Outcomes in Paediatric Epilepsy Treated with Ketogenic Diet Therapy

Can we Achieve Consensus?

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I worked as a ketogenic dietitian for several years in the NHS, supporting families with ketogenic diet (KD) therapies. A critical part of our KD service redesign was the identification of appropriate outcomes for paediatric patients and finding ways for these to be measured. Outcomes relating to seizures, and adverse effects, were important to monitor the success and safety of KD therapy.

Parents often reported, however, that: *"they had got their child back"* through improvements in cognition, behaviour, overall well-being and quality of life, which led to positive outcomes for the wider family. These functional health outcomes have rarely been explored in published literature, and arguably, are more challenging – but not impossible – to measure than physiological outcomes. Fast forward a few years, I registered for a part-time PhD and set out to identify 'Core Outcomes for Refractory Childhood Epilepsy treated with Ketogenic Diet Therapy' (the CORE-KDT study).

KD therapy explained

KD therapy is a well-established treatment for paediatric refractory epilepsy, with an increasing number of randomised controlled trials (RCT) demonstrating its efficacy.[1-7] National Institute for Health and Care Excellence guidance recommends seizure freedom as the primary outcome and seizure reduction, cognitive function and quality of life as secondary outcomes when treating epilepsy.[8] However, clinical trials contain a wide range of outcomes with differing measurement and reporting methods. Many of these might not be perceived as the most important outcomes by service users and those making healthcare decisions. A recent Cochrane review identified only one RCT that assessed KD therapy's effect on quality of life, cognition and behaviour.[9, 10] Previous studies have examined parental expectations,[11,12] and attitudes towards KD therapy via questionnaires,[13] but there has been no unified attempt to incorporate the views of patients' parents into the choice of outcomes for their child. Consequently, there is no consensus among healthcare professionals, parents or researchers regarding what outcomes should be measured and reported.

CORE-KDT is a mixed-methods study (see **Figure 1**) that aims to use consensus methodology to develop a core outcome set for refractory childhood epilepsy treated with KD therapy. Parents, professionals, researchers, charities and industry representatives, are consulted to ensure the final core outcome set reflect the interests of all and facilitates future decision-making processes. The core outcome set will identify outcomes to be measured in future clinical effectiveness trials, and guide audit and service evaluation in clinical practice. Ethical approval was granted (*London-Surrey REC19/LO/1680*), and the study registered on the Core Outcome Measures in Effectiveness Trials Initiative (COMET) online database of core outcome set studies (#1116).[14]

What is a 'core outcome set'?

A core outcome set is an agreed standardised set of outcomes that should be reported, as a minimum, in all clinical trials in a specific area of healthcare.[15] It should 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.[16] Martin-McGill *et al.*[9] recently concluded that meta-analysis was not possible in their systematic review, owing to the heterogeneity of outcomes and definitions used in the included RCTs of epilepsy treated with KD therapy. This inability to combine results is a significant detriment to refining treatments for this debilitating condition. Successful examples of core outcome sets include Outcome Measures in Rheumatology (OMERACT)[17] The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT)[18] and Harmonizing Outcome Measures in Eczema (HOME).[19]

A core set of outcomes has not yet been developed for refractory childhood epilepsy treated with KD therapy, so it is timely to address this. Crudgington *et al.*[20] recently developed a core outcome set for Rolandic childhood epilepsy (Rolandic epilepsy is often described as benign as most children outgrow the condition by puberty. It is characterised by centro-temporal spikes and is one of the most common types of epilepsy in children). In contrast to complex refractory epilepsy, Rolandic epilepsy can be well managed with anti-epileptic medications. While there are likely to be some shared outcomes, we expect our proposed set will include different outcomes reflecting the complexity of refractory epilepsy and the severity of associated comorbidities. These might include outcomes related to hospital related admissions, financial burden of KD therapy, adverse side effects and growth.

The importance of involving stakeholders

Core outcome sets are developed using consensus methods in partnership with major stakeholders, including experts in the clinical area, patients and their parents, where appropriate. This patient-centred approach seeks to ensure outcomes are clinically relevant and reflect the views of those being treated. From the outset, we have recognised the value and importance of parents and carers as stakeholders and worked closely with our lay research partners Emma Williams (Founder and CEO) and Val Aldridge (Trustee and Ketogenic Assistant) at Matthew's Friends, a charity supporting families with KD therapies. They were both actively involved in the study design, its recruitment and analysis.

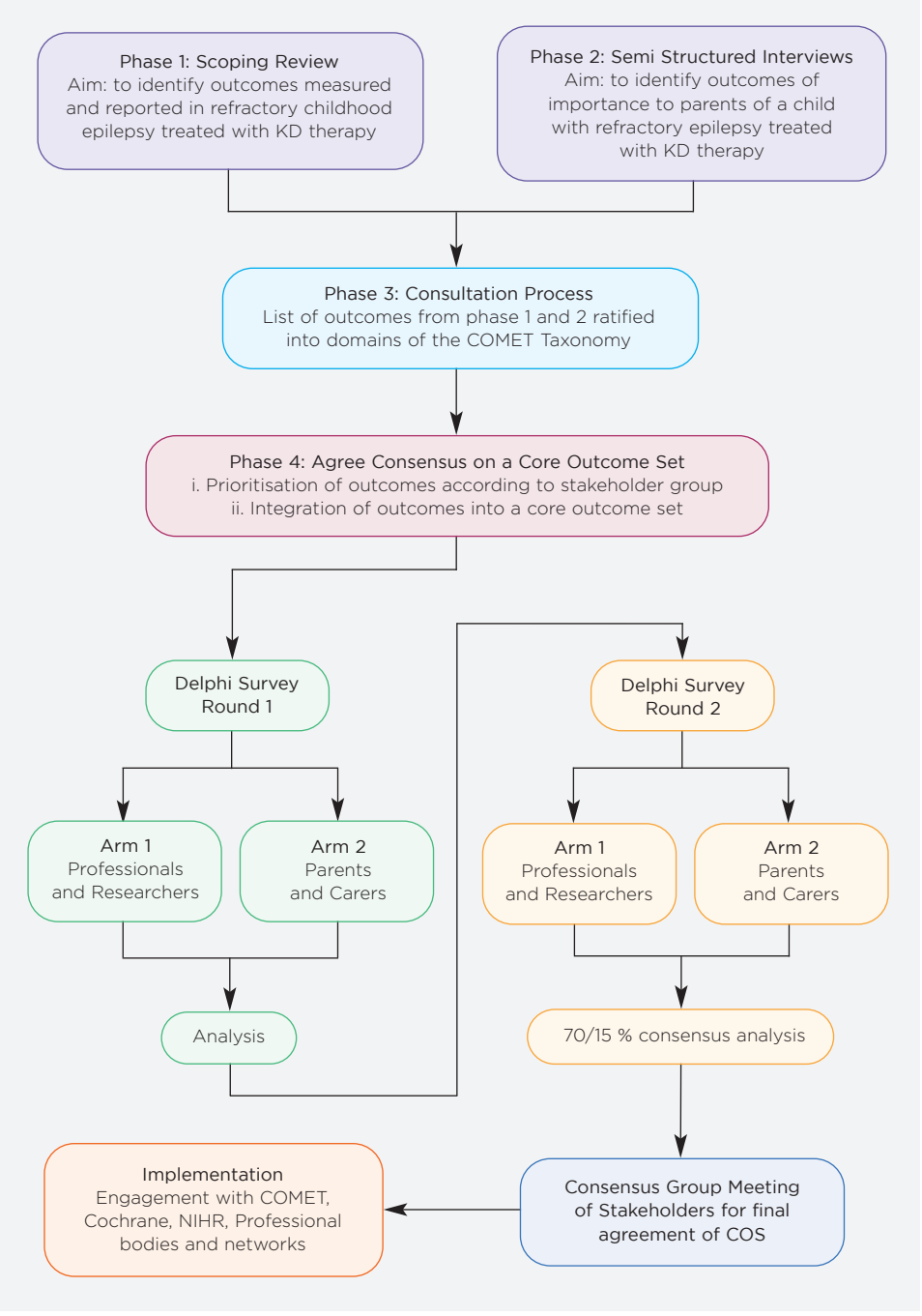
In addition, a patient and public involvement (PPI) consultation was undertaken, where two parents with experience of epilepsy and KD therapy were interviewed. Recruitment was supported by Young Epilepsy and Matthew's Friends. Key themes emerged from these discussions, including epilepsy bringing feelings of isolation, being overwhelmed when considering KD but also under pressure to get the day-to-day dietary management correct. Those consulted felt this study of outcomes was worthwhile research and welcomed the inclusion of parents as participants. 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 to agree the final list of outcomes for inclusion in the two-round Delphi survey. The Delphi technique is a method used for reaching consensus, comprising sequential surveys answered anonymously by participants with relevant and varied expertise.

Developing a core outcome set

The CORE-KDT study consists of four phases outlined in **Figure 1**. In Phase 1, a scoping review was undertaken to systematically identify, and describe, a comprehensive list of all outcomes documented in published studies of childhood epilepsy treated with KD therapy. The full inclusion and exclusion criteria, search strategy, approaches to study screening, data extraction and synthesis were stipulated a priori in a published protocol.[21] The review was undertaken and reported in line with the PRISMA extension for scoping reviews.[22]

In Phase 2, semi-structured interviews were undertaken with 21 parents of a child with epilepsy treated with KD therapy. The objective of this qualitative descriptive study was to establish which outcomes are valued by parents and carers. It was plausible that they would highlight new outcomes of importance not previously identified in the scoping review. A finding seen in other core outcome set studies that sought patient or public opinion.[23,24]

Figure 1: Phases of the CORE-KDT study



In addition, families' experiences of epilepsy and the day-to-day management of KD therapy were explored to broaden our understanding of the impact of epilepsy and KD therapy. Participants were eligible if they were a parent or carer to a child aged 0-18 years with refractory epilepsy currently, or recently, being treated with KD therapy, were English-speaking and were able to consent to, and participate in, the interview. Few children would have the understanding or capacity to participate in this study, so parent-proxy reporting was determined to be an acceptable approach. Maximum variation sampling was employed, and participants were recruited from the UK, and internationally, through three sources:

1) Nine UK ketogenic diet centres operated as Participant Identification Centres.
2) Charity organisations shared study information across a range of mediums, including webpages, social media, newsletters and forums.
3) Epilepsy – the Ketogenic way: a closed support group on Facebook where group administrators shared study information.

Participants were offered the opportunity to have their interview via telephone, video call or in their own home (UK only). Interviews were audio recorded, professionally transcribed verbatim, anonymised, and coded using NVivo software (QSR International). Content analysis identified all outcomes in the transcripts, including parents' priority outcomes. Thematic analysis is ongoing to identify core themes and subthemes in families' experiences of epilepsy and KD therapy.

Phase 3 involved a consultation process between the research team and the study advisory group, to agree on the final list of outcomes to be entered into the two-round Delphi survey. The purpose being to ratify the list of outcomes and group into domains of the COMET Taxonomy,[25] ensuring consistent, accessible language and definitions while avoiding duplication.

Phase 4 aimed to achieve consensus among parents, professionals and researchers on the most important outcomes to be prioritised into a core outcome set. A two-arm, two-round anonymous online Delphi survey was administered using DelphiManager software in line with recommended practices in developing core outcome sets.[15] Stakeholder group 1 included professionals and researchers recruited via professional networks, and group 2 included parents and carers recruited as described, above. In round one, participants were asked to rate the importance of the list of outcomes identified in phase 3 and to list any additional outcomes they felt were important but not represented. Respondents to the round one survey were invited to participate in round two, where all outcomes were carried forward from round one and new outcomes identified through a free text question. Participants were reminded of their own individual score for each outcome and were presented with the aggregate scores of both stakeholder groups. They were asked to reflect on their score and explain the rationale for any change from the original score. Presenting the aggregate scores for each stakeholder group has been shown to improve consensus between groups to determine what outcomes are important to retain in the final core outcome set.[26] The Delphi survey recently closed and analysis is ongoing. Later this year, the findings will be integrated into a core outcome set at a consensus group meeting with representation from all stakeholders.

Early findings

The scoping review highlighted little consistency in the wide range of outcomes used in research. These were often measured subjectively through parent, or clinician, reporting with validated assessment tools rarely used. Physiological clinical domain outcomes were most often reported, suggesting prioritisation of these outcomes over other domains that relate to functioning, resource use and quality of life. This focus on the physiological clinical domain risks overlooking outcomes that may have profound effects on day-to-day functioning, and quality of life for the child and wider family. Parents identified just over a third of the existing outcomes from the scoping review, suggesting the remainder may be less important to them. However, they identified seven new outcomes (see **Table 1**). In total, 77 outcomes were put forward to the two-round Delphi survey for rating by participants.

Conclusion

The qualitative and Delphi survey analysis is ongoing, and we look forward to sharing the final core outcome set early next year in line with the Core Outcome Set-Standards for Reporting (COS-STAR).[27] Medics often take the lead in core outcome set development, so this has been a unique opportunity for a dietitian to lead the development of an international core outcome set. I would encourage other dietitians to consider engaging in a similar process in their clinical area, to enhance outcome measurement and reporting. Finally, we would like to extend a very big thank you to the parents, professionals and charity organisations who have supported the CORE-KDT study by taking part.

Table 1: New outcomes identified by parents

Domain	Outcome
Physiological/Clinical	1. Use of rescue medication for status epilepticus 2. Seizure duration
Diet and Nutrition	3. Parent's confidence with KD
Global Quality of Life	4. Parent or primary carers health 5. Family life
Social and Emotional Functioning	6. Participation in everyday life 7. Independence

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