgements

Sections within this information leaflet have been reproduced with permission from the COMET plain language summary, available in full via the COMET website http://www.comet-initiative.org/

Appendix L. Consensus meeting preparation pack

CORE-KDT

Core Outcomes in Refractory Epilepsy with Ketogenic Diet Therapy

Consensus Meeting

Wednesday 23rd February 2022

10:30 -14:00

Agenda and Outcomes Pack

Please review prior to the meeting

Agenda
Consensus meeting Feb 23rd 10:30-14:00

Zoom link:
https://plymouth.zoom.us/j/93609539110?pwd=THMrWjNsYkR0Z2V5VTEzMnh1Mm9LZz09

Meeting ID: 936 0953 9110
Passcode: 507487

10:15-10:30	Please join the meeting using the link above
10:30	Welcome and Introductions
10:40	Overview of study findings and plan for the meeting
11:05	Discussion and voting on undecided outcomes
11:30	Coffee break
11:40	Discussion and voting on undecided outcomes
12:45	Lunch Break
13:15	Discussion and voting on undecided outcomes
13:50	Meeting evaluation
14:00	Meeting close

Preparation for Consensus meeting

Please could you review the documentation in this pack before the meeting.

Overview

Parents, carers, health professionals and researchers took part in a two round online Delphi survey to rate the importance of a long list of outcomes (89 in round 2) for use in childhood epilepsy treated with ketogenic diet therapy. The aim was to identify which outcomes are critically important to include in a core outcome set. This process resulted in 22 outcomes identified for inclusion and 17 outcomes for exclusion from the core outcome set. The remaining 50 outcomes are classified as 'undecided'. We cannot discuss and vote upon all 50 'undecided' outcomes at this consensus meeting, so we have prioritised those closest to achieving consensus.

For further information, please refer to the Consensus Meeting Information for Participants sheet shared via email when invited to join the consensus meeting.

Prior to the meeting

Before joining the meeting please complete these 3 tasks:

1. Review the 'undecided' outcomes which are closest to achieving consensus (Table 1) which we will prioritise for discussion and voting at the consensus meeting. You may wish to make notes about any points you wish to raise in the discussions.

2. Review the remaining 'undecided' outcomes (Table 2). These are very unlikely to achieve consensus, as few parents, carers, health professionals or researchers rated them as critically important for inclusion in the core outcome set. We are not planning to discuss and vote on these. Nevertheless, you do now have the chance to propose one or more of these outcomes to be discussed at the meeting. You just need to complete a simple online form saying which outcome you think we should discuss and why. **(deadline: Friday 18th February 2022)**

3. Please complete and return the consent form to core-kdt@plymouth.ac.uk

Useful Information to familiarise yourself with before the meeting

4. It is useful to be aware of the outcomes which have achieved consensus for inclusion (Table 3) or exclusion (Table 4) from the core outcome set. These will not be discussed at the meeting as consensus has already been achieved.

5. If you took part in the Delphi survey, a summary of your scores are also attached which you can refer to during the meeting.

6. At the end of this document you can find table 5. This is for you to use in case you experience technical difficulties with online voting during the consensus meeting. Simply manually record your rating for each outcome and we will collect this from you after the meeting. We will remind you of this contingency plan on the day.

Table 1. Undecided outcomes for discussion and voting in the consensus meeting

These 19 outcomes have been prioritised for discussion and voting because 70% or more of **one group** (group 1-parents and carers, group 2-health professionals and researchers) rated the outcome as critically important. These are highlighted in green. Less than 70% of the other group rated the outcome as critically important.

Outcome	Description	% Parents rated 7-9	% HP rated 7-9
Spasm freedom	Not having spasms	69	86
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)	68	70
Unplanned hospital admissions	Unexpectedly needing to be admitted to hospital for epilepsy or KD related issues	66	81
Behavioural feeding difficulties	Challenges with feeding, for example food fussiness, food refusal, difficulty with textures and long mealtimes	65	83
Physical feeding difficulties	For example, difficulty swallowing or unable to consume the necessary volume and hence requires tube feeding	54	74
Vitamin and mineral blood concentrations	Blood tests to check the concentration (levels) of vitamins, minerals and associated markers; aiding diagnosis of deficiency or toxicity	70	65
Concentration	Change in ability to focus on a given task while ignoring distraction. For example, from parents, teachers, or others perspective	82	62
Side effects of parenteral nutrition	Side effects experienced when having ketogenic parental nutrition (feeding into a vein; not oral or tube feeding)	63	77
Parents confidence with KD	Parents feelings towards being able to cope and manage the KD	64	86

Parent or primary carers quality of life	Parent or primary carers general well-being in terms of health, comfort and happiness	57	90
Parental stress associated with the management of KD therapy	The level of stress parents experience when managing KD for their child, this might change over time.	55	72
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	56	78
Side effects of anti-epileptic (AED) drugs	Side effects experienced with the use of anti-epileptic medications	85	48
Time to respond to KD	The point at which improvement in epilepsy is seen after commencing KD	51	73
KD duration	Length of time on KD which may encompass reasons for weaning from KD, length of KD trial, recommencing KD after a failed weaning attempt	39	78
Mood	Change in general sense of positive or negative mood	71	48
Developmental milestones	Progress in meeting milestones such as smiling, sitting without support, responding to requests, sorting shapes and colours	47	70
Growth	Changes in weight, length, height or growth centile	39	85
Cost effectiveness of KD	Is KD a cost effective treatment for epilepsy, this could include analysis of the keto or clinical trial team workload or the service delivery model in place (for example comparing the cost of virtual versus in person consultations)	36	73

Table 2. Undecided outcomes requiring proposal for voting at the consensus meeting

70% or less of **both groups** rated these 31 outcomes as critically important and hence they are unlikely to reach consensus for inclusion in the core outcome set. It is not feasible to discuss and vote upon these undecided outcomes, in addition to those in table 3.

However, if you feel strongly that an outcome listed below is critically important, you can propose it for voting at the meeting. We ask you to consider if it is **critically important** to measure for **all children** with epilepsy treated with ketogenic diet therapy, in addition to the **22 outcomes** (Table 3) already in the core outcome set. If the core outcome set contains too many outcomes it will have limited use in future research and clinical practice.

Propose an outcome for voting by following the link (deadline Fri 18th Feb)

https://plymouth.onlinesurveys.ac.uk/core-kdt-consensus-meeting-proposal-of-outcomes-for-voti-2

Outcome	Description	% Parents rated 7-9	% HP rated 7-9
Use of Emergency Services	Epilepsy or KD related issues leading to contact with emergency services (for example 999 or 112 calls), who then advise over the phone or send an ambulance. However, the reason for calling is managed or resolved so the child is not brought to A&E.	43	68
Bone fractures	Experiencing a broken bone	58	66
Carnitine deficiency	Carnitine is a natural substance that the body uses to process fat (for example from butter, cream, oil and nuts) and make energy. Deficiency (too little) may occur and if so dietary changes or supplements might be needed.	45	64

Bone health	Examining bone health through DEXA scanning, a high precision xray that measures bone mineral density and bone loss.	62	63
Quality adjusted life years for parent or primary carer of child on KD	Quality adjusted life years for parent or primary carer of child on KD	50	63
Length of hospital stays	Number of inpatient days in hospital in a given period of time, for example in the past year	56	62
Constipation	Difficulty in passing a stool (poo) or going to the toilet less often	50	62
Blood glucose levels	Blood concentrations (levels) of glucose (sugar) are often measured by a finger prick test. This outcome would include monitoring of low blood glucose levels called hypoglycaemia.	50	62
Electrolyte deficiency	Electrolytes are essential minerals in the body. The main electrolytes are sodium, potassium, chloride, bicarbonate, calcium and phosphate. These are regularly measured via a blood test when on KD. Deficiency (too little) may occur and if so dietary changes or supplements might be needed.	43	62
Parent or primary carers health	Parent or primary carers emotional, mental and physical wellbeing	50	60
Emotional development	Change in child's understanding of who they are and what they are feeling	68	42
Learning	Change in ability to gain new skills and knowledge For example, from parents, teachers, or others perspective	67	54
Memory	Change in short and long-term memory	66	50
Fatigue	Lacking in energy, feeling more tired or 'drained' than usual	63	51
Family life	Impact of epilepsy and KD on family life including siblings, parents relationship, work and career opportunities	61	58
Social skills	Change in ability to focus on a givne task while ignoring distraction. For	61	47

	example, from parents, teachers, or others perspective		
Side effects that affect hormones	For example, hormones that control mood, growth, development and metabolism	61	41
Onset of ketosis	The time taken to achieve ketosis after commencing KD	60	58
Speech and language	Change in child's ability to make themselves understood and their understanding when spoken to	60	48
Recovery time following a seizure (Postictal State)	The postictal state refers to the period that begins immediately after a seizure and ends when the child's condition returns to baseline. Some refer to this as the 'recovery time' after a seizure.	60	45
Activities of daily living	Change in ability to carry out key activities like feeding oneself, toileting, washing and dressing	60	40
Independence	Child becoming as independent as they can, for example; needing less supervision or walking to school alone	59	46
Time spent asleep	Total time spent asleep in each 24-hour period	58	46
Antiepileptic drug (AED) blood concentrations	The concentration or level of antiepileptic drugs in the blood	54	21
Educational attainment and progress	This describes the progress a child is making over time when comparing their results (attainments) in assessments or tests. Their teacher could assess this.	52	43
Thyroid function tests	A blood test to check levels of thyroid hormones	52	20
Electroencephalogram (EEG) findings	Changes in the EEG. An EEG looks at what is happening in the brain – the activity of the brain cells.	46	57
Gastro oesophageal reflux	High fat intake can exacerbate existing reflux for some children	46	54
Food preference	Change in preferred foods while on KD or when weaned from KD	38	54
Onset of therapeutic ketosis	The time taken to achieve therapeutic ketosis (target ketone level range agreed with the keto team) after commencing KD	38	52

Financial burden of ketogenic diet therapy	The additional cost of KD to the family. For example this might include equipment like weighing scales, food storage, shop bought or prescription products depending on country of residence.	32	55

Table 3. Outcomes IN the core outcome set

Results from the recent Delphi survey indicate that these 22 outcomes reached consensus for **inclusion** in the core outcome set. 70% or more of both groups (group 1-parents, group 2-health professionals + researchers) rated each outcome between 7-9 **i.e. critically important.**

Outcome	Description	% Parents rated 7-9	% HP rated 7-9
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.	97	100
Seizure freedom	Not having seizures	79	88
Seizure duration	How long a seizure lasts	83	89
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	78	93
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	89	96
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 minutes or more it is called status epilepticus or 'status'.	96	98
Use of rescue medication for status epilepticus	How often rescue medication is used	84	85

AED drug use	Number and dose of antiepileptic drugs to reflect recent changes such as weaning from an AED	78	88
Side effects that effect the liver	For example, deranged liver function blood tests and gallstones	71	81
Side effects that effect the heart	For example, high blood pressure and associated heart problems	70	78
Side effects that effect breathing	Side effects that affect breathing	73	77
Dietary adherence	How closely the patient follows the agreed dietary and monitoring plan	81	99
Ketone levels	Urine or blood concentrations (levels) of ketones including excess ketosis (hyperketosis)	78	81
Tolerability of KD	How well the child can manage the KD and its challenges	79	97
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)	75	76
Quality of life for child on KD	Childs general well-being in terms of health, comfort and happiness	86	96
Alertness	Change in level of alertness. Being awake, aware, attentive and prepared to act or react. The fog' lifting and being more present	86	76
Behaviour	Change in behaviour. Childs actions, reactions and functioning in response to everyday environment and situations. Their ability to adapt to surroundings and situations. For example, from parents, teachers, or others perspective	76	72
Participation in everyday life	Change in ability to join in and undertake activities, for example attending school, swimming, playing with friends, joining nursery and playgroups, sleepovers and school trips	83	70
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	70	80
Quality adjusted life	A 'quality adjusted life year' takes account of how a treatment affects a child's quantity and	74	77

years for child on KD	quality of life. It can be used to assess the cost effectiveness of treatments.		
Parents feel supported to manage KD therapy	Parents feel supported and enabled to manage and deliver the KD for their child. For example, this support might come from the keto team, charity organisations or the clinical trial team.	78	86

Table 4. Outcomes OUT of the core outcome set

Results from the recent Delphi survey indicate that these 17 outcomes reached consensus for **exclusion** from the core outcome set. 50% or less of each group (group 1-parents, group 2-health professionals or researchers) rated each outcome between 7-9 i.e. critically important.

Outcome	Description	% Parents rated 7-9	% HP rated 7-9
Non antiepileptic medication use	Name and dose of other non-antiepileptic medications including recent changes. For example, medication to help manage side effects of KD.	26	17
Cerebrospinal fluid (CSF) concentrations of neurotransmitters	Concentration (level) of key neurotransmitters in the cerebrospinal fluid, for example dopamine, serotonin and norepinephrine	16	4
Cholesterol levels	The concentration or level of cholesterol in the blood. This can increase for some children treated with KD	41	37
Gut bacteria	Changes in the types and proportions of bacteria in the gut	36	12
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.	30	10

Prophylactic potassium citrate use	If potassium citrate is used, does it reduce the incidence of kidney stones	44	44
Appetite	Change in the desire to eat food or drink	32	41
Resting energy expenditure (REE)	Change in resting energy expenditure (calories or energy needed to maintain normal function)	24	23
Energy utilisation	Change in breakdown of fat and carbohydrate measured using a respirometer	44	29
Hyperactivity	Change in level of hyperactivity which is described as being unusually and extremely active	39	43
Movement ability	Change in ability to sit, crawl, walk, run or jump	50	33
Coordination and balance	Change in ability to use parts of body together and efficiently for example riding a bike	35	30
Manual ability	Change in dexterity in handling objects like cutlery and toys	31	25
Daytime sleepiness	Feeling sleepy or actually sleeping during the day	50	41
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)	32	32
Hyperuricaemia	This occurs when there is too much uric acid in the blood. It can be measured via a urine or blood test.	40	27
Use of outpatient services and appointments	KD may result in a change in the frequency of outpatient appointments, for example GP visits or other health and social care appointments	22	38

Table 5. Manual voting if technical issues

If you are unable to vote online during the meeting owing to technical issues, please record your scores on this table following discussion of each outcome in the meeting. Please email your completed score sheet to core-kdt@plymouth.ac.uk.

- 1,2,3 indicates the outcome is **not important** and should not be added to the core outcome set
- 4,5,6 indicates the outcome is **important but not critical** and hence should not be added to the core outcome set

- 7,8,9 indicates the outcome is **critically important** and should be added to the core outcome set

Outcome	Score
Side effects of anti-epileptic (AED) drugs	
Concentration	
Mood	
Vitamin and mineral blood concentrations	
Parent or primary carers quality of life	
Spasm freedom	
Parents confidence with KD	
Growth	
Behavioural feeding difficulties	
Unplanned hospital admissions	
Kidney stones	
KD duration	
Side effects of parenteral nutrition	
Physical feeding difficulties	
Time to respond to KD	
Cost effectiveness of KD	
Parental stress associated with the management of KD therapy	
Palatability of KD formula and supplements	
Developmental milestones	
Use of Emergency Services	
Bone fractures	

Carnitine deficiency	
Bone health	
Quality adjusted life years for parent or primary carer	
Length of hospital stays	
Constipation	
Blood glucose levels	
Electrolyte deficiency	
Parent or primary carers health	
Emotional development	
Learning	
Memory	
Fatigue	
Family life	
Social skills	
Side effects that affect hormones	
Onset of ketosis	
Speech and language	
Recovery time following a seizure (Postictal State)	
Activities of daily living	
Independence	
Time spent asleep	
Antiepileptic drug (AED) blood concentrations	
Educational attainment and progress	
Thyroid function tests	

Electroencephalogram (EEG) findings	
Gastro oesophageal reflux	
Food preference	
Onset of therapeutic ketosis	
Financial burden of ketogenic diet therapy	

Evaluation of the CORE-KDT consensus meeting

Following the meeting, we would be very grateful if you would share your experiences and views of the meeting by completing our short online feedback form (link below) before Monday 28.02.22. This should take no more than 5-10 minutes.

https://plymouth.onlinesurveys.ac.uk/core-kdt-consensus-meeting-feedback-form-copy

Appendix M. Faculty ethical approval of PPI consultation

UNIVERSITY OF PLYMOUTH

15th February 2019

Jennifer Carroll
School of Health Professions
Faculty of Health and Human Sciences
University of Plymouth
Room SF11, Pennisula Allied Health Centre
Derriford Road
Plymouth
PL6 8BH

Dear Jennifer,

Application for Approval by Faculty Research Ethics and Integrity Committee

Reference Number: **18/19-1022**
Application Title: **Involving parents in the design of a study to examine outcomes of importance in childhood epilepsy treated with ketogenic diet therapy. (A patient and public involvement consultation)**

The Chair has granted ethical approval to conduct this patient and public involvement (PPI) consultation.

This approval is for the duration of the PPI consultation as stated on your application form (1st March 2019 to 31st August 2019). If you wish to continue beyond this date, you will need to seek an extension.

Please note that if you wish to make any MAJOR changes to your research you must inform the Committee. Please contact the Faculty Research Administrator, Maurice Bottomley (email hhsethics@plymouth.ac.uk).

Yours sincerely

Professor Paul H Artes, PhD MCOptom
Professor of Eye and Vision Sciences
Co-Chair, Research Ethics and Integrity Committee -
Faculty of Health & Human Sciences and
Faculty of Medicine & Dentistry

Professor Paul H Artes, PhD Co-Chair, Faculty of Health & Human Sciences Research Ethics and Integrity Committee,
4th Floor Rolle Building, University of Plymouth, Drake Circus, Devon PL4 8AA
T +44(0)1752 586992 E hhsethics@plymouth.ac.uk W www.plymouth.ac.uk

Appendix N. NHS HRA Ethical approval for the CORE-KDT study

Mrs Jennifer Carroll
Lecturer in Dietetic Practice

University of Plymouth
Institute of Health & Community, University of Plymouth, Penninsula Allied Health Centre
Derriford Road, Plymouth.
PL6 8BH

Email:
hra.approval@nhs.net
HCRW.approvals@wales.nhs.uk

14 November 2019 (Re-issued 15 November 2019)

Dear Mrs Carroll

HRA and Health and Care

Study title:	**Core Outcomes for Refractory childhood Epilepsy treated with Ketogenic Diet Therapy. The CORE-KDT study.**
IRAS project ID:	**251380**
Protocol number:	**1.3**
REC reference:	**19/LO/1680**
Sponsor	**The University of Plymouth**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **251380**. Please quote this on all correspondence.

Yours sincerely,

Nicole Curtis

Approvals Specialist

Email: hra.approval@nhs.net

Copy to: *Mrs Sarah C Jones*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Contract/Study Agreement template [Model NC PIC Agreements x 13]	V1.0	29 July 2019
Copies of advertisement materials for research participants [Advertising leaflet]	V1.1	01 July 2019
Covering letter on headed paper [Cover letter]		03 July 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor insurance certificates]	V1.1	24 May 2019
Interview schedules or topic guides for participants [Semi structured interview schedule]	V1.1	01 July 2019
IRAS Application Form [IRAS_Form_25092019]		25 September 2019
Letter from funder [BDA GET Grant confirmation]	V1.0	12 September 2019
Letter from sponsor [UofP Sponsor Letter]	V1.0	07 October 2019
Letter from statistician [Statistician review]		03 September 2018
Other [Webpage text]	V1.1	01 July 2019
Other [Social Media Post]	V1.0	15 May 2019
Other [Study logo]	V1.0	15 May 2019
Other [Response to REC feedback]	V1.0	21 October 2019
Other [Funder University of Plymouth V1.0]	V1.0	11 April 2018
Other [Response to HRA feedback V1.1]	V1.1	06 November 2019
Participant consent form [Consent form]	V1.0	18 October 2019
Participant consent form [Consent form CORE-KDT V1.3]	V1.3	18 October 2019
Participant information sheet (PIS) [PIS Parents CORE-KDT V1.5]	V1.5	06 November 2019
Participant information sheet (PIS) [PIS PRofessionals CORE-KDT V1.5]	V1.5	06 November 2019
Referee's report or other scientific critique report [protocol review]		09 May 2018
Research protocol or project proposal [Mixed Methods Protocol]	V1.4	21 October 2019
Summary CV for Chief Investigator (CI) [CV J Carroll V1.1]	V1.1	07 October 2019
Summary CV for student [CV J Carroll]	V1.1	07 October 2019
Summary CV for supervisor (student research) [Supervisor CV]	V1.0	07 October 2019
Summary CV for supervisor (student research) [Supervisor CV]	V1.0	07 October 2019
Summary CV for supervisor (student research) [A Collinson CV]		19 July 2019
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Summary flowchart CORE-KDT]	V3	08 August 2018

Appendix O. Faculty Ethical approval for the CORE-KDT study

RE: Faculty ethical approval following HRA and REC approval - Jennifer Carroll (IRAS 251380 FREIC 19/20-1197)

hhsethics

Thu 05/12/2019 11:59

To: Jennifer Carroll <jennifer.carroll@plymouth.ac.uk>
Cc: Plymouth Sponsor <plymouth.sponsor@plymouth.ac.uk>; Paul Artes <paul.artes@plymouth.ac.uk>

Dear Jennifer

Re: IRAS 251380 (FREIC ref 19/20-1197) - 'Core Outcomes for Refractory childhood Epilepsy treatec with Ketogenic Diet Therapy. The CORE-KDT study.'

Thank you for informing the Faculty Research Ethics and Integrity Committee (FREIC) about recent developments with this research. It has been noted that the research project has been granted ethica approval by the HRA (REC reference 19/LO/1680), so you will not require additional ethical approval from the FREIC.

Plymouth Sponsor office has been copied in to this email so they can also keep a note for their records.

Many thanks and best wishes,

Mo

Mo Bottomley
Research Administrator
Research Support Team
Faculty of Health: Medicine, Dentistry & Human Sciences
University of Plymouth, 4th Floor Rolle Building, Drake Circus,
Plymouth, PL4 8AA

Appendix P. Paper 3: Results of Phase 1-3

Seizure: European Journal of Epilepsy 99 (2022) 54–67

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

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

Jennifer H. Carroll [a,*], Kirsty J. Martin-McGill [b], J. Helen Cross [c], Mary Hickson [a], Emma Williams [d], Val Aldridge [d], Avril Collinson [a]

[a] Faculty of Health, University of Plymouth, Devon, United Kingdom
[b] The Centre for Advancing Practice, Health Education England, Liverpool, United Kingdom
[c] Developmental Neurosciences, UCL, NIHR BRC Great Ormond Street Institute of Child Health, London, United Kingdom
[d] Matthew's Friends, Lingfield, Surrey, United Kingdom

ARTICLE INFO

Keywords:
Ketogenic diet
Paediatric epilepsy
Outcome
Qualitative
Core outcome set
Scoping review

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

* Corresponding author.
E-mail address: jennifer.carroll@plymouth.ac.uk (J.H. Carroll).

https://doi.org/10.1016/j.seizure.2022.05.009
Received 28 February 2022; Received in revised form 23 April 2022; Accepted 10 May 2022
Available online 13 May 2022

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 **Di**et **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).

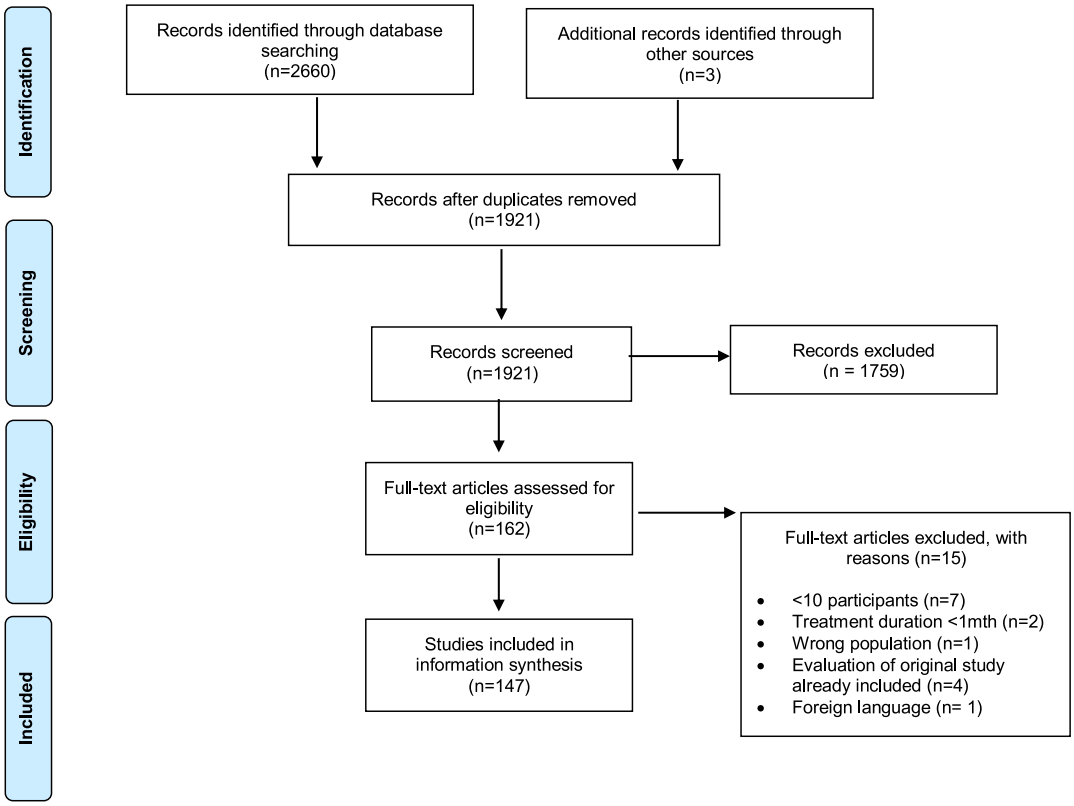


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of scoping review.

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

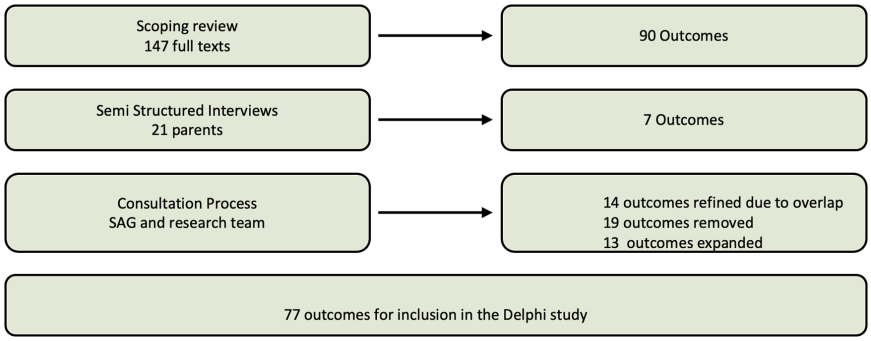


Fig. 2. Overview of identification and ratification of outcomes for inclusion in a Delphi Study.

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.

Funding

This review will contribute to a Doctor of Philosophy for JC, funding is received from the University of Plymouth and The British Dietetic

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

Association General Education Trust Fund.

JHC is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital.

There are no conflicts of interest to declare.

Acknowledgements

The authors would like to extend their thanks to the following participant identification centres who supported recruitment: Matthew's Friends, Young Epilepsy, Epilepsy – The Ketogenic Way, University Hospitals of Leicester NHS Trust, Leeds Teaching Hospitals NHS Trust, Sheffield Children's NHS Foundation Trust, Cambridge University Hospitals NHS Foundation Trust, Manchester University NHS Foundation Trust, Birmingham, Women's and Children's NHS Foundation Trust, Royal Devon and Exeter NHS Foundation Trust, Great Ormond Street Hospital for Children NHS Foundation Trust, Royal Berkshire NHS Foundation Trust. We thank Diana Lynch Bodger and Ellen Wilford (RD) for their support as members of the study advisory group.

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.

References

[1] Sillanpaa M, Schmidt D. Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. Brain 2006;129:617–24.
[2] Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. Epilepsia 2005;46(4):561–7.
[3] Wirrell E, Wong-Kisiel L, Mandraker J, Nickels K. Predictors and course of medically intractable epilepsy in young children presenting before 36 months of age: a retrospective, population-based study. Epilepsia 2012;53(9):1563–9.
[4] Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med 2011; 365(10):919–26.
[5] Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. Pediatrics 2012;129(2):256–64.
[6] Wilder RM. The effects of ketonemia on the course of epilepsy. Mayo Clin Proc 1921;2:307.
[7] Huttenlocher PR, Wilbourn AJ, Signore JM. Medium-chain triglycerides as a therapy for intractable childhood epilepsy. Neurology 1971;21(11):1097–103.
[8] Kossoff EH, Cervenka MC, Henry BJ, Haney CA, Turner Z. A decade of the modified Atkins diet (2003-2013): results, insights, and future directions. Epilepsy Behav 2013;29:437–42.
[9] Pfeifer HH, Thiele EA. Low-glycemic-index treatment: a liberalized ketogenic diet for treatment of intractable epilepsy. Neurology 2005;65(11):1810–2.
[10] Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: a randomized controlled trial. Epilepsia 2013;54(3):481–6.
[11] Lambrechts DA, de Kinderen RJ, Vles JS, de Louw AJ, Aldenkamp AP, Majoie HJ. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand 2017;135(2):231–9.
[12] Raju KN, Gulati S, Kabra M, Agarwala A, Sharma S, Pandey RM, et al. Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open labeled study. Epilepsy Res 2011;96(1–2):96–100.
[13] Kim JA, Yoon JR, Lee EJ, Lee JS, Kim JT, Kim HD, et al. Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy. Epilepsia 2016;57(1):51–8.
[14] Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7(6):500–6.
[15] Sharma S, Goel S, Jain P, Agarwala A, Aneja S. Evaluation of a simplified modified Atkins diet for use by parents with low levels of literacy in children with refractory epilepsy: a randomized controlled trial. Epilepsy Res 2016;127:152–9.
[16] El-Rashidy OF, Nassar MF, Abdel-Hamid IA, Shatla RH, Abdel-Hamid MH, Gabr SS, et al. Modified Atkins diet vs classic ketogenic formula in intractable epilepsy. Acta Neurol Scand 2013;128(6):402–8.
[17] IJff DM, Postulart D, Lambrechts DAJE, Majoie MHJM, de Kinderen RJA, Hendriksen JGM, et al. Cognitive and behavioral impact of the ketogenic diet in children and adolescents with refractory epilepsy: a randomized controlled trial. Epilepsy Behav 2016;60:153–7.
[18] Sondhi V, Agarwala A, Pandey RM, Chakrabarty B, Jauhari P, Lodha R, et al. Efficacy of ketogenic diet, modified Atkins diet, and low glycemic index therapy diet among children with drug-resistant epilepsy: a randomized clinical trial. JAMA Pediatr 2020;174(10):944–51.
[19] Sourbron J, Klinkenberg S, van Kuijk SMJ, Lagae L, Lambrechts D, Braakman HMH, et al. Ketogenic diet for the treatment of pediatric epilepsy: review and meta-analysis. Child's Nerv Syst 2020;36(6):1099–109.
[20] Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev 2020;(6). Article No.: CD001903.
[21] Murakami M, Tognini P. Molecular mechansims underlying the bioactive proeprties of ketogenic diet. Nutrients 2022;14(4):782.
[22] National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management clinical guideline [CG137]. (updated 2020); 2016.
[23] van Berkel AA, IJff DM, Verkuyl JM. Cognitive benefits of the ketogenic diet in patients with epilepsy: a systematic overview. Epilepsy Behav 2018;87:69–77.
[24] Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET handbook: version 1.0. Trials 2017;18(280).
[25] Sinha IP, Gallagher R, Williamson PR, Smyth RL. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. Trials 2012;13(103).
[26] Williamson P, Altman DG, Blazeby J, Clarke M, Gargon E. Driving up the quality and relevance of research through the use of agreed core outcomes. J Heal Serv Res Policy 2012;17(1):1–2.
[27] Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and Explanation. Ann Intern Med 2018;169(7):467–73.
[28] Core Outcome Measures in Effectiveness Trials (COMET) Initiative. CORE-KDT study registration [Internet]. [cited 2021 Jun 26]. Available from: https://www.comet-initiative.org/Studies/Details/1116.
[29] Carroll J, Martin-McGill K, Cross H, Hickson M, Collinson A. Outcome measurement and reporting in childhood epilepsy treated with ketogenic diet therapy: a scoping review protocol. JBI Database Syst Rev Implement Rep 2019; 17(5):633–9.
[30] Keeley T, Williamson P, Callery P, Jones LL, Mathers J, Jones J, et al. The use of qualitative methods to inform Delphi surveys in core outcome set development. Trials 2016;17(1).
[31] Cohen MZ, Kahn DL, Steeves RH. Hermeneutic phenomenological research: a practical guide for nurse researchers. London: Sage; 2000.
[32] Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005;15(9):1277–88.
[33] Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. J Clin Epidemiol 2018;96:84–92.
[34] Agarwal N, Arkilo D, Farooq O, Gillogly C, Kavak KS, Weinstock A. Ketogenic diet: predictors of seizure control. SAGE Open Med 2017;5:1–8.
[35] Amari A, Turner Z, Rubenstein JE, Miller JR, Kossoff EH. Exploring the relationship between preferences for high fat foods and efficacy of the ketogenic and modified Atkins diets among children with seizure disorders. Seizure 2015; 25:173–7.
[36] Arslan N, Kose E, Guzel O. The effect of ketogenic diet on serum selenium levels in patients with intractable epilepsy. Biol Trace Elem Res 2017;178(1):1–6.
[37] Arslan N, Guzel O, Kose E, Yılmaz U, Kuyum P, Aksoy B, et al. Is ketogenic diet treatment hepatotoxic for children with intractable epilepsy? Seizure 2016;43(6): 32–8.
[38] Ashrafi MR, Hosseini SA, Zamani GR, Mohammadi M, Tavassoli A, Badv RS, et al. The efficacy of the ketogenic diet in infants and young children with refractory epilepsies using a formula-based powder. Acta Neurol Belg 2017;117(1):175–82.
[39] Azevedo de Lima P, Baldini Prudêncio M, Murakami DK, Pereira de Brito Sampaio L, Figueiredo Neto AM, Teixeira Damasceno NR. Effect of classic ketogenic diet treatment on lipoprotein subfractions in children and adolescents with refractory epilepsy. Nutrition 2017;33:271–7.
[40] Baby N, Vinayan KP, Pavithran N, Roy AG. A pragmatic study on efficacy, tolerability and long term acceptance of ketogenic diet therapy in 74 South Indian children with pharmacoresistant epilepsy. Seizure 2018;58:41–6.
[41] Bansal S, Cramp L, Blalock D, Zelleke T, Carpenter J, Kao A. The ketogenic diet: initiation at goal calories versus gradual caloric advancement. Pediatr Neurol 2014;50(1):26–30.
[42] Barzegar M, Irandoust P, Mameghani ME. A modified Atkins diet for intractable childhood epilepsy. Iran J Child Neurol 2010;4(3):15–20.
[43] Beniczky S, Miranda MJ, Alving J, Heber Povlsen J, Wolf P. Effectiveness of the ketogenic diet in a broad range of seizure types and EEG features for severe childhood epilepsies. Acta Neurol Scand 2010;121(1):58–62.
[44] Bergqvist AGC, Schall JI, Stallings VA, Zemel BS. Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. Am J Clin Nutr 2008;88(6):1678–84.
[45] Caraballo RH, Vaccarezza M, Cersosimo R, Rios V, Soraru A, Arroyo H, et al. Long-term follow-up of the ketogenic diet for refractory epilepsy: multicenter Argentinean experience in 216 pediatric patients. Seizure 2011;20(8):640–5.
[46] Caraballo RH. Nonpharmacologic treatments of Dravet syndrome: focus on the ketogenic diet. Epilepsia 2011;52(2):79–82.
[47] Caraballo RH, Flesler S, Armeno M, et al. Ketogenic diet in pediatric patients with refractory focal status epilepticus. Epilepsy Res 2014;108:1912–6.
[48] Chen W, Kossoff EH. Long term follow-up of children treated with the modified Atkins diet. J Child Neurol 2012;27(6):754–8.
[49] Chomtho K, Suteerojntrakool O, Chomtho S. Effectiveness of medium chain triglyceride ketogenic diet in Thai children with intractable epilepsy. J Med Assoc Thail 2016;99(2):159–65.
[50] Christodoulides SS, Neal EG, Fitzsimmons G, Chaffe HM, Jeanes YM, Aitkenhead H, et al. The effect of the classical and medium chain triglyceride ketogenic diet on vitamin and mineral levels. J Hum Nutr Diet 2011;25(1):16–26.
[51] Coppola G, Verrotti A, Ammendola E, Operto FF, della Corte R, Signoriello G, et al. Ketogenic diet for the treatment of catastrophic epileptic encephalopathies in childhood. Eur J Paediatr Neurol 2010;14(3):229–34.
[52] Coppola G, Verrotti A, D'Aniello A, Arcieri S, Operto FF, Della Corte R, et al. Valproic acid and phenobarbital blood levels during the first month of treatment with the ketogenic diet. Acta Neurol Scand 2010;122(4):303–7.
[53] Coppola G, D'Aniello A, Messana T, Di Pasquale F, Della Corte R, Pascotto A, et al. Low glycemic index diet in children and young adults with refractory epilepsy: first Italian experience. Seizure 2011;20(7):526–8.
[54] Coppola G, Natale F, Torino A, Capasso R, D'Aniello A, Pironti E, et al. The impact of the ketogenic diet on arterial morphology and endothelial function in children and young adults with epilepsy: a case-control study. Seizure 2014;23(4):260–5.
[55] Cubukcu D, Guzel O, Arslan N. Effect of ketogneic diet on motor functions and daily living activities of children with multidrug-resistant epilepsy: a prospective study. J Child Neurol 2018;33(11):718–23.

[56] Dahlin M, Mansson J-E, Amark P. CSF levels of dopamine and serotonin, but not norepinephrine, metabolites are influenced by the ketogenic diet in children with epilepsy. Epilepsy Res 2012;99(1–2):132–8.
[57] de Kinderen RJA, Lambrechts DAJE, Wijnen BFM, Postulart D, Aldenkamp AP, Majoie MHJM, et al. An economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy: an interim analysis. Epilepsia 2016;57(1):41–50.
[58] Dekker CF, Van Den Hurk TAM, Van Nieuwenhuizen O. Does a preference for fatty foods prior to commencing treatment with the ketogenic diet predict the efficacy of this diet? Seizure 2010;19(7):421–5.
[59] Doksöz Ö, Güzel O, Yilmaz Ü, Işgüder R, Çeleğen K, Meşe T. Dispersion durations of P-wave and QT interval in children treated with a ketogenic diet. Pediatr Neurol 2014;50(4):343–6.
[60] Doksöz Ö, Çelelen K, Güzel O, Yilmaz Ü, Uysal U, Işgüder R, et al. The short-term effects of ketogenic diet on cardiac ventricular functions in epileptic children. Pediatr Neurol 2015;53(3):233–7.
[61] Doksöz Ö, Guzel O, Yilmaz Ü, Isguder R, Celegen K, Mese T, et al. The short term effect of ketogenic diet on carotid intima-media thickness and elastic properties of the carotid artery and the aorta in epileptic children. J Child Neurol 2015;30(12):1646–50.
[62] Dressler A, Stöcklin B, Reithofer E, Benninger F, Freilinger M, Hauser E, et al. Long-term outcome and tolerability of the ketogenic diet in drug-resistant childhood epilepsy-the austrian experience. Seizure 2010;19(7):404–8.
[63] Dressler A, Trimmel-Schwahofer P, Reithofer E, Mühlebner A, Gröppel G, Reiter-Fink E, et al. Efficacy and tolerability of the ketogenic diet in Dravet syndrome - comparison with various standard antiepileptic drug regimen. Epilepsy Res 2015;109(1):81–9.
[64] Dressler A, Trimmel-Schwahofer P, Reithofer E, Gröppel G, Mühlebner A, Samueli S, et al. The ketogenic diet in infants - advantages of early use. Epilepsy Res 2015;116:53–8.
[65] Dressler A, Haiden N, Trimmel-Schwahofer P, Benninger F, Samueli S, Gröppel G, et al. Ketogenic parenteral nutrition in 17 pediatric patients with epilepsy. Epilepsia Open 2018;3(1):30–9.
[66] Ebus SCM, Lambrechts DAJE, Herraets IJT, Majoie MJM, De Louw AJ, Boon PJ, et al. Can an early 24-hour EEG predict the response to the ketogenic diet? A prospective study in 34 children and adults with refractory epilepsy treated with the ketogenic diet. Seizure 2014;23(6):468–74.
[67] El-Rashidy OF, Nassar MF, El Gendy YG, Deifalla SM, Gaballa S. Experience with MAD on children with epilepsy in Egypt after classic KD failure. Acta Neurol Scand 2017;137(2):195–8.
[68] Ferraria N, Mendes P, Oliveira F, Martins C, Fonseca MJ, Monteiro JP. Ketogenic diet for refractory epilepsy in children-an institutional experience. Pediatr Ther 2013;3(3):1–4.
[69] Ghazavi A, Tonekaboni SH, Karimzadeh P, Nikibakhsh AA, Khajeh A, Fayyazi A. The ketogenic and Atkins diets effect on intractable epilepsy: a comparison. Iran J Child Neurol 2014;8(3):12–7.
[70] Groleau V, Schall JI, Stallings VA, Bergqvist CA. Long-term impact of the ketogenic diet on growth and resting energy expenditure in children with intractable epilepsy. Dev Med Child Neurol 2014;56(9):898–904.
[71] Güzel O, Yılmaz U, Uysal U, Arslan N. The effect of olive oil-based ketogenic diet on serum lipid levels in epileptic children. Neurol Sci 2016;37(3):465–70.
[72] Hallböök T, Sjölander A, Åmark P, Miranda M, Bjurulf B, Dahlin M. Effectiveness of the ketogenic diet used to treat resistant childhood epilepsy in Scandinavia. Eur J Paediatr Neurol 2015;19(1):29–36.
[73] Hong AM, Turner Z, Hamdy RF, Kossoff EH. Infantile spasms treated with the ketogenic diet: prospective single-center experience in 104 consecutive infants. Epilepsia 2010;51(8):1403–7.
[74] Heo Pharm G, Kim SH, Chang MJ. Effect of ketogenic diet and other dietary therapies on anti-epileptic drug concentrations in patients with epilepsy. J Clin Pharm Ther 2017;42(6):758–64.
[75] Hussain SA, Shin JH, Shih EJ, Murata KK, Sewak S, Kezele ME, et al. Limited efficacy of the ketogenic diet in the treatment of highly refractory epileptic spasms. Seizure 2016;35:59–64.
[76] Ismayilova N, Leung MA, Kumar R, Smith M, Williams RE. Ketogenic diet therapy in infants less than two years of age for medically refractory epilepsy. Seizure 2018;57:5–7.
[77] Jung DE, Kang HC, Kim HD. Long-term outcome of the ketogenic diet for intractable childhood epilepsy with focal malformation of cortical development. Pediatrics 2008;122(2):330–3.
[78] Jung DE, Chung JY, Kang HC, Kim HD. Improving tolerability of the ketogenic diet in patients with abnormal endoscopic findings. Brain Dev 2008;30(6):416–9.
[79] Jung DE, Kang HC, Lee JS, Lee EJ, Kim HD. Safety and role of ketogenic parenteral nutrition for intractable childhood epilepsy. Brain Dev 2012;34(8):620–4.
[80] Kang HC, Lee YJ, Lee JS, Lee EJ, Eom S, You SJ, et al. Comparison ofshort- versus long-term ketogenic diet for intractable infantile spasms. Epilepsia 2011;52(4):781–7.
[81] Kang JW, Rhie SK, Yu R, Eom S, Hong W, Kim SH, et al. Seizure outcome of infantile spasms with focal cortical dysplasia. Brain Dev 2013;35(8):816–20.
[82] Kapetanakis M, Liuba P, Odermarsky M, Lundgren J, Hallböök T. Effects of ketogenic diet on vascular function. Eur J Paediatr Neurol 2014;18(4):489–94.
[83] Karimzadeh P, Taberestani S, Mahvelati F, Tonekaboni SH, Ghofrani M. Intractable seizure disorders: efficacy of the classic ketogenic diet. Iran J Child Neurol 2009:15–20.
[84] Karimzadeh P, Sedighi M, Beheshti M, Azargashb E, Ghofrani M, Abdollahe-Gorgi FL. Glycemic index treatment in pediatric refractory epilepsy: the first middle east report. Seizure 2014;23(7):570–2.
[85] Kayyali HR, Gustafson M, Myers T, Thompson L, Williams M, Abdelmoity A. Ketogenic diet efficacy in the treatment of intractable epileptic spasms. Pediatr Neurol 2014;50(3):224–7.
[86] Kayyali HR, Luniova A, Abdelmoity A. Ketogenic diet decreases emergency room visits and hospitalizations related to epilepsy. Epilepsy Res Treat 2016:1–4.
[87] Kessler SK, Gallagher PR, Shellhaas RA, Clancy RR, Bergqvist AGC. Early EEG improvement after ketogenic diet initiation. Epilepsy Res 2011;94(1–2):94–101.
[88] Khoo TB, Tukimin SMB, Syed Zainal Abidin SMB, Lai JJ, Yusoof NAB. Long-term outcome and tolerability of ketogenic diet treatment for refractory epilepsies in children – A tertiary centre Malaysian experience. Neurol Asia 2016;21(1):17–21.
[89] Kim JT, Kang HC, Song JE, Lee MJ, Lee YJ, Lee EJ, et al. Catch-up growth after long-term implementation and weaning from ketogenic diet in pediatric epileptic patients. Clin Nutr 2013;32(1):98–103.
[90] Kim SH, Kang HC, Lee EJ, Lee JS, Kim HD. Low glycemic index treatment in patients with drug-resistant epilepsy. Brain Dev 2017;39(8):687–92.
[91] Kose E, Guzel O, Demir K, Arslan N. Changes of thyroid hormonal status in patients receiving ketogenic diet due to intractable epilepsy. J Pediatr Endocrinol Metab 2017;30(4):411–6.
[92] Kose E, Guzel O, Arslan N. Analysis of hematological parameters in patients treated with ketogenic diet due to drug-resistant epilepsy. Neurol Sci 2018;39(1):85–9.
[93] Kossoff EH, Dorward JL, Turner Z, Pyzik PL. Prospective study of the modified Atkins diet in combination with a ketogenic diet liquid supplement during the initial month. J Child Neurol 2011;26(2):147–51.
[94] Kossoff EH, Hedderick EF, Turner Z, Freeman JM. A case-control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms. Epilepsia 2008;49(9):1504–9.
[95] Kossoff EH, Laux LC, Blackford R, Morrison PF, Pyzik PL, Hamdy RM, et al. When do seizures usually improve with the ketogenic diet? Epilepsia 2008;49(2):329–33.
[96] Kossoff EH, Bosarge JL, Miranda MJ, Wiemer-Kruel A, Kang HC, Kim HD. Will seizure control improve by switching from the modified Atkins diet to the traditional ketogenic diet? Epilepsia 2010;51(12):2496–9.
[97] Kumada T, Imai K, Takahashi Y, Nabatame S, Oguni H. Ketogenic diet using a Japanese ketogenic milk for patients with epilepsy: a multi-institutional study. Brain Dev 2018;40(3):188–95.
[98] Lambrechts DAJE, Bovens MJM, de la Parra NM, Hendriksen JGM, Aldenkamp AP, Majoie MJM. Ketogenic diet effects on cognition, mood, and psychosocial adjustment in children. Acta Neurol Scand 2012;127(2):103–8.
[99] Lambrechts DAJE, de Kinderen RJA, Vles HSH, de Louw AJ, Aldenkamp AP, Majoie MJM. The MCT-ketogenic diet as a treatment option in refractory childhood epilepsy: a prospective study with 2-year follow-up. Epilepsy Behav 2015;51:261–6.
[100] Lambrechts DAJE, Brandt-Wouters E, Verschuure P, Vles HSH, Majoie MJM. A prospective study on changes in blood levels of cholecystokinin-8 and leptin in patients with refractory epilepsy treated with the ketogenic diet. Epilepsy Res 2016;127:87–92.
[101] Laux L, Blackford R. The ketogenic diet in Dravet syndrome. J Child Neurol 2013;28(8):1041–4.
[102] Lee HF, Chi CS, Liao JH. Use of cooking oils in a 2:1 ratio classical ketogenic diet for intractable pediatric epilepsy: long-term effectiveness and tolerability. Epilepsy Res 2018;147:75–9.
[103] Lee YJ, Kang HC, Kim DW, Lee JS, Eun BL, Eun SH, et al. Usefulness of liquid ketogenic milk for intractable childhood epilepsy. Eur E J Clin Nutr Metab 2010;5. e203–7.
[104] Lee J, Lee JH, Yu HJ, Lee M. Prognostic factors of infantile spasms: role of treatment options including a ketogenic diet. Brain Dev 2013;35(8):821–6.
[105] Lemmon ME, Terao NN, NG Y-T, Reisig W, Rubenstein JE, Kossoff EH. Efficacy of the ketogenic diet in Lennox–Gastaut syndrome: a retrospective review of one institution's experience and summary of the literature. Dev Med Child Neurol 2012;54(5):464–8.
[106] Li B, Tong L, Jia G, Sun R. Effects of ketogenic diet on the clinical and electroencephalographic features of children with drug therapy-resistant epilepsy. Exp Ther Med 2013;5(2):611–5.
[107] Lin A, Turner Z, Doerrer SC, Stanfield A, Kossoff EH. Complications during ketogenic diet initiation: prevalence, treatment, and influence on seizure outcomes. Pediatr Neurol 2017;68:35–9.
[108] Liu YMC, Lowe H, Zak MM, Kobayashi J, Chan VW, Donner EJ. Can children with hyperlipidemia receive ketogenic diet for medication-resistant epilepsy? J Child Neurol 2013;28(4):479–83.
[109] McNally MA, Pyzik PL, Rubenstein JE, Hamdy RF, Kossoff EH. Empiric use of oral potassium citrate reduces symptomatic kidney stone incidence with the ketogenic diet. Pediatrics 2009;124(2):300.
[110] Mehta R, Goel S, Sharma S, Jain P, Mukherjee S, Aneja S. Efficacy and tolerability of the modified Atkins diet in young children with refractory epilepsy: indian experience. Ann Indian Acad Neurol 2016;19(4):523–7.
[111] Miranda MJ, Mortensen M, Povlsen JH, Nielsen H, Beniczky S. Danish study of a modified Atkins diet for medically intractable epilepsy in children: can we achieve the same results as with the classical ketogenic diet? Seizure 2011;20(2):151–5.
[112] Alireza MS, Hassan TS, Mohammadreza G, Eznollah A, Fatemeh AG, Mohammad G. Efficacy of the ketogenic diet as a therapy for intractable epilepsy in children. Iran J Child Neurol 2010;4(2):27–36.

[113] Mohammadreza A, Mohammadreza G, Farhad M, Karimzadeh P, Mohammadreza S, Hassan TS. The effect of the ketogenic diet on the growth and biochemical parameters of the children with resistant epilepsy. Iran J Child Neurol 2010;3(4):41–4.
[114] Morrison PF, Pyzik PL, Hamdy RF, Hartman AL, Kossoff EH. The influence of concurrent anticonvulsants on the efficacy ofthe ketogenic diet Peter. Epilepsia 2009;50(8):1999–2000.
[115] Muzykewicz DA, Lyczkowski DA, Memon N, Conant KD, Pfeifer HH, Thiele EA. Efficacy, safety, and tolerability of the low glycemic index treatment in pediatric epilepsy. Epilepsia 2009;50(5):1118–26.
[116] Nabbout R, Copioli C, Chipaux M, Chemaly N, Desguerre I, Dulac O, et al. Ketogenic diet also benefits Dravet syndrome patients receiving stiripentol: a prospective pilot study. Epilepsia 2011;52(7):54–7.
[117] Nathan JK, Purandare AS, Parekh ZB, Manohar HV. Ketogenic diet in Indian children with uncontrolled epilepsy. Indian Pediatr 2009;46(8):669–73.
[118] Nation J, Humphrey M, Mackay M, Boneh A. Linear growth of children on ketogenic diet: does the protein-to-energy ratio matter? J Child Neurol 2014;29 (11):1496–501.
[119] Neal EG, Chaffe HM, Edwards N, Lawson MS, Schwartz RH, Cross JH. Growth of children on classical and medium-chain triglyceride ketogenic diets. Pediatrics 2008;122(2):334–40.
[120] Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia 2009;50(5):1109–17.
[121] Ni Y, Wang XH, Zhang LM, et al. Prospective study of the efficacy of a ketogenic diet in 20 patients with Dravet syndrome. Seizure 2018;60:144–8.
[122] Nizamuddin J, Turner Z, Rubenstein JE, Pyzik PL, Kossoff EH. Management and risk factors for dyslipidemia with the ketogenic diet. J Child Neurol 2008;23(7): 758–61.
[123] Numis AL, Yellen MB, Chu-Shore CJ, Pfeifer HH, Thiele EA. The relationship of ketosis and growth to the efficacy of the ketogenic diet in infantile spasms. Epilepsy Res 2011;96(1–2):172–5.
[124] Ozdemir R, Kucuk M, Guzel O, Karadeniz C, Yilmaz U, Mese T. Does ketogenic diet have any negative effect on cardiac systolic and diastolic functions in children with intractable epilepsy?: One-year follow-up results. Brain Dev 2016; 38(9):842–7.
[125] Özdemir R, Güzel O, Küçük M, Karadeniz C, Katipoglu N, Yilmaz Ü, et al. The effect of the ketogenic diet on the vascular structure and functions in children with intractable epilepsy. Pediatr Neurol 2016;56:30–4.
[126] Ozdemir R, Guzel O, Kucuk M, Karadeniz C, Yilmaz Ü, Calik T, et al. The impact of 3:1 ketogenic diet on cardiac repolarization changes in children with refractory seizures: a prospective follow-up study. Neuropediatrics 2016;47(3):157–61.
[127] Pasca L, Caraballo RH, De Giorgis V, Reyes JG, Macasaet JA, Masnada S, et al. Ketogenic diet use in children with intractable epilepsy secondary to malformations of cortical development: a two- centre experience. Seizure 2018; 57:34–7.
[128] Patel A, Pyzik PL, Turner Z, Rubenstein JE, Kossoff EH. Long-term outcomes of children treated with the ketogenic diet in the past. Epilepsia 2010;51(7): 1277–82.
[129] Paul E, Conant KD, Dunne IE, Pfeifer HH, Lyczkowski DA, Linshaw MA, et al. Urolithiasis on the ketogenic diet with concurrent topiramate or zonisamide therapy. Epilepsy Res 2010;90(1–2):151–6.
[130] Pires ME, Ilea A, Bourel E, Bellavoine V, Merdariu D, Berquin P, et al. Ketogenic diet for infantile spasms refractory to first-line treatments: an open prospective study. Epilepsy Res 2013;105(1–2):189–94.
[131] Porta N, Vallée L, Boutry E, Fontaine M, Dessein AF, Joriot S, et al. Comparison of seizure reduction and serum fatty acid levels after receiving the ketogenic and modified Atkins diet. Seizure 2009;18(5):359–64.
[132] Remahl S, Dahlin MG, Åmark PE. Influence of the ketogenic diet on 24-Hour electroencephalogram in children with epilepsy. Pediatr Neurol 2008;38(1): 38–43.
[133] Rezaei S, Kavoosi M, Badv RS, Mohammadi M, Zamani GR, Ashrafi MR, et al. The influence of ketogenic diet on liver function in children and adolescents with intractable epilepsy. J Compr Pediatr 2017;8(3):e12609.
[134] Sariego-Jamardo A, García-Cazorla A, Artuch R, Castejón E, García-Arenas D, Molero-Luis M, et al. Efficacy of the ketogenic diet for the treatment of refractory childhood epilepsy: cerebrospinal fluid neurotransmitters and amino acid levels. Pediatr Neurol 2015;53(5):422–6.
[135] Schoeler NE, Bell G, Yuen A, Kapelner AD, Heales SJR, Cross JH, et al. An examination of biochemical parameters and their association with response to ketogenic dietary therapies. Epilepsia 2017;58(5):893–900.
[136] Selter JH, Turner Z, Doerrer SC, Kossoff EH. Dietary and medication adjustments to improve seizure control in patients treated with the ketogenic diet. J Child Neurol 2015;30(1):53–7.
[137] Sharma S, Jain P, Gulati S, Sankhyan N, Agarwala A. Use of the modified Atkins diet in Lennox Gastaut syndrome. J Child Neurol 2015;30(5):576–9.
[138] Sharma S, Gulati S, Kalra V, Agarwala A, Kabra M. Seizure control and biochemical profile on the ketogenic diet in young children with refractory epilepsy-Indian experience. Seizure 2009;18(6):446–9.
[139] Sharma S, Gulati S. The ketogenic diet and the QT interval. J Clin Neurosci 2012; 19(1):181–2.
[140] Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet in infantile spasms refractory to first-line treatment. Seizure 2012;21(1):45–8.
[141] Simm PJ, Bicknell-Royle J, Lawrie J, Nation J, Draffin K, Stewart KG, et al. The effect of the ketogenic diet on the developing skeleton. Epilepsy Res 2017;136: 62–6.
[142] Spilioti M, Pavlou E, Gogou M, Katsanika I, Papadopoulou-Alataki E, Grafakou O, et al. Valproate effect on ketosis in children under ketogenic diet. Eur J Paediatr Neurol 2016;20(4):555–9.
[143] Spulber G, Spulber S, Hagenas L, Amark P, Dahlin M. Growth dependence on insulin-like growth factor-1 during the ketogenic diet. Epilepsia 2009;50(2): 297–303.
[144] Stradomska TJ, Bachański M, Pawłowska J, Syczewska M, Stolarczyk A, Tylki-Szymańska A. The impact of a ketogenic diet and liver dysfunction on serum very long-chain fatty acids levels. Lipids 2013;48(4):405–9.
[145] Suo C, Liao J, Lu X, Fang K, Hu Y, Chen L, et al. Efficacy and safety of the ketogenic diet in Chinese children. Seizure 2013;22(3):174–8.
[146] Tagliabue A, Bertoli S, Trentani C, Borrelli P, Veggiotti P. Effects of the ketogenic diet on nutritional status, resting energy expenditure, and substrate oxidation in patients with medically refractory epilepsy: a 6-month prospective observational study. Clin Nutr 2012;31(2):246–9.
[147] Taub katherine S, Kessler SK, Bergqvist AGC. Risk of seizure recurrence after achieving initial seizure freedom on the ketogenic diet. Epilepsia 2014;55(4): 579–83.
[148] Thammongkol S, Vears DF, Bicknell-Royle J, Nation J, Draffin K, Stewart KG, et al. Efficacy of the ketogenic diet: which epilepsies respond? Epilepsia 2012;53 (3):55–9.
[149] Tonekaboni SH, Mostaghimi P, Mirmiran P, Abbaskhanian A, Gorji FA, Ghofrani M, et al. Efficacy of the atkins diet as therapy for intractable epilepsy in children. Arch Iran Med 2010;13(6):492–7.
[150] Tumas R, Cardoso AL, Marques-Dias MJ, Vieira MA. Ketogenic diet in epileptic children: clinical and laboratory assessment. Nutr Hosp 2010;25(2):317–8.
[151] van Delft R, Lambrechts D, Verschuure P, Hulsman J, Majoie M. Blood beta-hydroxybutyrate correlates better with seizure reduction due to ketogenic diet than do ketones in the urine. Seizure 2010;19(1):36–9.
[152] Van Der Louw EJ, Desadien R, Vehmeijer FOL, Van Der Sijs H, Catsman-Berrevoets CE, Neuteboom RF. Concomitant lamotrigine use is associated with decreased efficacy of the ketogenic diet in childhood refractory epilepsy. Seizure 2015;32:75–7.
[153] Vehmeijer FOL, Van Der Louw EJTM, Arts WFM, Catsman-Berrevoets CE, Neuteboom RF. Can we predict efficacy of the ketogenic diet in children with refractory epilepsy? Eur J Paediatr Neurol 2015;19(6):701–5.
[154] Ville D, Chiron C, Laschet J, Dulac O. The ketogenic diet can be used successfully in combination with corticosteroids for epileptic encephalopathies. Epilepsy Behav 2015;48:61–5.
[155] Villeneuve N, Pinton F, Bahi-Buisson N, Dulac O, Chiron C, Nabbout R. The ketogenic diet improves recently worsened focal epilepsy. Dev Med Child Neurol 2009;51(4):276–81.
[156] Walker I, Said RR. Predictors of ketogenic diet Eeficacy in children based on the electroencephalogram (EEG). J Child Neurol 2015;30(10):1270–4.
[157] Wang YS, Hsieh MY, Hung PC, Chou ML, Lin JJ, Chou IJ, et al. Medium-chain triglyceride ketogenic diet for drug-resistant epilepsy in Taiwan: a prospective study in a single center. Neurol Asia 2016;21(4):341–7.
[158] Weber S, Mølgaard C, Taudorf K, Uldall P. Modified Atkins diet to children and adolescents with medical intractable epilepsy. Seizure 2009;18(4):237–40.
[159] Weijenberg A, van Rijn M, Callenbach PMC, de Koning TJ, Brouwer OF. Ketogenic diet in refractory childhood epilepsy: starting with a liquid formulation in an outpatient setting. Child Neurol Open 2018;5:1–7.
[160] Whiting S, Donner E, RamachandranNair R, Grabowski J, Jetté N, Duque DR. Decreased health care utilization and health care costs in the inpatient and emergency department setting following initiation of ketogenic diet in pediatric patients: the experience in Ontario. Canada. Epilepsy Res. 2017;131:51–7.
[161] Wibisono C, Rowe N, Beavis E, Kepreotes H, Mackie FE, Lawson JA, et al. Ten-year single-center experience of the ketogenic diet: factors influencing efficacy, tolerability, and compliance. J Pediatr 2015;166(4):1030–6.
[162] Wiemer-Kruel A, Haberlandt E, Hartmann H, Wohlrab G, Bast T. Modified Atkins diet is an effective treatment for children with Doose syndrome. Epilepsia 2017; 58(4):657–62.
[163] Wijnen BFM, de Kinderen RJA, Lambrechts DAJE, Postulart D, Aldenkamp AP, Majoie MHJM, et al. Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy. Epilepsy Res 2017;132:91–9.
[164] Wirrell E, Eckert S, Wong-Kisiel L, Payne E, Nickels K. Ketogenic diet therapy in infants: efficacy and tolerability. Pediatr Neurol 2018;82:13–8.
[165] Worden LT, Turner Z, Pyzik PL, Rubenstein JE, Kossoff EH. Is there an ideal way to discontinue the ketogenic diet? Epilepsy Res 2011;95(3):232–6.
[166] Wu YJ, Zhang LM, Chai YM, Wang J, Yu LF, Li WH, et al. Six-month efficacy of the Ketogenic diet is predicted after 3 months and is unrelated to clinical variables. Epilepsy Behav 2016;55:165–9.
[167] Xie G, Zhou Q, Qiu CZ, Dai WK, Wang HP, Li YH, et al. Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy. World J Gastroenterol 2017;23(33):6164–71.
[168] Wu Q, Wang H, Fan YY, Zhang JM, Liu XY, Fang XY, et al. Ketogenic diet effects on 52 children with pharmacoresistant epileptic encephalopathy: a clinical prospective study. Brain Behav 2018;8(5):1–8.
[169] Zamani GR, Mohammadi M, Ashrafi MR, Karimi P, Mahmoudi M, Badv RS, et al. The effects of classic ketogenic diet on serum lipid profile in children with refractory seizures. Acta Neurol Belg 2016;116(4):529–34.
[170] Zhang Y, Wang Y, Zhou Y, Zhang L, Yu L, Zhou S. Therapeutic effects of the ketogenic diet in children with Lennox-Gastaut syndrome. Epilepsy Res 2016;128: 176–80.

[171] Zhang Y, Zhou S, Zhou Y, Yu L, Zhang L, Wang Y. Altered gut microbiome composition in children with refractory epilepsy after ketogenic diet. Epilepsy Res 2018;145:163–8.
[172] Zhu D, Wang M, Wang J, Yuan J, Niu G, Zhang G, et al. Ketogenic diet effects on neurobehavioral development of children with intractable epilepsy: a prospective study. Epilepsy Behav 2016;55:87–91.
[173] Fish R, Sanders C, Adams R, Brewer J, Brookes ST, DeNardo J, et al. A core outcome set for clinical trials of chemoradiotherapy interventions for anal cancer (CORMAC): a patient and health-care professional consensus. Lancet Gastroenterol Hepatol 2018;3(12):865–73.
[174] World Health Organization. International classification of functioning, disability and health. Geneva: Switzerland; 2001.
[175] Washington AE, Lipstein SH. The patient-centered outcomes research institute – promoting better information, decisions, and health. N Engl J Med 2011;365(15): 436–45.
[176] Arnold LM, Crofford LJ, Mease PJ, Burgess SM, Palmer SC, Abetz L, et al. Patient perspectives on the impact of fibromyalgia. Patient Educ Couns 2008;73(1): 114–20.
[177] Kirwan J, Heiberg T, Hewlett S, Hughes R, Kvien T, Ahlmèn M, et al. Outcomes from the patient perspective workshop at OMERACT 6. J Rheumatol 2003;30(4): 868–72.
[178] Rosenbaum SE, Glenton C, Nylund HK. Oxman AD. User testing and stakeholder feedback contributed to the development of understandable and useful Summary of Findings tables for Cochrane reviews. J Clin Epidemiol 2010;63(6):607–19.
[179] Fayed N, Cameron S, Fraser D, Cameron JI, Al-Harbi S, Simpson R, et al. Priority outcomes in critically ill children: a patient and parent perspective. Am J Crit Care 2020;29(5):e94–103.
[180] Kerr C, Nixon A, Angalakuditi M. The impact of epilepsy on children and adult patients' lives: development of a conceptual model from qualitative literature. Seizure 2011;20(10):764–74.
[181] Woodgate RL, Edwards M, Ripat JD, Borton B, Rempel G. Intense parenting: a qualitative study detailing the experiences of parenting children with complex care needs. BMC Pediatr 2015;15(1).
[182] Harden J, Black R, Chin RFM. Families' experiences of living with pediatric epilepsy: a qualitative systematic review. Epilepsy Behav 2016;60:225–37.
[183] Webster M. When intesive mothering becomes a necessity. In: Harman V, Cappellini B, Faircloth C, editors. Feeding children inside and outside the home. London: Routledge; 2019. p. 191–206.
[184] Webster M. Siblings' caring roles in families with a child with epilepsy. Sociol Health Illn 2018;40(1):204–17. Jan 1.
[185] Smith G, Wagner J, Andrews J, Austin J, Mueller M, Carter E, et al. Caregiving in pediatric epilepsy: results of focus groups and implications for research and practice. Epilepsy Behav 2014;34(5):34–41.

Appendix Q. Mapping of themes, subthemes, codes and sample qoutes

Candidate Theme and definition	Sub Theme	Code	Sample quotes
1. Epilepsy is all consuming The theme *epilepsy is all consuming* explores the impact of drug resistant epilepsy on the family, the uncertainty they face and the search for answers.	Impact on the family	- Impact on child with epilepsy - Impact on parents - Impact on siblings	*'I guess if you asked what the impact of seizures on our life was, it was our life for quite a number of years. That's what we read and that's what we did, and it was all based around the children. My husband and I didn't really get a look in. Plus, we're at the hospital every two weeks with appointments. We worked full time throughout that as well, both of us, so it was quite a lot going in in the house.' (FP10)*
	Uncertainty of epilepsy	- Day to day uncertainty - Future uncertainty - Searching for the answer - Difficult decisions - Other people are worse off	*'So yeah, 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. The unknown with Dravet, even if he's doing well now, that can change overnight. Prior performance is no guarantee of future outcome. I'm a program manager, I plan. I have plans, and I have my backup plans. Not being able to even envision or plan anything concrete – I know technically you can't for any kid – but it's just extra hard here.' (FP11)*
	Fight for my child	- Unsupportive health professionals - Delay in accessing KD	*'I had to take the initiative and I don't think that's right, because I only know what I know. If I knew nothing about that, how would I know? Surely the professionals should be saying this [KD] is an option.' (FP2)* *'Its [KD] still very much the poor relation, in my view, it feels like the diet's not given an even – that its not an even playing field, which I think is a shame because there are people out there who could benefit from it who are potentially not because they not as pushy as I was and they haven't done the research that I did because of my own background and interest.' (FP1)* *'Everything's a battle, that's one thing we learned. Nothing is easy, nothing's straightforward. A lot of people are nice, and they mean well, but it's a paid job, they don't live it.' (FP14)*

Candidate Theme and definition	Sub Theme	Code	Sample quote
2.Opening the window to new opportunities The theme *opening the window to new opportunities* explores the motivators for KD therapy and the positive outcomes experienced for the child and wider family	Hopes and expectations of trialling KD therapy	- Side effects of ASMs are a motivator for KD - Health professionals who actively encourage and support KD - The possibility for progress - Evolving expectations	*'then you think, well, they talk about balance, which you come back to almost trying to have some better seizure control with a better quality of life rather than trying to dose up... But they're wiped out and they're a bit of a zombie. That's not fair either'. (FP6)* *'from very early on, she [consultant] said you ought to think about the KD. At that point because X was only about 6 and her sister was 9, I just thought I couldn't get my head around that…so we put it off for 2 years…we're exceptionally lucky because had she only asked me once or twice and I'd said no and then she stopped, we probably would never have done it. But because she kept asking me, almost with that smile, have you thought about the diet'. (FP8)* *'We went into it [KD] hopeful that – also the fact that we'd tried the strongest drugs that were available and they hadn't worked, we were kind of like maybe it will work, lets give it a try, we've got nothing to lose…So we thought ok if it knocks it down to one or two [seizures] a year that's great, that's an improvement in itself, and if we could get her off the damn drugs that would be a good impetus. …So yes, we went into it open minded, but we were a little bit sceptical.' (MP1)*
	No longer a passenger	- Parent's sense of purpose and control	*'it was something that we could do. It would take work and effort from us, whereas everything else was just kind of out of our control. It was like, well we should do something to feel like we're trying. We feel like we're doing everything we can do, and give you a bit of control in the scenario, that you've got no control over.' (FP11)*
	I've got my child back	- Benefits of KD - Parent's feelings in response to KD - Positive impacts on family life	*'Be that little bit proud, yes, you're actually doing stuff now.. it's almost opening the window up to him learning those new skills that he never had that possibility before**....**.the KD has just given me a bigger window of hope for there's still options out there for him.' (FP12)* *'Oh the ketogenic diet has been amazing. Yep. We're definitely winning [laughs] so yeah, it's definitely been the best medication that we've tried.' (FP16)* *'I just sort of think, you'd do anything for your children, wouldn't you? So regardless of the effort that it takes, if it means that X doesn't have that one fall per week that he was having on average, then categorically it's worth it. As a whole our family is better off for it. We're able to go out for our little family walks or put him on his balance bike and let him have a little ride, and do things together as a family unit.' (FP19 MP2)*

Candidate Theme and definition	Sub Theme	Code	Sample quote
3. Reality of KD therapy The theme *reality of KD therapy* explores day to day life with KD and how families adapt	KD can be challenging	- time consuming - cost and access to ketogenic friendly foods - KD outside the home (holidays, eating out, birthday parties, other carers, school and respite) and fitting in - trying to identify the mistake - coping with illness - rigid and inflexible - others don't understand - family eating habits changed - unsuccessful recipes and meal plans	*'Socially it's awkward, financially it's a bit hmm, shopping's a bit hmm, but at the end of the day there's no chocolate bar out there that's worth going back to how he was.' (FP7)* *'I would spend god knows how much money on all this stuff and god knows how many hours in the kitchen making all these meals and he wouldn't even touch it and he'd say he wanted hotdogs. I'd be like for god's sake. He literally wouldn't touch it.'(FP9)* *'One thing I wasn't expecting was if you get caught out. If you're out longer than – so say we go visit family and we take her morning tea but we stay and it is lunchtime. To try to fashion something quickly and away from home is difficult. The grandparents were the hardest because they obviously like the treats, the sweets, the chocolate.' (FP15)* *'You're different than everyone else, but we've tried to make it as easy as possible for him…things like school camp was very challenging and the school didn't really actually understand the problem…we had to drive to the camp and drop the food off every day'. (FP10)* *'There were a couple of parties like that where he sat there with everybody else with this food, which – and said what are you having at the party? So I tried to replicate what they were having so he still felt part of it. Even for his own party, because he had two whilst he was on diet, and again, just trying to make the food as similar to what he was eating. It worked.' (FP6)*
	The evolving KD mindset	- Starting out - Adapting to KD - It gets easier	*'So it's challenging but it's got easier as time has gone on. I created probably about 10 different menus and what was within those parameters of 12 or 13 grams [of carbohydrate] a day and the right amount of fat serves. Probably for the first 3 months I used those menus religiously to stick to the parameters and now I just use a mixture of all the menus.' (FP16)*

		- The importance of firsts (holidays, eating out)	*'I think I had a bit of tunnel vision, I think I had a bit of lack of being able to think outside the box…You can become quite - obviously you're tunnelled vision, I couldn't have anybody talking to me when I was in the kitchen trying to prepare something. I needed quiet.' (FP2)* *'I mean, I think the first time we managed to go out for a meal, that felt like a win. ..Yeah, that felt like, oh actually, we can do normal things and you know?.' (FP18)*
	A support network is crucial	- Charities - Health professionals - Family - Peer support - Online networks	*'Yeah we've probably had one of the best experiences of X hospital that you could ever have. We had fantastic consultants all the way through. We didn't wait particularly long to see anybody ever. Our dietitian was absolutely fantastic. Our epilepsy nurse, I used to phone her crying down the phone, I don't know what to do, what am I going to do. She would just reassure me.' (FP9)* *'Matthew's Friends [KD charity] have got brilliant recipes but only about 20% work for us [son fussy eater], Matthews Mum was brilliant because when we were still trying X with the breakfast cereals and we couldn't get any of them, she was fantastic. She literally posted me a whole box. There's a support Group..its a closed group just for people and carers who are going through the ketogenic diet. I do find that really useful.' (FP2)* *'the level of support that I've had from Daisy Garland [KD charity] is another level, …they will always respond, Daisy's Mum, they go over and above.' (FP14)* *'We've actually signed up to the Young Epilepsy [charity for young people with epilepsy and their families], obviously the research part of things. So, we've attended a couple of days, which has been really useful.' (FP6)* *'…when your new to it, I think it's really important for you to hear the positive stories and speak to the parents that have gone through it and actually hear that it really isn't as bad as it sounds.' (FP9*

Candidate Theme and definition	Sub Theme	Code	Sample quote
4. Looking to the future The theme *looking to the future* explores the factors that would help to make KD easier for families	Enhanced awareness and understanding of KD	- Health professionals - Family and friends and general public	*'So yeah, whatever I can do to shed light on how or why it works or at least to get more people on it, so we've got more data to collect, I'm here to help.' (FP11)*
	Variety and access to ketogenic foods	- Prescribable products - Shop bought foods and drinks	*'I think well, this is a big asking actually, but if you could do to a shop and buy something that was in your childs specific ratio.' (FP17)* *'..more prescription items. So instead of all these fancy fours and stuff, why doesn't someone come up with one and put it on prescription? Make our lives easier." (FP14)* *'I think having more access to ready meals, stuff that you could buy off the shelf, or on prescription ideally on prescription.' (FP8)*
	Support and education	- Social education - ketogenic cookery days - Peer mentoring - Support group for children - After KD what's next; trepidation of weaning from KD and transitioning to adult care	*'We had a keto cookery workshop on Saturday..That's the first one we've had. It was fantastic, not just helpful. Absolutely amazing. So many little tips that I picked up for her.' (FP8)* *'So I just think if there was any way in that initial period where you can kind of go in and have a group of you and have some slightly more hands on training, I would have benefited from that in the beginning certainly.' (FP1)* *'So to have somebody [a keto buddy or peer mentor] that – yes that's, come on, keep going, it's worth it, and we've all been there, we've all been there, you'll get through to the other side, just something like that, that actually has the experience of starting the diet and knew about the constipation, they knew about the reflux and all their suggestions. That would have been really good actually yes.' (FP13)* *'So yes, worried about 18 [years old], we really are worried about 18. There's a lot of stuff to change, there's school finishing, there's benefits changing, there's medical care decisions. There's an awful lot I need to wrap my head around. He's my one and only and I've not done this before so I kind of feel like I'm feeling my way around in the dark . I'm nervus, very very nervous. I don't know who we're transferring to….so yes transitioning to adult care is scary.' (FP7)* ' *I was quite sad. I really wanted it to work …but I was really glad we'd given it a shot.' (FP1)*

Appendix R. Parent reported side effects of anti-seizure medications

Antiseizure medication (generic & brand names)	Side effect	Sample quotes
Levetiracetam Keppra	- Allergic reaction - Aggression - Hyperactivity - Poor sleep	*'He tried keppra and had a very bad allergic reaction, he had respiratory problems and it was awful. I mean I will never forget those two months until the day I die; it was awful. He would just hold his head in his hands and say, mummy my head feels wrong, there's something wrong with my head. He couldn't articulate it really, it just felt wrong, and he would sit on the floor and he would cry for hours, and my son is not the sort of child who cries. He would just cry for hours and hours and he was aggressive.' (FP1)* *We did then wean Keppra and that was probably at our request, because we didn't like the effect on his mood that he got with Keppra, the anger and he would get - he'd certainly get very cross whilst on Keppra.' (FP18)* *'Three years he's been on levetiracetam. So, we hadn't changed that dosage at all. So, we've just started to go up that one a little bit and we had noticed he's been a little bit more short-tempered recently, very frustrated and quite quick to lash out…I think maybe when we started the levetiracetam which may have been a couple of months after the Epilim was started. He started to have difficulty sleeping, so he would be up until midnight being - literally climbing the walls, tossing, turning, up and down.' (FP6)*
Carbamazepine Tegretol	- Allergic reaction inducing status - Rash	*'Unfortunately, with Tegretol he had an allergic reaction to it, so what happened there is that he ended up in status nonconvulsive probably 24, 36 hours. That basically destroyed all his brain development. From there we've basically, I've still got the 10 months old developed mental child. But he's now a 13-year-old boy, but I still just call him my baby for life, because there's that much brain damage that unfortunately he's been struggling with a lot of things.' (FP12)* *'We tried Tegretol, so carbamazepine, but that brought him out in a rash, so we stopped that.' (FP18)*
Phenytoin Dilantin	- Hallucinations	*'We didn't really get much change with the Epilim and then we did actually try Dilantin and Dilantin was not at all a drug for us so it caused B to have hallucinations and have - and she was having to go to the sick bay and have a sleep every day at school because she was hallucinating at night. So we were on that drug for about three weeks…before we weaned her off but that took about another three weeks so it wasn't very pleasant.' (FP16)*

Antiseizure medication (generic & brand names)	Side effect	Sample quotes
Sodium valproate Epilim	- Poor sleep - Apraxia - Irritability - Hyperactivity - Cognitive slowing - Suicidal thoughts	*'It caused more problems in his sleep patterns and it affected his apraxia even more.' (FP12)* *'Epilim are - that both girls were on, were a lot of shakiness. So difficulty with writing, which was particularly harder for my six-year-old because she was diagnosed just before she started school so she hadn't really started to learn to write. So yeah, but yeah, definitely shakiness and just slowdown in terms of cognitive processing, I guess.' (FP16)* *'She was really hyperactive and hard to settle and focus at her daycare. She was throwing the most horrible tantrums. It was out of control. Very crazy screaming over really small, not in the - what I would consider a normal two-year-old.' (FP15)* *'When she threw a tantrum, she used to bang her head on the ground. She stopped doing that almost immediately once we stopped the Epilim.' (FP15)* *'He went from being a very, very happy child to a suicidal one. He was putting his head through windows, he was soiling, he was crying. You couldn't talk to him without him bursting into tears…. Yes, he disappeared, he completely changed. Everything about him changed and it was honestly horrific.' (FP7)*
Oxcarbazepine Trileptal	- Rash	*'we've also tried oxcarbazepine and that brought him out in quite a severe rash, so he ended up two nights in Walsgrave [hospital] last week.' (FP18)*
Ruffinamide	- Nausea - Appetite depressant	*'Unfortunately, the rufinamide did not agree at all with her. It made her feel sick, killed her appetite and made her feel sick.' (FP8)*
Lamotrigine Lamictal	- Rash - Brain fog in combination with topiramate	*'Lamotrigine, so they put him on lamotrigine and within days he came out in a skin rash, which obviously scared me because I'd been warned if that happens, stop immediately, because it could be quite dangerous, so we stopped. I took him straight to the GP and we stopped the lamotrigine straightaway.' (FP19 MP2)* *'As soon as she started the medication she got - brain fog is the only way I can describe it really. She was there but she wasn't really there as such. She was subdued. At that point X was on I think 150mg of lamotrigine twice a day and 150mg of Topamax twice a day. So she was totally tuned out mentally.' (MP1)*

Antiseizure medication (generic & brand names)	Side effect	Sample quotes
Clobazam Frisium	- Irritability - Hyperactivity - Cognitive slowing - Fatigue - Drooling - Brain fog	*'She was really hyperactive and hard to settle and focus at her daycare. She was throwing the most horrible tantrums. It was out of control. Very crazy screaming over really small, not in the - what I would consider a normal two-year-old.' (FP15)* *'Particularly on the - probably the Frisium was the one that we found we think had quite an impact on their cognition and their academic learning, I suppose and just fatigue. Just needing a lot more sleep than most kids their age, probably.' (FP16)* *'We wanted to come down off the clobazam which we didn't really feel was working; had terrible side effects.' (FP6)* *'we put her on a dose of clobazam just in the evening, and that turned her into a complete zombie. She was almost drugged on her feet to the point where I didn't know whether it was - it looked like she was just about to fall asleep, going to fall over because she was falling asleep, but I suspect actually those were seizure.' (FP8)* *'So, when T was on the clobazam, when he was on a proper dose of it - we weaned that quite quickly, I didn't like him being on that - he stopped talking completely. He would just point and uh, uh, uh. He would just sit on the sofa dribbling, bless him, just covered in dribble.' (FP9)*
Topiramate Topamax	- Development - Brain fog in combination with Lamotrigine	*'I don't really know the medical side effects, but I feel like there were things suppressing him and his development and he was a little bit of a zombie on some of the medication, especially topiramate, I didn't like that at all.' (FP4)* *'As soon as she started the medication she got - brain fog is the only way I can describe it really. She was there but she wasn't really there as such. She was subdued. At that point X was on I think 150mg of lamotrigine twice a day and 150mg of Topamax twice a day. So she was totally tuned out mentally.' (MP1)*
Perampanel Fycompa	- Aggression	*'we've been really playing around with the adjustment of the medication. We trialled perampanel more recently but that made him very aggressive, so we came off of that quite quickly.'(FP6)*
Zonisamide Zonegran	- Reduced appetite	*'She's also been on zonisamide, which I didn't realise at the time but strongly affected her appetite…negatively.' (FP8)*

Antiseizure medication (generic & brand names)	Side effect	Sample quotes
General reported effects not attributed to specific ASMs	- Fatigue - Behavioural issues - Drooling - Brain fog and disengagement - Memory - Hyperactive - Brain fog and disengagement	*'he's constantly shattered and exhausted and feeling rubbish as a side effect of the drug.', (FP1)* *'Then they said we'll add in another drug, because this one works really well and complements the Epilim, so we tried that. It didn't, his behaviour went really bad, didn't it?* *Male Interviewee:Yeah.* *Female Interviewee:Really, really off the wall personality change. So we took him off that one and put him on another one. I'm trying to remember what that one was even called and he just turned into a vegetable, just sat there drooling, no response at all, no life in him. I think he had…Male Interviewee: No interest in life, to be honest.' (FP19 MP2)* *'Her memory is very much affected by - I don't know whether it's the epilepsy or the medication. I mean, sometimes it seems to me like the medication was dulling her head, but you don't really know - like I just talked to the neurologist about it before, it's very hard to tell whether or not it's medication or the actual epilepsy itself. Her memory has been totally messed up now for [a number of years]. She's forgotten lots of things that she should remember. (FP3)* *They were quite terrible for him. They made him not like a child that might have ADHD, and climbing the walls and hyperactive, or they would put him to sleep, where he was like a zombie, sitting there but couldn't talk to you and couldn't do anything. He had one end of the scale or the other, and nothing was very nice, and nothing stopped the seizures, either, so it wasn't like you got the side effects and the seizures stopped. There was still lots of seizures.' (FP10)*
Antiseizure medication (generic & brand names)	**Side effect**	**Sample quotes**
Positive benefits attributed to ASMs		
Vigabatrin	Improved mood and less brain fog	*'When we introduced Vigabatrin when he was about four or five years old, that was the breakthrough drug for him, which kind of helped him not be in a drugged [haze] so much. His personality came out, and he smiled more, and he was happier. We got more interaction out of him.' (FP7)*
Keppra	Development and absences improved	*'they put him on Keppra, the levetiracetam. We thought that we saw very quick results with that, not only on his absences but also his general development. So we were quite excited about that drug. I know that's probably unusual for families to say.' (FP19 MP2)*

Appendix S. COREQ 32 item checklist for qualitative research

Consolidated criteria for Reporting Qualitative research (Tong *et al.,* 2007)

Manuscript: Core outcome set development for childhood epilepsy treated with ketogenic diet therapy: results of a scoping review and parent interviews (Carroll *et al.,* 2022b)

*Page numbers refer to the original manuscript submitted to Seizure.

Item No. and Topic	Guide questions/description	Reported on Page No.
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Inter viewer/facilitator	Which author/s conducted the inter view or focus group?	6
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	1
3. Occupation	What was their occupation at the time of the study?	6
4. Gender	Was the researcher male or female?	6
5. Experience and training	What experience or training did the researcher have?	6
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	6
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	6
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	6
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	5,7
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	5-6
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	6
12. Sample size	How many participants were in the study?	9
13. Non-participation	How many people refused to participate or dropped out? Reasons?	9
Setting		

14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	11
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	NA
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	11
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	9
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	NA
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	7
20. Field notes	Were field notes made during and/or after the interview or focus group?	6
21. Duration	What was the duration of the inter views or focus group?	9
22. Data saturation	Was data saturation discussed?	NA
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	One with a second reviewer
25. Description of the coding tree	Did authors provide a description of the coding tree?	14-15
26. Derivation of themes	Were themes identified in advance or derived from the data?	7
27. Software	What software, if applicable, was used to manage the data?	7
28. Participant checking	Did participants provide feedback on the findings?	No
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	16-18
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Yes
31. Clarity of major themes	Were major themes clearly presented in the findings?	Yes
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Received: 18 November 2022 | Revised: 17 January 2023 | Accepted: 17 January 2023

DOI: 10.1111/epi.17513

Epilepsia®

RESEARCH ARTICLE

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

Jennifer H. Carroll[1] | **J. Helen Cross**[2] | **Mary Hickson**[1] | **Emma Williams**[3] | **Val Aldridge**[3] | **Avril Collinson**[1]

[1]Faculty of Health, University of Plymouth, Devon, UK

[2]Developmental Neurosciences, University College London–National Institute for Health Research Biomedical Research Centre Great Ormond Street Institute of Child Health, London, UK

[3]Matthew's Friends, Lingfield, UK

Correspondence
Jennifer H. Carroll, Faculty of Health, University of Plymouth, Plymouth, Devon, UK.
Email: jennifer.carroll@plymouth.ac.uk

Funding information
British Dietetic Association General Education Trust Fund, Grant/Award Number: 19/11; Nutricia Ltd; University of Plymouth

Abstract

Objective: Ketogenic diet therapy (KDT) can result in benefits (seizure-related 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 prioritize outcomes of importance for inclusion in a core outcome set. This informed a stakeholder consensus meeting and consultation process to finalize the core outcome set.

Results: In total, 97 outcomes were identified; 90 from the scoping review and seven from parent interviews. These were rationalized 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 2. Sixty-six percent of participants (30 parents and 66 professionals) completed Round 2, where 22 outcomes met criteria for inclusion. In the consensus meeting (nine 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 standardize outcome

selection and reporting, facilitate data synthesis, and ultimately enhance the relevance of outcomes to parents, researchers, and health professionals.

KEYWORDS
core outcome set, Delphi, ketogenic diet, outcomes, pediatric epilepsy

1 | INTRODUCTION

Epilepsy is one of the most common serious neurological conditions of childhood,[1] estimated to affect one in 418 children in the first 3 years of life.[2] A significant proportion (35%) of children will develop drug-resistant epilepsy, experiencing regular debilitating seizures despite treatment with multiple antiseizure medications (ASMs).[3,4] There is a high risk of cognitive and behavioral comorbidity[5] and early mortality,[6] the burden of which extends to the broader family, where parents describe a cycle of uncertainty, characterized by changing symptoms and behaviors 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, whereas 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 exclude parents' views. These challenges in outcome reporting are not unique to childhood epilepsy but 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 (Core Outcomes in Refractory childhood Epilepsy treated with Ketogenic Diet Therapy; www.plymouth.ac.uk/core-kdt)[8,17] was undertaken to develop a COS, motivated by the necessity to identify seizure-related 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 semistructured parent interviews (Phase 2).[8] The identified outcomes were ratified (Phase 3), and consensus was 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 COS-STAR (Core Outcome Set–STAndards for Reporting) guidance (see checklist in Appendix S1).[18]

Key Points

- 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
- The CORE-KDT core outcome set is the first international Delphi consensus on outcomes for childhood epilepsy treated with ketogenic diet
- The core outcome set encompasses parent, health professional, researcher, charity, and industry views from 33 countries in an inclusive and transparent manner
- Implementation in research and clinical settings will standardize outcome selection and reporting, facilitate data synthesis, and enhance relevance of outcomes
- Future work will focus on identifying appropriate outcome measurement instruments

2 | MATERIALS AND METHODS

2.1 | Study overview

The scope of the COS was defined according to criteria recommended by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative.[14] The health condition was drug-resistant (refractory) epilepsy in a pediatric 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 (COS-STAD [Core Outcome Set–STAndards for Development],[19] COS-STAP [Core Outcome Set–Standardized Protocol items][20]). Figure 1 outlines the stages of development of the COS.

2.2 | 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.

2.3 | Patient and public involvement and engagement

From the outset, we have recognized the importance of parents and carers as stakeholders, ensuring representation in each phase. Two parent partner coinvestigators (E.W., V.A.) 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 a trustee (V.A.) and chief executive officer (E.W.). A patient and public involvement and engagement (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 7 days per 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.

2.4 | Stakeholder participants and eligibility

Parent, health professional (consultant pediatric neurologists, pediatricians, ketogenic dietitians, epilepsy specialist nurses, and neuropsychologists), researcher, industry, and charity representation was sought. Charity and industry representatives would likely be professionals, so they 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 centers operating as Participant Identification Centres (UK participants), charity organizations (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.

2.5 | 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 categorized into domains according to the COMET taxonomy.[23] Outcomes of importance to parents were identified through semistructured interviews, using open-ended questions to facilitate parent-led discussion. Outcomes were identified directly by asking parents to identify and then prioritize 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.

2.6 | Phase 4: Prioritization of outcomes

2.6.1 | Delphi survey

Parents, health professionals, and researchers were invited to participate in a two-round international Delphi survey to

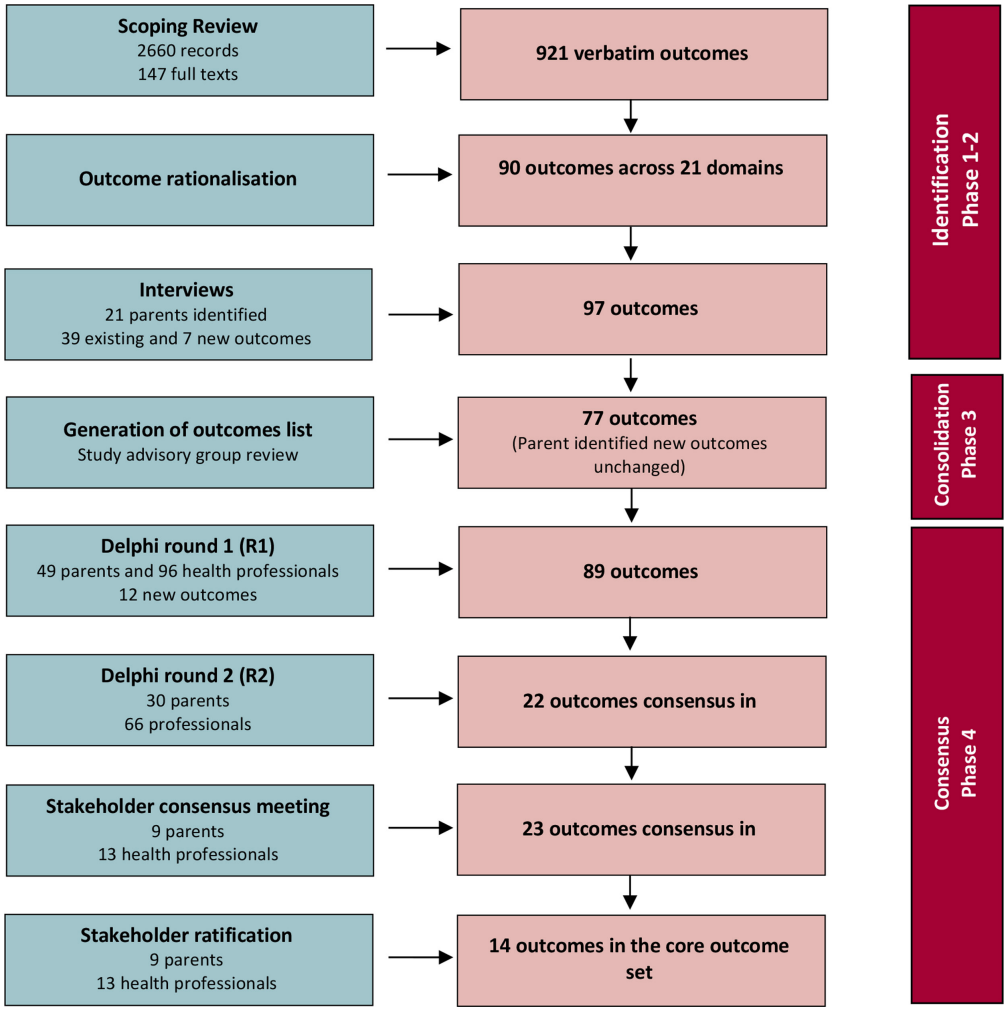


FIGURE 1 Overview of core outcome set development.

prioritize 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 to 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, (1) parents and (2) health professionals and researchers were analyzed 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 summarized 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 categorized 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 categorized as undecided.

2.6.2 | 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 determine whether 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 outcomes in the online meeting were 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 were 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 might lead to frustration among parent participants that their views were not being heard if outcomes they perceived to be important failed to reach consensus because health professionals scored them less important. This risked introducing bias into the discussion and scoring. Therefore, the decision was taken to analyze scores after the meeting and share the provisional COS within 1 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.

2.7 | Ethical approval

Ethical approval was granted by the National Health Service Health Research Authority (London–Surrey REC19/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.

2.8 | 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 circumstances in their anal cancer COS and proposed revised criteria, whereby outcomes were excluded if 50% or fewer 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.

3 | RESULTS

3.1 | Identification of outcomes

The scoping review and interviews with parents have been described elsewhere[8] and are summarized 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 rationalized to 77; however, parent-identified new outcomes remained unchanged.

3.2 | Prioritization of outcomes

3.2.1 | 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 prioritized 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 they're livable. The cognitive benefits for him were my biggest step forward and that was just amazing
>
> (FP7).

3.2.2 | Delphi survey

In total, 145 participants from 33 countries (49 parents, 96 health professionals and researchers) participated in R1. Table 2 summarizes participant characteristics. Most professional participants were pediatric dietitians or pediatric neurologists, with 40% of these professionals reporting >10 years of 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 summarizes 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).

TABLE 1 Interviewed parents' prioritization of outcomes.

Domain[23]	Outcome	Identified, *n*
Physiological clinical	Seizure reduction	6
Cognition	Learning and cognition	6
Physiological clinical	Antiseizure 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 behavior	1

Scores from 96 R2 participants were analyzed (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."

3.2.3 | Consensus meeting

The online consensus meeting was held on February 23, 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 prioritized. 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 (1) "the heart," (2) "the liver," and (3) "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

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)
	North America	4 (8)	2 ((7)
	Australia and 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)
	MCT KD	6 (12)	4 (13)
	Not stated	2 (4)	0 (0)
	Duration of KD treatment		
	≤3 months	3 (6)	1 (3)
	4 months–1 year	9 (18)	4 (13)
	1–2 years	14 (29)	11(36)
	>2 years	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)

(Continues)

TABLE 2 (Continued)

Stakeholder group	Variable	Round 1 (%)	Round 2 (%)
	Asia	9 (9)	7 (11)
	Australia and 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)
	Pediatric neurologist	15 (16)	9 (14)
	MD, neurology	6 (6)	5 (8)
	Neuropediatrician	1 (1)	1 (1)
	Pediatrician	4 (4)	3 (5)
	Physician	2 (2)	2 (3)
	Professor of pediatric neurology	1 (1)	1 (1)
	Clinical fellow, pediatric epilepsy	1 (1)	1 (1)
	Clinical/epilepsy specialty nurse	5 (5)	3 (5)
	Pediatric 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 year	9 (9)	8 (12)
	2–5 years	21 (22)	16 (24)
	6–10 years	27 (28)	15 (23)
	>10 years	38 (40)	26 (39)
	Not stated	1 (1)	1 (1)

Abbreviations: F, female; KD, ketogenic diet; M, male; MCT, medium chain triglyceride; MD, medical doctor.

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 1 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. Ninety-four percent felt comfortable communicating their views. When asked if the consensus meeting produced a fair result, 56% agreed or strongly agreed, likely because the

TABLE 3 Delphi R1 and R2 percentage scores for both stakeholder groups.

	R1, %							R2, %						
	Parents, $n = 49$			HPs, $n = 96$			Delphi R1	Parents, $n = 30$			HPs, $n = 66$			Delphi R2
Outcome	1–3	4–6	7–9	1–3	4–6	7–9	consensus	1–3	4–6	7–9	1–3	4–6	7–9	consensus
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[a]
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. ASM use	4	21	75	0	25	75	In	0	21	78	0	13	88	**In**
10. ASM blood concentrations	9	25	65	17	48	34	Undecided	0	46	54	17	62	21	Undecided
11. Side effects of ASMs	4	24	72	1	48	52	Undecided	0	16	85	2	50	48	Undecided[a]
12. Non-ASM use	23	34	43	12	54	34	Out	18	56	26	12	71	17	Out
13. CSF concentrations of neurotransmitters	28	36	36	53	34	13	Out	38	45	16	69	27	4	Out
14. 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[a]
16. Cholesterol levels	8	44	48	2	46	52	Undecided	0	60	41	4	59	37	Out
17. Gastroesophageal 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[a]
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

(Continues)

TABLE 3 (Continued)

Outcome	R1, %						Delphi R1 consensus	R2, %						Delphi R2 consensus
	Parents, $n = 49$			HPs, $n = 96$				Parents, $n = 30$			HPs, $n = 66$			
	1–3	4–6	7–9	1–3	4–6	7–9		1–3	4–6	7–9	1–3	4–6	7–9	
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[a]
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[a]
36. Tolerability of KD	2	30	67	0	8	92	Undecided	4	18	79	0	3	97	**In**
37. Parent or primary carer confidence with KD	4	30	67	1	24	75	Undecided	4	32	64	2	12	86	Undecided[a]
38. Palatability of KD formula and supplements	4	23	72	3	35	62	Undecided	4	28	68	4	27	70	Undecided[a]
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[a]
41. Behavioral feeding difficulties	8	28	64	1	28	72	Undecided	9	26	65	0	18	83	Undecided[a]
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[a]
44. REE	12	42	46	14	49	36	Out	12	62	24	10	69	23	Out

TABLE 3 (Continued)

Outcome	R1, %						Delphi R1 consensus	R2, %						Delphi R2 consensus
	Parents, $n = 49$			HPs, $n = 96$				Parents, $n = 30$			HPs, $n = 66$			
	1–3	4–6	7–9	1–3	4–6	7–9		1–3	4–6	7–9	1–3	4–6	7–9	
45. Energy utilization	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[a]
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 carer quality of life	9	29	62	0	18	82	Undecided	11	32	57	2	8	90	Undecided[a]
49. Parent or primary carer 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 and emotional functioning outcomes														
51. Alertness	0	13	87	1	33	65	Undecided	0	15	86	0	24	76	**In**
52. Behavior	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[a]
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[a]
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[a]
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

(Continues)

TABLE 3 (Continued)

Outcome	R1, %						Delphi R1 consensus	R2, %						Delphi R2 consensus
	Parents, $n = 49$			HPs, $n = 96$				Parents, $n = 30$			HPs, $n = 66$			
	1–3	4–6	7–9	1–3	4–6	7–9		1–3	4–6	7–9	1–3	4–6	7–9	
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 and 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[a]
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[a]
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 R2														
78. Hyperuricemia							–	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**

TABLE 3 (Continued)

Outcome	R1, %						Delphi R1 consensus	R2, %						Delphi R2 consensus
	Parents, $n = 49$			HPs, $n = 96$				Parents, $n = 30$			HPs, $n = 66$			
	1–3	4–6	7–9	1–3	4–6	7–9		1–3	4–6	7–9	1–3	4–6	7–9	
85. Parental stress associated with the management of KD therapy							–	7	37	55	2	27	72	Undecided[a]
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

Abbreviations: ASM, antiseizure medication; CSF, cerebrospinal fluid; EEG, electroencephalographic; HP, health professional; KD, ketogenic diet; R1, Round 1; R2, Round 2; REE, resting energy expenditure.

[a]Scored as critically important (7–9) by ≥70% of one stakeholder group, representing those prioritized for discussion and scoring at the stakeholder consensus meeting.

provisional COS had not yet been shared. The same question was repeated 1 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.

4 | DISCUSSION

The CORE-KDT COS 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, and 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 overinfluence 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 hypothesized that the CORE-KDT set would capture additional outcomes relevant to the complexity of drug-resistant epilepsy, the severity of associated comorbidities, and monitoring of KDT. As expected, the CORE-KDT set includes outcomes specific to KDT that are not adequately captured in any existing published COS. Although no guidance exists on the ideal number of outcomes, it is likely that a larger COS will be difficult to implement and less likely to be

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

Outcome	Parents, $n = 9$, %			HPs, $n = 13$, %			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 ASMs	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
Behavioral 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

Abbreviations: ASM, antiseizure medication; EEG, electroencephalographic; HP, health professional; KD, ketogenic diet.

adopted. We reduced 89 outcomes to only 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 prioritized by interviewed parents) and three functional outcomes (all prioritized 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," which

TABLE 5 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: ≥90% reduction, ≥50% reduction, or <50% reduction in seizure activity
	Seizure freedom	Not having seizures
	Seizure severity	Duration and severity of seizures considering the impact on the child during and afterward; for example, injuries, falls, incontinence, confusion, and time to recover
	Status epilepticus and use of rescue medication	Frequency of status episodes and the number of rescue medications administered
	Antiseizure medication use	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: • Challenges of ketogenic diet • Tolerance of prescribed ketogenic formula, supplements, and foods • Duration of treatment with ketogenic diet • Behavioral 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 come from the keto team, charity organizations, 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	Child's 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, and attentive and ability to focus; the fog is lifting and being more present
	Behavior	Change in behavior and ability to adapt to surroundings and situations; child's actions, reactions, and functioning in response to everyday environment and situations
Resource use	Accident and 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

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, behavior, 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 the importance perceived by parents but warrants further investigation. Our findings are similar to Murugupillai et al.'s[28] outcomes study, where sleep was not prioritized. 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 prioritized "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 overstratified, 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 although parents voted in "concentration" 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 was improving, it was a sign that "things might improve further," such as social interactions and academic performance.

Defining outcomes with standard terminology and standardized 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, to develop a COS that is relevant and trusted by patients.[32] Parent coinvestigators 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 emphasized 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 homeschooling 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.

5 | 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 that perhaps represents the parent who has the most to say on the topic. The parent group may be biased toward the beneficial effects of KDT, as all children experienced seizure reduction. However, their viewpoints can be generalized to children with epilepsy who trial and continue KDT. Significant participant attrition occurred from Delphi R1 to R2 (34%), despite many extensions and personalized 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 these data may have provided further insights into the study population.

6 | CONCLUSIONS

The CORE-KDT COS has identified 14 outcomes that should guide outcome selection in future clinical trials and practice. Measurement of these multidimensional 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 COSMIN (COnsensus-based Standards for the Selection of health Measurement INstruments).[33] Future work will also explore the potential to adapt the CORE-KDT set for other settings where KDT is utilized, including pediatric metabolic disorders and adult drug-resistant epilepsy.

AUTHOR CONTRIBUTIONS

Jennifer H. Carroll: Conceptualization, methodology, investigation, resources, data curation, writing–original draft, project administration. J. Helen Cross, Mary Hickson, Avril Collinson: Conceptualization, methodology, writing–review and editing, supervision. Emma Williams, Val Aldridge: Conceptualization, validation, writing–review and editing.

ACKNOWLEDGMENTS

The authors would like to extend their thanks to the participants who gave their time to participate in the CORE-KDT study. Appendix S3 lists the consensus meeting participants and their roles. Thanks go to the following participant identification centers that supported recruitment: Matthew's Friends, Young Epilepsy, Epilepsy–The Ketogenic Way, University Hospitals of Leicester NHS Trust, Leeds Teaching Hospitals NHS Trust, Sheffield Children's NHS Foundation Trust, Cambridge University Hospitals NHS Foundation Trust, Manchester University NHS Foundation Trust, Birmingham Women's and Children's NHS Foundation Trust, Royal Devon and Exeter NHS Foundation Trust, Great Ormond Street Hospital for Children NHS Foundation Trust, Royal Berkshire NHS Foundation Trust. We thank Dr Kirsty Martin-McGill for her role as second reviewer in the scoping review, Dr Louise Mole for facilitating the consensus group meeting, and Diana Lynch Bodger and Ellen Wilford for their support as members of the study advisory group. This article will contribute to a Doctor of Philosophy for J.H.Ca. The study was supported by a grant from the University of Plymouth and the British Dietetic Association General Education Trust Fund. J.H.Cr.'s research is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital. She holds an endowed chair at UCL Great Ormond Street Institute of Child Health, and grants from NIHR, EPSRC, GOSH Charity, ERUK, the Waterloo Foundation, and the Great Ormond Street Hospital Biomedical Research Centre.

CONFLICT OF INTEREST STATEMENT

J.H.Ca. has received personal fees, speaker honoraria, and grant funding from Nutricia. J.H.Cr. has acted as an investigator for studies with GW Pharma/Jazz, Zogenix, Vitaflo, Ovid, Marinius, Ultragenyx, and Stoke Therapeutics. She has been a speaker and on advisory boards for GW Pharma, Biocodex, Zogenix, and Nutricia; all remuneration has been paid to her department. The other authors declare that they have no competing interests.

ORCID

Jennifer H. Carroll https://orcid.org/0000-0001-9256-7925
J. Helen Cross https://orcid.org/0000-0001-7345-4829

REFERENCES

1. Joint Epilepsy Council. Epilepsy prevalence, incidence and other statistics; 2011.
2. Symonds JD, Elliott KS, Shetty J, Armstrong M, Brunklaus A, Cutcutache I, et al. Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants. Brain. 2021;144(9):2879–91.
3. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med. 2011;365(10):919–26.
4. Wirrell E, Wong-Kisiel L, Mandrekar J, Nickels K. Predictors and course of medically intractable epilepsy in young children presenting before 36 months of age: a retrospective, population-based study. Epilepsia. 2012;53(9):1563–9.
5. Berg AT, Langfitt JT, Testa FM, Levy SR, DiMario F, Westerveld M, et al. Global cognitive function in children with epilepsy: a community-based study. Epilepsia. 2008;49(4):608–14.
6. Jennum P, Pickering L, Christensen J, Ibsen R, Kjellberg J. Morbidity and mortality of childhood and adolescent-onset epilepsy: a controlled national study. Epilepsy Behav. 2017;66:80–5.
7. Webster M. The cycle of uncertainty: parents' experiences of childhood epilepsy. Sociol Heal Illn. 2019;41(2):205–18.
8. Carroll JH, Martin-McGill KJ, Cross JH, Hickson M, Williams E, Aldridge V, et al. Core outcome set development for childhood epilepsy treated with ketogenic diet therapy: results of a scoping review and parent interviews. Seizure. 2022;99:54–67.
9. Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the international ketogenic diet study group. Epilepsia Open. 2018;3(2):175–92.
10. Sourbron J, Klinkenberg S, van Kuijk SMJ, Lagae L, Lambrechts D, Braakman HMH, et al. Ketogenic diet for the treatment of pediatric epilepsy: review and meta-analysis. Childs Nerv Syst. 2020;36(6):1099–109.
11. Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev. 2020;(6):CD001903.
12. National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management clinical guideline [CG137]. (updated 2020); 2016. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001903.pub5/full
13. Baker GA, Camfield C, Camfield P, Cramer JA, Elger CE, Johnson AL, et al. Commission on outcome measurement in epilepsy, 1994-1997: final report. Epilepsia. 1998;39(2):213–31.

14. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET handbook: version 1.0. Trials. 2017;18:280.
15. Williamson P, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13:132.
16. Williamson P, Altman DG, Blazeby J, Clarke M, Gargon E. Driving up the quality and relevance of research through the use of agreed core outcomes. J Heal Serv Res Policy. 2012;17(1):1–2.
17. Carroll JH, Cross JH, Hickson M, Williams E, Aldridge V, Collinson A. The CORE-KDT study: a mixed methods protocol to establish core outcomes for refractory childhood epilepsy treated with ketogenic diet therapy. Trials. 2022;23(1):675.
18. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Devane D, et al. Core outcome set–STAndards for reporting: the COS-STAR statement. PLoS Med. 2016;13(10):e1002148.
19. Kirkham JJ, Davis K, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core outcome set-STAndards for development: the COS-STAD recommendations. PLoS Med. 2017;14(11):e1002447.
20. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core outcome set-STAndardised protocol items: the COS-STAP statement. Trials. 2019;20(1):116.
21. Core outcome measures in effectiveness trials (COMET) initiative. CORE-KDT Study Registration [Internet]. [cited 2021 Jun 26]. Available from: https://www.comet-initiative.org/Studies/Details/1116
22. Carroll J, Martin-McGill K, Cross H, Hickson M, Collinson A. Outcome measurement and reporting in childhood epilepsy treated with ketogenic diet therapy: a scoping review protocol. JBI Database Syst Rev Implement Reports. 2019;17(5):633–9.
23. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. J Clin Epidemiol. 2018;96:84–92.
24. Shoshan HN, Wehrt W. Understanding "zoom fatigue": a mixed-method approach. Appl Psychol. 2022;71(3):827–52.
25. Fish R, Sanders C, Adams R, Brewer J, Brookes ST, DeNardo J, et al. A core outcome set for clinical trials of chemoradiotherapy interventions for anal cancer (CORMAC): a patient and health-care professional consensus. Lancet Gastroenterol Hepatol. 2018;3(12):865–73.
26. Scottish Intercollegiate Guidelines Network (SIGN). Epilepsies in children and young people: investigative procedures and management (SIGN Publication no. 159). . Edinburgh: SIGN; 2020.
27. Crudgington H, Rogers M, Bray L, Carter B, Currier J, Dunkley C, et al. Core Health Outcomes in Childhood Epilepsy (CHOICE): development of a core outcome set using systematic review methods and a Delphi survey consensus. Epilepsia. 2019;60(5):857–71.
28. Murugupillai R, Ranganathan SS, Wanigasinghe J, Muniyandi R, Arambepola C. Development of outcome criteria to measure effectiveness of antiepileptic therapy in children. Epilepsy Behav. 2018;80:56–60.
29. Winsor AA, Richards C, Bissell S, Seri S, Liew A, Bagshaw AP. Sleep disruption in children and adolescents with epilepsy: a systematic review and meta-analysis. Sleep Med Rev. 2021;57:101416.
30. Gibbon FM, Maccormac E, Gringras P. Sleep and epilepsy: unfortunate bedfellows. Arch Dis Child. 2019;104(2):189–92.
31. Hallbook T, Lundgren J, Rosen I. Ketogenic diet improves sleep quality in children with therapy-resistant epilepsy. Epilepsia. 2007;48(1):59–65.
32. COMET Initiative. Checklist for public research partners and core outcome set developers involved in designing a COS study. 2021. Available from: https://www.comet-initiative.org/assets/downloads/cos study development-ppi checklist 16-03-16.pdf
33. Prinsen CAC, Vohra S, Rose MR, Boers M, Tugwell P, Clarke M, et al. How to select outcome measurement instruments for outcomes included in a "Core outcome set" – a practical guideline. Trials. 2016;17(1):449.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Carroll JH, Cross JH, Hickson M, Williams E, Aldridge V, Collinson A. A core outcome set for childhood epilepsy treated with ketogenic diet therapy (CORE-KDT study): International parent and health professional consensus. Epilepsia. 2023;00:1–18. https://doi.org/10.1111/epi.17513

Appendix U. The COS-STAR checklist

Core Outcome Set-STAndards for Reporting: The COS-STAR Statement (Kirkham et al 2016)

Page numbers refer to the original manuscript submitted to Epilepsia (Carroll et al., 2023)

SECTION/TOPIC	ITEM No.	CHECKLIST ITEM	Page
TITLE/ABSTRACT			
Title	1a	Identify in the title that the paper reports the development of a COS	1
Abstract	1b	Provide a structured summary	3
INTRODUCTION			
Background and Objectives	2a	Describe the background and explain the rationale for developing the COS.	2-4
	2b	Describe the specific objectives with reference to developing a COS.	4
Scope	3a	Describe the health condition(s) and population(s) covered by the COS.	4
	3b	Describe the intervention(s) covered by the COS.	4
	3c	Describe the setting(s) in which the COS is to be applied.	4
METHODS			
Protocol/Registry Entry	4	Indicate where the COS development protocol can be accessed, if available, and/or the study registration details.	5
Participants	5	Describe the rationale for stakeholder groups involved in the COS development process, eligibility criteria for participants from each group, and a description of how the individuals involved were identified.	5-6
Information Sources	6a	Describe the information sources used to identify an initial list of outcomes.	6
	6b	Describe how outcomes were dropped/combined, with reasons (if applicable).	6-7
Consensus Process	7	Describe how the consensus process was undertaken.	6-7
Outcome Scoring	8	Describe how outcomes were scored and how scores were summarised.	7
Consensus Definition	9a	Describe the consensus definition.	7
	9b	Describe the procedure for determining how outcomes were included or excluded from consideration during the consensus process.	7-8
Ethics and Consent	10	Provide a statement regarding the ethics and consent issues for the study.	9
RESULTS			
Protocol Deviations	11	Describe any changes from the protocol (if applicable), with reasons, and describe what impact these changes have on the results.	8-9
Participants	12	Present data on the number and relevant characteristics of the people involved at all stages of COS development.	10 -14 Fig.1, Tbl. 2 Appx. 4
Outcomes	13a	List all outcomes considered at the start of the consensus process.	Appx. 2
	13b	Describe any new outcomes introduced and any outcomes dropped, with reasons, during the consensus process.	Appx 3
COS	14	List the outcomes in the final COS.	Table 3

DISCUSSION			
Limitations	15	Discuss any limitations in the COS development process.	20-21
Conclusions	16	Provide an interpretation of the final COS in the context of other evidence, and implications for future research.	16-21
OTHER INFORMATION			
Funding	17	Describe sources of funding/role of funders.	22
Conflicts of Interest	18	Describe any conflicts of interest within the study team and how these were managed.	22

Appendix V. Mapping of outcome consolidation in pre-delphi consultation

Outcomes	Reasoning
Removed outcomes (N=19)	
Comparison of treatments	Comparison of treatments is not an outcome
Risk factors for development of hypothyroidism	A risk factor is not an outcome
Predictors of growth on KD	A predictor is not an outcome
Predictors of response to KD	A predictor is not an outcome
Predictors of weaning rate	A predictor is not an outcome
Predictors of worsening during weaning of KD	A predictor is not an outcome
Predictors of gut side effects	A predictor is not an outcome
Predictors of severity of side events	A predictor is not an outcome
Predisposing factors for abnormal fat levels	Predisposing factors are not an outcome
KD weaning approach	Not a true outcome
Severity of side effects	This is more a descriptor for each side effect experienced rather than a separate outcome on its own and will be covered in each side effects category
Reasons for not commencing KD	These are influencing factors rather than outcomes
Reasons for KD continuation	These are influencing factors rather than outcomes
Reason for KD discontinuation	These are influencing factors rather than outcomes
Retention	Trial terminology and overlaps with KD duration so remove and leave KD duration in which is better lay language
Recommend KD to other families	These are influencing factors rather than outcomes
Impact of dietary changes and supplementary interventions on dyslipidaemia	Not an outcome
Recollection of KD	Not an outcome
Efficacy of KD in different epilepsy syndromes	Will be assessed by the individual outcomes regardless of epilepsy type so remove
Merged outcomes (N=14)	
Long-term seizure outcomes	This is related to follow up duration rather than a separate outcome in itself so merge with existing seizure outcomes
Seizure remission	Captured in seizure freedom
Seizure cluster	Captured in seizure frequency
Seizure recurrence	Captured in seizure frequency
Seizure intensity	Captured in seizure severity
Neurological improvement	Vague outcome, will be captured in more specific outcomes addressing cognition
Leptin levels	Captured in side effects that affect hormones
cholecystokinin 8	Captured in side effects that affect hormones
Treatments for side effects	Captured in non-ASM medications
Neuropsychological ability	Captured in cognition outcomes
Psychosocial adjustment	Captured in behaviour
Dietary intake	Captured in dietary adherence
Optimising ketosis	Captured in ketone levels, tolerance and adherence

Outcomes	Reasoning
Concentration of norepinephrine dopamine and serotonin	Captured in CSF concentration of neurotransmitters
Expanded outcomes (N=total of 13*)	
Side effects that affect the gut (gastrointestinal) expanded to GORD and constipation	Side effects are listed as individual outcomes if stated in parent interviews
Side effects that affect the bones expanded to bone health and bone fractures	Side effects are listed as individual outcomes if stated in parent interviews
Seizure frequency expanded to seizure frequency and seizure freedom	Often classified as primary and secondary outcomes so separate
Spasm frequency expanded to Spasm reduction and freedom	In line with seizure frequency
Sleep expanded to time spent asleep and daytime sleepiness	To align with the CHOICE core outcome set terminology (Crudgington *et al.*, 2019)
Alertness expanded to alertness and concentration	Defined differently so separate into two outcomes
Cognition expanded to 3 outcomes: memory, speech + language, learning	Cognition expanded for clarity
Motor function expanded to 3 outcomes: movement ability, coordination and balance and manual ability	Motor function expanded for clarity
General adverse effects expanded to fatigue, keto rash, behavioural feeding issues and physical feeding issues	A general adverse effects outcome is likely too vague, these four were stated by parents and hence listed individually. Assess if further are suggested by participants during Delphi round one

KD- ketogenic diet, ASM – Anti seizure medication, CSF – cerebrospinal fluid, GORD – gastroesophageal reflux disease, CHOICE – Core Health Outcomes in Childhood Epilepsy.

** N=13 calculated by totalling the 'additional' outcomes. For example, side effects that effect the gut being split to two outcomes creates 1 additional, previously unaccounted for outcome. Cognition splitting to 3 outcomes creates two additional outcomes.*

Calculation of number of outcomes being put forward to the Delphi survey
97
-19 removed outcomes
- 14 merged outcomes
+ 13 expanded outcomes
= 77 outcomes

Appendix W. New outcomes proposed by participants in round 1 (N=68) and justifcation for inclusion or exclusion

Proposed new outcome	Mapped to existing outcome	Existing outcome description	Add to R2 yes/no	Justification for in/exclusion
PHYSIOLOGICAL CLINICAL OUTCOMES				
1. SUDEP risk			No	Not an outcome, instead related to resolution of convulsive seizures
2. Hyperuricaemia			**YES**	Specific parameter and adverse effect
3. Electrolyte deficiency			**YES**	Specific parameter and adverse effect
4. Carnitine deficiency			**YES**	Specific parameter and adverse effect
5. Managing intermittent use of emergency steroids when on KD			NO	Not an outcome
6. EEG background 7. Epileptiform discharges 8. Hypsarrhythmia or its variants 9. Flat amplitude 10. Electrical status epilepticus in sleep	EEG findings	Changes in the EEG. An EEG looks at what is happening in the brain – the activity of the brain cells.	NO NO NO NO NO	This is syndrome dependent – overall improvement or change in background and change in epileptiform discharges/ or activity would be seen as EEG outcomes
11. Seizures, clinical or subclinical			NO	Not an outcome of KD, instead relates to initial assessment and identification of seizure type
12. Head MRI or CT lesion			NO	Change in MRI could not be attributed to an outcome of KD
13. Genetic tests positive			NO	Not an outcome of KD, instead relates to initial assessment
14. Identification of syndromes for which ketogenic diet may be used earlier in treatment choices			NO	Not an outcome of KD, research question

Proposed new outcome	Mapped to existing outcome	Existing outcome description	Add to R2 yes/no	Justification for in/exclusion
15. Post ictal state (many patients note improvement in recovery time post seizure after starting keto)			YES	Related to existing seizure outcomes but unique in that this focusses on recovery
16. Patients weight eg if a child has struggled to gain weight and KD has improved this	Growth	Changes in weight, length, height or growth centile	NO	Addressed in an existing outcome
17. If patient was subjected to stem cell therapy, has there been improvement in the child			NO	Not an outcome of KD therapy
18. Frequency of changes in their antiseizure treatment	Antiseizure medication (ASM) use	Number and dose of antiseizure medications to reflect recent changes such as weaning from an ASM	NO	It's a nuance of the outcome ASM use, the frequency of changes can be mapped as part of this outcome
19. Variance in seizure control (how stable seizure control is)	Seizure reduction Or Seizure freedom	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	NO	It's a nuance of both these outcomes. The variance will be tracked by nature of assessing change in seizure reduction or freedom status since last review
DIET AND NUTRITION OUTCOMES				
20. Blood glucose			YES	Blood concentrations (levels) of glucose (sugar) are often measured by a finger prick test. This outcome would include monitoring of low blood glucose levels called hypoglycaemia Often monitored at beginning of KD.
21. Length of time between initiation of KD and therapeutic ketosis	Onset of ketosis	The time taken to achieve ketosis after commencing KD	YES	The time taken to achieve therapeutic ketosis (target ketone level range agreed with the keto team) after commencing KD
22. Benefit of follow-on versions (ie going from strict KD to low glycaemic index diet for long term)			NO	Not an outcome – too broad

Proposed new outcome	Mapped to existing outcome	Existing outcome description	Add to R2 yes/no	Justification for in/exclusion
23. Financial burden of KD treatment			YES	Parents also discussed in interviews
24. Impact of buying extra food/ spending more in supermarket			NO	Duplicate of above outcome
]25. Length of time to the financial burden being outweighed by seizure improvement			NO	Not an outcome, too subjective and assumes it is a financial burden - won't be for all. Could be explore as part of financial burden.
26. How many parents never start/give up because diet is too challenging?			NO	This is a research question/service evaluation consideration for KD services but not an outcome of actual KD therapy
27. If discontinued diet indicate reason for discontinuation			NO	This is a factor for decision making in KD therapy not an outcome
28. What specific issues make it too challenging?			NO	This is a research question/service evaluation consideration for KD services but not an outcome of actual KD therapy
29. How many children go back on diet after withdrawal?			NO	This is a research question/service evaluation consideration for KD services but not an outcome of actual KD therapy
30. What length of time do parents want to trial diet before deciding ineffective?			NO	This is a research question/service evaluation consideration for KD services but not an outcome of actual KD therapy
31. Happiness or comfort with specific type of KD	Tolerability of KD	How well the child can manage the KD and its challenges	NO	Addressed in tolerability of KD outcome
32. How long to fine tune and or switch diets before weaning off KD?			NO	A research question/service evaluation consideration for KD services but not an outcome of actual KD therapy
33. Quality of ingredients in dietary products such as Ketocal and Calogen – organic, "real" ingredients			NO	A research question or influencing factor in personal choice and acceptance of specialist products and not an outcome of actual KD therapy

Proposed new outcome	Mapped to existing outcome	Existing outcome description	Add to R2 yes/no	Justification for in/exclusion
34. If child has a food allergy			NO	This is part of baseline nutritional assessment influencing initial decision making to commence KD and if so, the associated meal plans but not an outcome of KD therapy
35. Dietary intake quantification based on food diary	Dietary adherence	How closely the patient follows the agreed dietary and monitoring plan	NO	Dietary analysis is not an outcome but how closely they are adhering to KD prescription is
36. Objective measure of compliance like some questionnaire/tool	Dietary adherence	How closely the patient follows the agreed dietary and monitoring plan	NO	Ideally, we will agree an objective measure of how to assess this but it is covered by existing outcome
37. Parents feel supported by KD staff			YES	Related to parents' confidence with KD but different. 'Parents feel supported and enabled to manage and deliver the KD for their child. For example, this support might come from the keto team, charity organisations or the clinical trial team'
38. Level of help or support given (might impact good outcomes of diet and ability to stay on diet) or something around this? I don't think I could have managed so well without Daisy garland and Matthew's Friends			NO	Duplicate of above
39. Family education in KD			NO	Too broad and lacks specificity
GLOBAL QUALITY OF LIFE OUTCOMES				
40. Long term effects on family	Family life	Impact of epilepsy and KD on family life including siblings, parents' relationship, work and career opportunities	NO	outcome can become a 'longterm' outcome by continuing to measure it, e.g. seizure improvement parent health, quality of life etc.
41. Siblings perspective on effect of KD			NO	This is covered in the outcome Family life.

Proposed new outcome	Mapped to existing outcome	Existing outcome description	Add to R2 yes/no	Justification for in/exclusion
42. Improvements in parents work opportunities (can now go out to work as child's health is better)			NO	This is covered in the outcome Family life.
43. Improvements on parents mental/heath	Parent or primary carers health	Parent or primary carers emotional and physical wellbeing	NO but modify existing definition if included in COS	Parent or primary carers emotional, **mental** and physical wellbeing
44. Relationships with other children/siblings around challenges of KD	Social skills	Change in ability to engage and interact with others, for example siblings and friends	NO but modify existing definition if included in COS	Change in ability to engage and interact with others, for example **relationships with** siblings and friends
45. Teacher's perspectives on relationships	Social skills	Change in ability to engage and interact with others, for example siblings and friends	NO	The outcome remains the same it's the perspective that is different. Up to KD team and family to identify the changing perspective
46. Parental stress associated with administering diet			**YES**	It is different to the outcome - Parents Confidence with KD outcome
47. Child's sense of wellbeing	Quality of life for child on KD	Childs general well-being in terms of health comfort and happiness	NO	Addressed in outcome 'Quality of life for child on KD'
SOCIAL AND EMOTIONAL FUNCTIONING OUTCOMES				
48. Longterm outcomes: independent living	Independence	Child becoming as independent as they can, for example, needing less supervision or walking to school alone	NO	Independent living is an example of independence. Any specific outcome can become a 'longterm' outcome by continuing to measure
49. Childs ability to enjoy independence from parents and medical monitors	Independence	Child becoming as independent as they can, for example, needing less supervision or walking to school alone	NO	As above
50. Parents being able to let their child grow independently and realise some of the normality of childhood	Independence	Child becoming as independent as they can, for example, needing less supervision or walking to school alone	NO	Subjective but relates to Independence

Proposed new outcome	Mapped to existing outcome	Existing outcome description	Add to R2 yes/no	Justification for in/exclusion
51. Ability of child to stare at somebody talking	Concentration	Change in ability to focus on a given task while ignoring distraction	NO	This is an example of Concentration
52. Teachers perspective on concentration	Concentration	Change in ability to focus on a given task while ignoring distraction	NO	The outcome remains the same it's the perspective that is different. Up to KD team and family to identify the changing perspective
53. Teachers perspective on behaviour	Behaviour	Change in behaviour. Childs actions, reactions and functioning in response to everyday environment and situations. Ability to adapt to surroundings and situations	NO	The outcome remains the same it's the perspective that is different. Up to KD team and family to identify the changing perspective
54. Childs ability to participate in 'normal' life (sleep overs, school residential trips)	Participation in everyday life	Change in ability to join in and undertake activities, for example, swimming, playing with friends, joining nursery and playgroups	NO but modify existing definition if included in COS to include these examples	Change in ability to join in and undertake activities, for example, **attending school,** swimming, playing with friends, joining nursery and playgroups, **sleepovers and school trips.**
55. School attendance, child and sibling	Participation in everyday life	Change in ability to join in and undertake activities, for example, swimming, playing with friends, joining nursery and playgroups	NO but modify existing definition if included in COS to include these examples	Change in ability to join in and undertake activities, for example, **attending school,** swimming, playing with friends, joining nursery and playgroups, **sleepovers and school trips.**
COGNITION OUTCOMES				
56. Impact on school and education			NO	Too broad
57. Educational attainment and progress	Learning	Change in ability to gain new skills and knowledge	**YES**	Related to learning but educational attainment is subtly different
58. Longterm outcome: completed education			NO	Addressed in the outcome educational attainment and progress
59. Teacher's perspective on child development	Learning Or Developmental milestones	Change in ability to gain new skills and knowledge Or Progress in meeting milestones such as smiling, sitting without support, responding to requests, sorting shapes and colours	NO modify existing definition if included in COS to include these examples	The outcome remains the same it's the perspective that is different. Up to KD team and family to identify the changing perspective 'Change in ability to gain new skills and knowledge For example, from parents, teachers, or others perspective'

Proposed new outcome	Mapped to existing outcome	Existing outcome description	Add to R2 yes/no	Justification for in/exclusion
PHYSICAL FUNCTIONING OUTCOMES				
60. Change in feeding ability with KD treatment (as part of developmental gains section)	Activities of daily living	Change in ability to carry out key activities like feeding oneself, toileting, washing and dressing	NO	Covered in outcome Activities of Daily Living
RESOURCE USE				
61. Number of emails/messages/phone calls to providers			NO	Service level data rather than outcome of KD
62. Workload to neurologists on the keto team			NO	Service level data rather than outcome of KD
63. Workload/stress to dietitians on the keto team			NO	Service level data rather than outcome of KD
64. Time to commence treatment after referral received			NO	Service level data (access to KD) rather than an outcome of KD treatment
65. Adaptability/cooperation of school officials around KD			NO	Too broad and a factor of KD delivery not a direct outcome of treatment with KD
66. Reduction in GP/other appointments as child's health is better			**YES**	A&E and hospital admission outcomes considered so justifiable to have an outpatient equivalent too
67. Reduction of 999 calls			**YES**	As above, A&E attendance considered so add 'emergency service call outs'
68. Reduction of AEDS and then associated reduction in cost to NHS	Cost effectiveness of KD	Is KD a cost-effective treatment for epilepsy	NO	This is an example of how one might assess the Cost Effectiveness of KD so is covered by this outcome

Appendix X. Consensus meeting participants and role

Name	Stakeholder group	Expertise	Country
Claire Dunne	Parent	Parent to a child with epilepsy treated with KD	Ireland
Britta Urban	Parent	Parent to a child with epilepsy treated with KD	England
Kay Smith	Parent	Parent to a child with epilepsy treated with KD	England
Julie Chambers	Parent	Parent to a child with epilepsy treated with KD	England
St John Russell	Parent	Parent to a child with epilepsy treated with KD	England
Corrin Warmington	Parent	Parent to a child with epilepsy treated with KD	Northern Ireland
Brigitta Dampier	Parent	Parent to a child with epilepsy treated with KD	Austria
Ellen Wilford	Health professional	Study advisory group member and dietitian	England
Sheffali Gulatti	Health professional	Paediatric Neurologist	India
Eric Kossoff	Health professional	Paediatric Neurologist	USA
Anita Devlin	Health professional	Paediatric Neurologist	England
Stéphane Auvin	Health professional	Paediatric Neurologist	France
Zoe Simpson	Health professional	Dietitian	England
Hannah Chaffe	Health professional	Clinical/epilepsy specialist nurse	England
Bridget Lambert	Health professional	Dietitian (Industry)	England
Jianxing Liao	Health professional	Paediatric Neurologist	China
Lisa O Brien	Health professional	Clinical/epilepsy specialist nurse, Young Epilepsy representative	England
Clare Szwec	Health professional	Dietitian (Industry)	England
Niamh Brannelly	Health professional	Dietitian (Industry)	Netherlands
Emma Williams	Parent, research team	Parent to a child with epilepsy treated with KD, Matthew's Friends representative	England
Val Aldridge	Parent, research team	Parent to a child with epilepsy treated with KD, Matthew's Friends representative	England
Helen Cross	Research team	Paediatric Neurologist	England
Louise Mole	(non-voting)	Meeting Facilitator and chair	England
Jen Carroll	Research team (non-voting)	Principle investigator, Dietitian	England
Mary Hickson	Research team (non-voting)	Dietitian	England
Avril Collinson	Research team (non-voting)	Dietitian	England

Appendix Y. The core outcome set and justifcation for ammendments

No.	Outcome	Description	Justification for amendments
1.	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.	Now includes spasm reduction to reflect consensus meeting discussions
2.	Seizure freedom	Not having seizures	Now includes spasm freedom to reflect consensus meeting discussions
3.	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.	Seizure severity and duration outcomes combine as duration will be considered in severity
4..	Status epilepticus and use of rescue medication	The frequency of status episodes and the number of rescue medications administered	Frequency of status epilepticus and use of rescue medication combined as closely related
5.	Anti-seizure medication use	The number and dose of antiseizure medications	Unchanged
6.	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.	Adverse effects combined into one all-encompassing outcome for 3 reasons; 1. to reflect consensus meeting discussions 2. cardiac, respiratory and hepatic side effects were voted in but arguably as important outcomes were not – growth, renal and gastrointestinal side effects 3. doing so reduces the total number of outcomes in the core outcome set
7.	Ketone levels	Monitoring of ketosis to include: - urine or blood concentrations (levels) of ketones - excess ketosis (hyperketosis) - time point at which target therapeutic ketosis is reached	Onset of therapeutic ketosis and ketone levels combined to reflect the consensus meeting discussions
8.	Dietary adherence or compliance	Compliance with the agreed dietary and monitoring plan.	'Or compliance' added to outcome title as this terminology is most often used. However, adherence is more positive language as the patient choses to adhere

No.	Outcome	Description	Justification for amendments
9.	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	The scope of this outcome is extended to reflect consensus meeting discussion and now encompasses duration of KD therapy, palatability of formula and supplements and behavioural feeding difficulties
10.	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	Parental confidence added to the descriptor to reflect consensus meeting discussions
11	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	Quality adjusted life years and Quality of Life combined to reflect consensus meeting discussions. QALY assessment is comlex and shouldn't be imposed upon every future study. Participation in everyday life and sleep pattern and quality also added as key examples of quality of life and can be assessed as part of this.
12.	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.	Alertness and concentration combined to reflect consensus meeting discussions and the fact that both terms are commonly used interchangeably
13.	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.	Unchanged
14.	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.	Unplanned hospital admission is the only outcome voted in from the consensus meeting. Combined with A&E attendance to reflect the consensus meeting discussions

Final changes in response to consensus meeting participants feedback following review of the core outcome set

Outcome 11 - sleep pattern and quality added. Outcome 12 - ability to interact added. Outcome 14 - unplanned added to the outcome title.