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Draft for consultation

Epilepsies in children, young people and adults: diagnosis and management

[12] Evidence review: Ketogenic diets for drug-resistant epilepsy

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Evidence review underpinning recommendation 8.1.1 and a research recommendation in the NICE guideline

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1

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Contents

1. Ketogenic diets in drug-resistant epilepsy 5
1.1. Review question 5
1.1.1. Introduction 5
1.1.2. Cochrane collaboration 5
1.1.3. Summary of the protocol 5
1.1.4. Summary of the effectiveness evidence 6
1.1.5. Summary of studies included in the effectiveness evidence 6
1.1.6. Economic evidence 15
1.1.7. Summary of included economic evidence 17
1.1.8. Economic model 20
1.1.9. Evidence statements 20
1.1.10. The committee's discussion and interpretation of the evidence 20
1.1.11. Recommendations supported by this evidence review 23
References 24

Appendices 26
Appendix A Review protocols 26
Appendix B Literature Search Strategy 34
Appendix C Economic evidence study selection 35
Appendix D Economic evidence tables 36
Appendix E Health economic model 41
Appendix F Excluded studies 41
Appendix G Research recommendations 42

1

1. Ketogenic diets in drug-resistant epilepsy

1.1. Review question

What is the effectiveness of ketogenic diets in drug-resistant epilepsy?

1.1.1. Introduction

The ketogenic diet (KD) is a high-fat, low carbohydrate and protein diet designed to mimic the biochemical response of the body to starvation. Ketogenic diets can refer to any diet that is designed to produce ketones: Classical KD Medium-chain triglyceride (MCT) KD Modified Atkins diet (MAD) Low glycaemic index treatment (LGIT).

The classical diet has been adapted, in-part to improve tolerance, and become part of treatment options in the management of childhood onset drug-resistant epilepsy. There are a number of metabolic epilepsies were dietary treatments have an important role to play, including, but not limited to; GLUT-1 deficiency, and mitochondrial disorders although the exact mechanism of action is unclear. Whilst the role of dietary interventions in childhood epilepsy is more established, it is less clear the effectiveness or tolerability for adults, or the safe duration of therapy. It is recognised the diet requires careful monitoring because of possible adverse effects, including weight loss, elevated total cholesterol and gastrointestinal symptoms.

1.1.2. Cochrane collaboration

An overlap was identified between the Cochrane review 'Ketogenic diets for drug-resistant epilepsy' and the question within the NICE Epilepsies guideline scope on ketogenic diets for people with Epilepsies. NICE and the NGC developers agreed to collaborate with the Cochrane epilepsy group for them to update their review and to incorporate this within the guideline. The NGC technical team and the Epilepsies guideline committee worked with the Cochrane group to finalise the review protocol. The evidence review was conducted in its entirety by the Cochrane team, the full Cochrane review can be found here. A summary of the included studies and evidence is given below.

This review summarises the findings of the Cochrane systematic review to answer what is the effectiveness of the ketogenic diet in epilepsy.

1.1.3. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Children, young people and adults with drug-resistant epilepsy Strata: evidence in people with learning disabilities will be presented separately from evidence in people without learning disabilities
Interventions	Ketogenic diet (4:1 ratio of total energy from fat to carbohydrate and protein combined) Any diet that is designed to produce ketones: Classical KD Medium-chain triglyceride (MCT) KD Modified Atkins diet (MAD) Low glycaemic index treatment (LGIT)
Comparisons	Placebo/Usual care/Sham One diet vs another diet

Outcomes	• seizure freedom (100% reduction in seizure frequency at study endpoint • seizure frequency (50% or greater reduction in seizure frequency at study endpoint • quality of life (as measured by validated scales) • adverse events (all e.g., diarrhoea / constipation / vomiting / renal stones (all GI heading)) at study endpoint • attrition rate
Study design	RCTs with a minimum study period of 1 month

1.1.4. Summary of the effectiveness evidence

1.1.4.1. Included studies

We included 13 studies in this review (n = 932). These studies were conducted across various healthcare systems worldwide. Seven studies compared a ketogenic diet (KD) to a usual care group [4, 7, 8, 11, 15, 16, 19], and six studies compared one KD intervention to another type of KD intervention [1, 5, 6, 9, 13, 14].

1.1.5. Summary of studies included in the effectiveness evidence

Study	Intervention and comparison	Population	Outcomes	Comments
Bergqvist 2005[1]	Speed of introduction of KD: Fast KD (< 48 hour fast, followed by 4:1 KD with increase in portion size over 6 days) or Grad KD (gradual increase in KD ratio from 1:1 to 4:1 over 6 days)	48 children, 24 in each of the 2 arms, aged 1-14 years (mean 5.3, SD 2.7 years), having ≥ 1 seizures per 28 days, tried at least 3 AEDs and a discontinuation of steroidal medication 3 months previous.	Proportion of participants with > 50% seizure reduction in target seizure type. Level of ketosis. Adverse effects.	All generalised and focal seizures included.
El-Rashidy 2013[4]	Participants were randomised into 1 of 3 groups: MAD (15 participants), KD (10 participants) and control (polytherapy) (15 participants). 4:1 refers to 4 g fat to 1 g of carbohydrate and protein combined.	40 children aged 12-36 months (mean 27.13, SD 6.63) with symptomatic intractable epilepsy.	Reduction in seizure frequency. Adverse effects. Attrition rate. Data were collected at 3 and 6 months.	Two children in the classic group had infantile spasms and one child in the classic group had myoclonic encephalopathy.
Kim 2016[5]	Randomised into 1 of 2 groups; MAD (10 g carbohydrate per day for the first month, followed by increase to 10% of	104 participants aged 1 to 18 years, with drug-resistant epilepsy, experiencing more than 4	Seizure reduction. Seizure freedom. Adverse effects.	4:1 refers to 4 g fat to 1 g of carbohydrate and protein combined. All recruited participants were

Study	Intervention and comparison	Population	Outcomes	Comments
	total energy requirements, with energy restriction to 75% of recommended daily intake) and classic KD (4:1 ratio) for a 6-month period.	seizures per month, with treatment failure following 2 or more AEDs.	Compliance. Attrition.	hospitalised to commence the diet and followed a non-fasted initiation protocol. Epilepsy syndromes included Lennox-Gastaut syndrome, West syndrome, myoclonic astatic epilepsy and Dravet syndrome.
Kossoff 200[6]	MAD with randomisation either to 10 g (10 children) or 20 g (10 children) of carbohydrate and cross-over at 3 months.	20 children aged 3-18 years with intractable epilepsy, with a prior use of at least 2 AEDs and experiencing daily seizures. All seizure types included.		Epilepsy syndromes included were idiopathic (15 children), Rett syndrome (2 children), cortical dysplasia (2 children) and tuberous sclerosis complex (1 child).
Kverneland 2018[7]	MAD (up to 16 g carbohydrate per day, excluding fibre; 37 participants) compared to usual care (38 participants) over a three-month period.	75 adult participants aged 16 years or over, with focal or multifocal epilepsy, at least three countable seizures per month, tried at least three AEDs, BMI > 18.5kg/m2, motivated and capable of adhering to the diet, with assistance if required.	Seizure reduction. Adverse effects. Changes in body weight. Changes in selected biomarkers.	
Lambrechts 2017[8]	Randomised into 1 of 2 groups: KD (classic KD and MCT KD) and control (usual care) for a four-month period	57 participants aged 1 to 18 years with drug-resistant epilepsy, seizures not adequately controlled by 2 or more AEDs and surgical remedial causes of epilepsy not viable.	Seizure reduction. Adverse effects. Attrition. Quality of life. Cost-effectiveness. Cognitive and behavioural changes.	Epilepsy syndromes included West syndrome, Lennox-Gastaut syndrome, Doose syndrome, Dravet syndrome, childhood absence epilepsy, epilepsy with myoclonic absences, generalised epilepsies and localisation-related epilepsies.
McDonald 2018[9]	A comparison of two MAD interventions: 1.	80 adult participants aged 18 years and	Seizure reduction.	

Study	Intervention and comparison	Population	Outcomes	Comments
	MAD plus KetoCal during first month, followed by MAD alone in second month (intervention) to 2. MAD alone in the first month, followed by MAD plus KetoCal during second month (control) with MAD consisting of 20 g net carbohydrates per day. The intervention was conducted for two months, with a six-month follow-up period.	over, four quantifiable seizures per month minimum, failed trial of two or more AEDs.	Dietary adherence. Tolerability. Adverse effects.	
Neal 2008[11]	Participants were randomised to commence a KD (either classic or MCT) immediately (73 participants) or after a further 3 months of seizure recording (usual care group, 72 participants). Those in the KD arm were then randomised to receive classical KD or MCT	145 children (aged 2-16 years), with daily seizures and > 7 seizures/week, who had not responded to ≥ 2 AEDs who had not previously been treated with a KD. All seizure types included.	Reduction in seizure frequency. Tolerability.	4:1 refers to 4 g fat to 1 g of carbohydrate and protein combined.
Raju 2011[13]	Participants were randomised into 1 of 2 groups; a 4:1 ratio KD (19 participants) and 2.5:1 KD (19 participants) and followed for 3 months.	38 children aged 6 months to 5 years, with drug-resistant epilepsy, at least 2 seizures/month, despite appropriate use of at least 2 AEDs and at least 1 newer AED.		4:1 refers to 4 g fat to 1 g of carbohydrate and protein combined. 2.5:1 refers to 2.5 g fat to 1 g of carbohydrate and protein combined. Epilepsy syndromes included were West, Lennox-Gastaut, Doose and unclassified syndromes. The trial included participants with cerebral palsy.
Seo 2007[14]	Participants were randomised into 2 groups, 4:1 KD group (40 participants) and 3:1 KD group (36 participants) and	76 children (aged 4 months to 16 years), with > 4 seizures/month and seizures were not controlled by at least 3 AEDs.	Seizure reduction rate. Tolerability.	4:1 refers to 4 g fat to 1 g of carbohydrate and protein combined. 3:1 refers to 3 g fat to 1 g carbohydrate

Study	Intervention and comparison	Population	Outcomes	Comments
	the diet was followed for 3 months;	All seizure types included. Epilepsy syndromes included Lennox-Gastaut syndrome, and the study also included participants with infantile spasms.		and protein combined. After a three-month period of the diet, children who were seizure free in the 4:1 group were recommended to change to a 3:1 ratio, and children who were not seizure free in the 3:1 group were recommended to change to a 4:1 ratio and re-evaluated after a further three months.
Sharma 2013[16]	Randomised into 1 of 2 groups; MAD (50 participants) or a normal diet (52 participants) for a period of 3 months.	102 children aged 2-14 years with drug-resistant epilepsy and 2-14 daily seizures, having previously tried 3 AEDs.	Seizure frequency. Tolerability. Adverse effects.	Epilepsy syndromes included: West syndrome and myoclonic astatic epilepsy.
Sharma 2016[15]	Randomised into 1 of 2 groups; sMAD (10 g carbohydrate per day, delivered with simplified dietary methods) and usual care (normal diet) for a 3-month period.	81 participants aged 2-14 years, with drug-resistant epilepsy, experiencing daily seizures (or more than 7 seizures per week) despite 2 or more AEDs.	Seizure reduction. Adverse effects. Non-seizure domains. Tolerability.	This study modified the traditional educational techniques used to implement the diet, to promote the inclusion of children with parents who have low levels of literacy and who are of poor socioeconomic status. Epilepsy syndromes included West syndrome and Lennox-Gastaut syndrome.
Zare 2017[19]	Randomised into 1 of 2 groups; MAD (carbohydrates limited to 15 g per day; approximate macronutrient intakes as a percentage of total energy: 4% to 6% carbohydrate, 20% to 30% protein, 60% to 70% fat) and usual care for a 2-month period.	66 adult participants aged 18 years or over, with drug-resistant epilepsy (2 or more AEDs and 2 or more seizures per month).	Seizure reduction. Adverse effects.	

1

1.1.5.1. Ketogenic diet (KD) compared to usual care for children with drug-resistant epilepsy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with KD				
Seizure freedom (100% reduction in seizure frequency) Follow-up: 3 months to 4 months	Study population 21 per 1000	66 per 1000 (25 to 174)	RR 3.16 (1.20 to 8.35)	385 (4 RCTs)	⨁⊖⊖⊖ Very low [a,c]	
50% or greater reduction in seizure frequency Follow-up: 3 months to 4 months	Study population 78 per 1000	453 per 1000 (272 to 754)	RR 5.80 (3.48 to 9.65)	385 (4 RCTs)	⨁⨁⊖⊖ Low [a,b]	
Adverse effects Follow-up: 3 months to 4 months	The most frequent adverse effects reported by participants in dietary intervention groups were vomiting, constipation and diarrhoea. These adverse effects were also commonly reported by participants in the usual care groups. Other less common adverse effects reported included: dysphagia, lethargy, lower respiratory tract infection, hyperammonaemic encephalopathy, weight loss, nausea, infections (pneumonia, sepsis), acute pancreatitis, decrease in bone matrix density, gallstones, fatty liver, nephrocalcinosis, hypercholesterolaemia, status epilepticus, acidosis, dehydration, tachycardia, hypoglycaemia, hunger, abdominal pain, clinically relevant reduction in height, hypercalcinaemia and renal stones.			425 (5 RCTs)	⨁⨁⊖⊖ Low [a,d]	
Cognition and behaviour Follow-up: 4 months	Children randomised to KD were more active (P = 0.005), more productive (P = 0.039) and less anxious (P = 0.049) after four months, than children randomised to the usual care group.			57 (1 RCT)	⨁⊖⊖⊖ Very low [a,c,d]	
Quality of life Follow-up: 4 months	There were no significant differences in QALYs between KD and usual care treatment groups at four or 16 months.			57 (1 RCT)	⨁⊖⊖⊖ Very low [a,c,d]	
Treatment withdrawal Follow-up: 3 months to 6 months	Study population 184 per 1000	198 per 1000 (136 to 288)	RR 1.08 (0.74 to 1.57)	425 (5 RCTs)	⨁⨁⊖⊖ Low [a,b]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; KD: ketogenic diet; MAD: modified Atkins diet; MCT: medium-chain triglyceride; QALY: quality of life-adjusted year; RCT: randomised controlled trial RR: risk ratio; sMAD: simplified modified Atkins diet

[a]Downgraded once due to risk of bias: some included studies were not blinded, had missing data or unclear methodological details reported.
[b]Downgraded once due to imprecision: low overall sample size, plus low number of events (< 200). Confidence in results from small number of participants is low.
[c]Downgraded twice due to imprecision: low overall sample size, plus low number of events (< 50). Confidence in results from small number of participants is low.
[d]Downgraded once due to imprecision: a narrative synthesis was used for this outcome.

1.1.5.2. Ketogenic diet (KD) compared to usual care for adults with drug-resistant epilepsy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with KD				
Seizure freedom Follow-up: 2 months to 3 months	No adults in either the MAD or the usual care group achieved seizure freedom, therefore we were unable to calculate an effect.			141 (2 RCTs)	⨁⊖⊖⊖ Very low [a,b]	
50% or greater reduction in seizure frequency Follow-up: 2 months to 3 months	Study population 29 per 1000	144 per 1000 (7 to 1000)	RR 5.03 (0.26 to 97.68)	141 (2 RCTs)	⨁⊖⊖⊖ Very low [a,b,d]	
Adverse effects Follow-up: 2 months to 3 months	Common adverse effects reported by participants receiving MAD were vomiting, constipation and diarrhoea. One study reported a significant reduction in BMI, as well as an increase in cholesterol in the MAD group, whilst the other study reported significant weight loss. Other adverse effects included: anorexia, lethargy, lower respiratory tract infections and hyperammonaemic encephalopathy.			141 (2 RCTs)	⨁⊖⊖⊖ Very low [a,b,c]	
Cognition and behaviour	Outcome not reported				N/A	
Quality of life	Outcome not reported				N/A	
Treatment withdrawal Follow-up: 2 months to 3 months	Study population 86 per 1000	461 per 1000 (36 to 1000)	RR 5.38 (0.42 to 69.53)	141 (2 RCTs)	⨁⊖⊖⊖ Very low [a,b,d]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with KD				
BMI: body mass index; CI: confidence interval; KD: ketogenic diet; MAD: modified Atkins diet; NA: not applicable; RCT: randomised controlled trial; RR: risk ratio.						

[a]Downgraded once due to risk of bias: some included studies were not blinded, had missing data or unclear methodological details reported.
[b]Downgraded twice due to imprecision: low overall sample size, plus low number of events (< 50). Confidence in results from small number of participants is low.
[c]Downgraded once due to imprecision: a narrative synthesis was used for this outcome.
[d]Downgraded once due to inconsistency: significant statistical heterogeneity was detected (P < 0.10 and I^2 > 50%).

1.1.5.3. Ketogenic diets (KDs) compared with other KDs for children with drug-resistant epilepsy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Correspond-ing risk				
	Other KDs	KDs				
Seizure freedom (100% reduction in seizure frequency) Follow-up: 3 months to 6 months	Proportion of children achieving seizure freedom ranged from 10% to 25% on MAD. There was no information about whether the seizure freedom varied depending on the restriction of carbohydrates (10 mg/d versus 20 mg/d). 21% of children on 2:5:1 KD achieved seizure freedom compared to 26% to 55% on 4:1 KD and 35% on the 3:1 KD. 33% of children on a classic KD were seizure free at 3 months. 21% of both children randomised to fasting-onset KD and gradual-onset KD became seizure free.		Not estimable	286 (5 RCTs)	⨁⊖⊖⊖ Very low [a,b,d,e]	Due to heterogeneity of both interventions and methodology, meta-analysis could not be conducted
Seizure reduction (50% or greater reduction in seizure frequency) Follow-up: 3 months to 6 months	The proportion of children achieving seizure reduction ranged from 42% to 60% on MAD, however, the rate decreased to 10% when daily carbohydrate intake was increased to 20 mg/d, compared to 10 mg/d. 43% of children on a classic KD achieved seizure reduction with 58% to 85% on 4:1 KD, 72% on the 3:1 KD and		Not estimable	286 (5 RCTs)	⨁⊖⊖⊖ Very low [a,b,c,e]	

	63% on 2.5:1 KD. 58% on the fasting-onset KD and 67% on the gradual-onset KD attained 50% or greater reduction in seizure frequency.				
Adverse effects Follow-up: 3 months to 6 months	The most frequent adverse effects reported by children were vomiting, constipation and diarrhoea. Two studies reported weight loss, with one study stating that weight loss and gastrointestinal disturbances were more frequently reported with 4:1 KD versus 3:1 KD. One study reported a significantly high incidence rate for hypercalciuria amongst children receiving classic KD compared to MAD at three months. There was no significant difference in weight loss between treatment groups given 20 mg/d versus 10 mg/d carbohydrates. Other adverse effects reported included: dysphagia, lethargy, lower respiratory tract infection, hyperammonaemic encephalopathy, nausea, infections (pneumonia, sepsis), acute pancreatitis, decrease in bone matrix density, gallstones, fatty liver, nephrocalcinosis, hypercholesterolaemia, status epilepticus, acidosis, dehydration, tachycardia, hypoglycaemia, hunger, abdominal pain, clinically relevant reduction in height, hypercalcinaemia and renal stones.	Not estimable	286 (5 RCTs)	⨁⊖⊖⊖ Very low [a,b,c,e]	
Cognition and behaviour Follow-up: NA	Outcome not reported			NA	
Quality of life Follow-up: NA	Outcome not reported			NA	

Attrition rate Follow-up: 3 months to 6 months	Proportion of individuals withdrawing from KD groups were: 8% gradual-onset KD; 16% on 2:5:1 KD and 4:1 KD; 17% on fasting-onset KD and on the 3:1 KD; 32% on MAD; and 33% on the classic KD.	Not estimable	286 (5 RCTs)	⨁⊖⊖⊖ Very low [a,b,c,e]	

*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; KD: ketogenic diet; MAD: modified Atkins diet; NA: not applicable; RCT: randomised controlled trial

[a]Downgraded once due to risk of bias: some included studies were not blinded, had missing data or unclear methodological details reported.
[b]Downgraded once due to inconsistency: studies are heterogeneous with regards to interventions examined and comparisons made.
[c]Downgraded once due to imprecision: low overall sample size, plus low number of events (< 200). Confidence in results from small number of participants is low.
[d]Downgraded twice due to imprecision: very low overall sample size, plus low number of events (< 50). Confidence in results from small number of participants is low.
[e]Downgraded once due to imprecision: a narrative synthesis was used for this outcome.

1.1.5.4. Ketogenic diets (KDs) compared with other KDs for adults with drug-resistant epilepsy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other KDs	KDs				
Seizure freedom (100% reduction in seizure frequency) Follow-up: 6 months	No adult participants achieved seizure freedom with either MAD plus KetoCal in month one (intervention) or MAD plus KetoCal in month two (control).		Not estimable	80 (1 RCT)	⨁⊖⊖⊖ Very low [a,b,c]	No adults in either the MAD or the control group achieved seizure freedom; therefore, we were unable to calculate an effect.
Seizure reduction (50% or greater reduction in seizure frequency) Follow-up: 6 months	The proportion of adults achieving 50% or greater reduction in seizure frequency at one month was 32.5% for the intervention group (MAD plus KetoCal month one) and 42.5% for the control (MAD plus KetoCal month two). This decreased to 25% versus 32.5%, respectively at two months. At three months, 10% of adults in both groups		Not estimable	80 (1 RCT)	⨁⊖⊖⊖ Very low [a,b,c]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other KDs	KDs				
	maintained a 50% or greater reduction in seizure frequency.					
Adverse effects Follow-up: 6 months	Constipation was reported more frequently by adults in the MAD plus KetoCal group (17.5%) compared to MAD only treatment group (5%). Diarrhoea and increase/change in seizure pattern/semiology were also commonly reported (17.5% to 20% of participants). Other less commonly reported adverse effects included: abdominal pain, headache, irregular menses, halitosis, somnolence, nephrolithiasis, kidney infection, nausea, easy bruising, vaginal odour and brittle hair/nails.		Not estimable	80 (1 RCT)	⨁⊖⊖⊖ Very low [a,b,c]	
Cognition and behaviour	Outcome not reported				NA	
Quality of life	Outcome not reported				NA	
Attrition rate Follow-up: 6 months	12.5% of adults withdrew from the intervention group (MAD plus KetoCal month one) compared to 32.5% from the control group (MAD plus KetoCal month two).		Not estimable	80 (1 RCT)	⨁⊖⊖⊖ Very low [a,b,c]	
*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; KD: ketogenic diet; MAD: modified Atkins diet; NA: not applicable; RCT: randomised controlled trial						

[a]Downgraded once due to risk of bias: the study did not appear to be blinded, it was not clear whether there was missing data. Unclear methodological details were reported.
[b]Downgraded twice due to imprecision: low overall sample size, plus low number of events (< 50). Confidence in results from small number of participants is low. Unable to conduct a meta-analysis.
[c]Downgraded once due to imprecision: a narrative synthesis was used for this outcome.

1.1.6. Economic evidence

1.1.6.1. Included studies

Three health economic studies comparing ketogenic diet to usual care in children and young people with drug-resistant epilepsy were included in this review.[3 2, 18]These are summarised

in the health economic evidence profile below (**Table 2**) and the health economic evidence tables in Appendix D.

No studies with relevant comparisons in adults with drug-resistant epilepsy were identified.

1.1.6.2. Excluded studies

One economic study relating to this review question was identified but was excluded due to a combination of limited applicability and methodological limitations.[17] This is listed in Appendix F, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix B.

1.1.7. Summary of included economic evidence

Table 2: Health economic evidence profile: Ketogenic diet versus usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
De Kinderen 2015 [3] (Netherlands)	Partially applicable [(a)]	Potentially serious limitations[(b)]	• Probabilistic model based on two RCTs (Neal 2008[11] and Sharma 2013 [16]) • Cost-utility analysis (QALYs) • Population: Children (1-18 years) with intractable epilepsy who have tried two or more drugs and are not eligible for resective surgery • Comparators: 1.Usual care 2.Ketogenic diet (80% medium chain triglyceride diet, 15% classic diet and 5% diet via tube feeding) • Time horizon: 1 and 5 years	1 year: £9,346 5 years: £13,855 [(c)]	1 year: 0.031 QALYs 5 years: 0.185 QALYs	1 year: £302,169 per QALY gained 5 years: £74,933 per QALY gained	Probability ketogenic diet being cost effective (€20K = circa £17.5K threshold): 0% (at 1 and 5 years) Deterministic sensitivity analyses undertaken to explore different types of ketogenic diet. The percentage of classic diet users was increased from 15% to 100% and simultaneously lowered the ketogenic diet initiation costs by assuming no hospitalisation required. This resulted in a higher probability ketogenic diet was cost effective at 5 years (26% at threshold of €20K = circa £17.5K).
De Kinderen 2016[2]/Wijnen 2017[18] (Netherlands)	Partially applicable [(d)]	Potentially serious limitations[(e)]	• Within trial analysis (associated RCT Lambrechts 2017[8]) • Cost-utility analysis (QALYs) • Population: Children and adolescents (age 1 to 18 years) with intractable	4 months: £3,963 16 months: £8,930[(f)]	4 months: 0.003 QALYs 16 months: 0.002 fewer QALYs	4 months: £1,321,094 per QALY gained 16 months:	Probability ketogenic diet cost effective (€50k = circa £43.5K threshold): 3% Bootstrapping undertaken, presented both from societal (4 months and 16 months) and healthcare

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			epilepsy not eligible for epilepsy surgery • Comparators: 1.Usual care 2.Ketogenic diet (69.2% medium chain triglyceride diet, 26.9% classic diet and 3.9% mix of the two diets) • Follow-up: 4 months/16 months			Usual care dominates ketogenic diet	perspective (4 months only). Healthcare perspective at 4 months presented above. Responder analysis presented (cost per responder) = £12,456 and £181,171 per responder for ketogenic diet compared to usual care at 4 and 16 months respectively. A hypothetical sensitivity analysis (from societal perspective only) undertaken where intervention costs decreased and simultaneously increased classical diet from 32% to 100%. This increased probability of ketogenic diet being cost effective (from 5% to 32% at a threshold of £43.5K).

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial

(a) Dutch healthcare perspective. Incorrect discounting applied. Unclear if EQ5D or other utility measure used for estimating quality of life.

(b) Includes 2 of 4 included RCTs and so may not reflect full body of clinical evidence. Dutch costs. Children on ketogenic diet would follow the dietary treatment for a maximum of 24 months, after this period they were treated with usual care. Model assumed that a responder remains a responder and a non-responder remains a non-responder for the rest of the study period (i.e., patients do not switch between health states after 2 4months). Other complications, such as gastrointestinal complaints and hoarseness, were not incorporated in the model; there are many, with generally a limited or short-term impact on quality of life or costs.

(c) 2013 Euros converted to 2013 UK pounds.[12]. Cost components incorporated: number of neurologist visits, number of seizure related hospitalisations (both linked to the health states of how seizure free someone is). Initiation costs of ketogenic diet, including 5-day admission to epilepsy centre, visits of neurologist, paediatrician, dietician and epilepsy nurse and laboratory costs. Costs related to the ketogenic diet were vitamin and diet supplements and keto sticks. Cost of antiepileptic drugs and the cost of side-effects due to antiepileptic drugs were not taken into account; they were assumed to be equal in both arms.

(d) Dutch healthcare perspective. Incorrect discounting applied. Does not use EQ5D to estimate quality of life, but rather a non-preference-based measure of quality of life: TAPQOL and TACQOL. Includes parent and child QoL in total QALYs.

(e) Includes 1 of 4 included RCTs and so may not reflect full body of clinical evidence. Dutch 2013 costs. The primary outcome measure of the trial was seizure reduction therefore, sample size possibly too small to detect QoL changes. Short time horizon for 4-month analysis. Extrapolation of usual care arm from 4 months to 16 months. It was noted that, in some centres offering a ketogenic diet only the classical ketogenic diet may be available which is also cheaper. In addition, at other centres patients initiating ketogenic diet may not incur such high costs due to patients not being admitted to hospital for five days upon initiation of ketogenic diet.

(f) 2013 Euros converted to 2013 UK pounds[12]. Cost components incorporated: Healthcare costs (including but not limited to): visits (for example GP, nurse, specialist), hospitalisations, EEG and MRIs, other (for example social services) and medication. Intervention costs (including diet and ketosis check costs). Societal costs reported but not presented here.

1.1.8. Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.9. Evidence statements

1.1.9.1. Economic

- One cost utility analysis found that ketogenic diet was not cost effective compared to usual care for treating children with drug refractory epilepsy (ICER: £302,169 per QALY gained at 1 year and £74,993 per QALY gained at 5 years). This study was assessed as partially applicable with potentially serious limitations.
- One cost utility analysis found that ketogenic diet was not cost effective compared to usual care for treating children with drug refractory epilepsy (ICER: 1,321,094 per QALY gained at 4 months). At 16 months usual care was dominant (less costly and more effective). This analysis was assessed as partially applicable with potentially serious limitations.

1.1.10. The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

All the outcomes included in this review were of critical importance. 'Seizure freedom' 'reduction in seizure frequency of 50% or greater' and treatment withdrawal were the only outcomes meta-analysed in the review. All other outcomes were reported narratively due to the lack of uniformity in reporting across studies.

1.1.10.2. The quality of the evidence

The quality of the evidence included was rated as low or very low. The trials included in the review had small sample sizes and were downgraded for significant risk of bias. This was largely due to a lack of blinding and unclear methodological reporting. There were missing data for several of the included studies and imprecision in the data for many outcomes. Heterogeneity observed in data sets resulted in further downgrading of the quality for inconsistency. Overall, the committee agreed the evidence for this review had been limited by the associated risk of bias, the observed heterogeneity between studies, and the low number of participants recruited to study populations, and this reduced the confidence the committee had in the findings of the review.

1.1.10.3. Benefits and harms

The evidence from two pooled RCTs suggested ketogenic diets were unable to achieve seizure freedom in people with drug resistant epilepsy when compared to usual care, with a larger number of people withdrawing from treatment in the ketogenic diet arm of trials. Despite a large increase in the number of people achieving 50% or greater seizure reduction with ketogenic diets, one trial suggested increased adverse events with ketogenic diet. As all the outcomes were graded very low quality and the pooled outcomes were highly heterogeneous, the results could not be relied upon to form the basis of recommendations.

Along with the more generically termed drug-resistant epilepsy, some of the children included in the Cochrane review also had the following specific conditions: infantile spasms, myoclonic astatic epilepsy, Dravet syndrome and Lennox-Gastaut syndrome. The committee commented that these childhood onset epilepsies are complex to treat and as the response to ASM therapy is often variable, ketogenic diets are sometimes used as an adjunctive treatment.

The meta-analyses included for ketogenic diets versus usual care suggested benefits of ketogenic diets for achieving seizure freedom and reducing seizure frequency by 50% or greater. However, these outcomes graded as very low to low quality respectively were highly uncertain. The committee therefore could not confidently extrapolate to benefit of ketogenic diets for drug-resistant epilepsy in children.

The guideline committee were aware of cases in clinical practice where ketogenic diets have shown credible benefit for select individuals with respect to significant improvements in seizure control and improved quality of life. However, the evidence presented in the Cochrane review was unable to replicate this.

The guideline committee were mindful of the importance of keeping ketogenic diets as an option for people in whom other treatment options have been exhausted. They therefore agreed that although ketogenic diets should not be routinely recommended, it should continue to be available as a treatment option within the NHS based on individual clinical need.

Determining the effectiveness and tolerability of ketogenic diets in adults was particularly difficult due to the limited trials in adults with epilepsy. Furthermore, as the evidence comparing one type of ketogenic diet to another in both adults and children's populations was only narratively reported, the individual diets could not be adequately assessed. The committee acknowledged more precise data of higher quality is required to truly assess the effectiveness of ketogenic diets. The committee expressed the need for trials to be conducted that compared the effectiveness of specific ketogenic diets and decided to make a research recommendation for both adults and children evaluating the effectiveness of both long-term and short-term ketogenic diets.

1.1.10.4. Cost effectiveness and resource use

Three cost utility analyses were included that compared ketogenic diet (including a 5-day inpatient stay for diet initiation) to usual care for treating children with intractable epilepsy (de Kinderen, 2015, de Kinderen, 2016 and Wijnen, 2017). These analyses were from a Dutch health care perspective.

De Kinderen 2015 was a probabilistic model based on two RCTs (Neal 2008 and Sharma 2013) in which children start on the treatments and after 3 months may have switched from active intervention (ketogenic diet) to usual care or have died. After the first cycle children enter one of these health states: seizure-free, improvement (50% or more seizure reduction), no improvement (less than 50% seizure reduction) or death (from sudden unexpected death in epilepsy or other causes). This study found that ketogenic diet was not cost effective compared to usual care, with incremental cost effectiveness ratios of £304,169 per QALY and £74,933 per QALY at a 1- and 5-year time horizons, respectively. This analysis was assessed as partially applicable (non-UK perspective, incorrect discounting applied, unclear if EQ5D was used for estimating quality of life), with potentially serious limitations (includes 2 of 4 RCTs included in the clinical review, non-UK NHS costs, assumes that if a child responds at 24 months which is the end of the diet, they will remain responsive until the end of the time horizon, 5 years).

The second and third cost-utility analyses (de Kinderen 2016 and Wijnen 2017) were within trial analyses of an RCT by Lambrechts 2017. De Kinderen 2016 presented the results of the 4 month follow up and Wijnen 2017 presented results of the 16 month follow up. The studies analysed individual level data for health outcomes (seizure frequency and severity) as well as quality of life (measured using the TAPQOL and TACQOL with parent proxy). Resource use was captured, and unit costs applied. These studies found that ketogenic diet was not cost effective compared to usual care, with an incremental cost effectiveness ratio of £1,321,094 per QALY at 4 months and ketogenic diet is dominated (more costly, less effective than usual care) at 16 months. These analyses were assessed as partially applicable (non-UK perspective and non-EQ5D quality of life used) with potentially serious

limitations (includes 1 of the 4 RCTS included in the clinical evidence non-NHS UK costs, short time horizon and extrapolation of usual care arm from 4 months to 16 months). In all these analyses, the ketogenic diet was costly, this was due in part due to the inpatient stay to a tertiary epilepsy centre for the diet initiation but also the regular and frequent appointments thereafter with an epilepsy nurse and a dietician. Furthermore, the protocols required regular ketosis level checks and appointments with other health care professionals. The benefit in terms of QALYs reported in these analyses was very small. When this was discussed with the committee, they noted that a reduction in seizures may improve quality of life and reduce the risk of SUDEP, but also noted that a seizure reduction is not as clinically important as seizure freedom. The committee did appreciate that severe drug resistant epilepsy can have a severe negative impact on a person's quality of life and that in people with drug resistant epilepsy any reduction in seizures may be beneficial. The committee also discussed in detail that seizures are not the only factor which may impact adversely on the quality of life in a person with epilepsy. For example, a person's quality of life may be negatively affected if they have reached the end of the epilepsy treatment pathway and are still drug refractory.

The de Kinderen 2016 and Wijnen 2017 analyses were based on Lambrechts 2017 which was the only RCT in the clinical review to report quality of life outcomes. No clinical difference between ketogenic diet and usual care was seen for this outcome. In discussion, the committee noted that ketogenic diet could associated with a decrease in quality of life as it may remove pleasure associated with eating and the gastrointestinal adverse events can be challenging.

The committee noted that the health economic studies included in the evidence review were based on RCTs with small patient populations (de Kinderen 2015 was based on Neal 2008 [n=145] and Shama 2013 [n=102], and de Kinderen 2016 and Wijnen 2017 was based on Lambrechts 2017 [n=57]) and all clinical studies included in the review were graded as low or very low-quality evidence.

No health economic evidence was identified in an adult population. Therefore, based on the clinical evidence and the premise that ketogenic diet is not cost effective in children, the committee agreed to make a recommendation to only consider a ketogenic diet in people with drug resistant epilepsy if all other treatment options have been unsuccessful, or for certain childhood epilepsies (such as, infantile spasms, myoclonic astatic epilepsy, Dravet syndrome, and Lenox-Gastaut syndrome).

The committee acknowledged that the analyses by de Kinderen 2016 and Wijnen 2017 (which showed usual care was dominant) included the cost of 5-day hospital admission when initiating a ketogenic diet. The committee noted this was not reflective of UK current practice and people initiating a ketogenic diet in the UK would not typically be admitted as an inpatient. In addition, the committee stressed the importance for people with drug refractory epilepsy, where all other treatment options have been unsuccessful, to have the option of a ketogenic diet available to them if deemed clinically appropriate by a tertiary epilepsy specialist.

The recommendations are unlikely to constitute a big change in current practice as ketogenic diets are not routinely offered. The committee agreed to make research recommendation given the limited clinical evidence (both short and long term) of ketogenic diet in children and adults.

1.1.10.5. Other factors the committee took into account

The committee recognised that ketogenic diet does have a specific role in people with Glut-1 deficiency, however this population was not reviewed in the evidence.

1.1.11. Recommendations supported by this evidence review

This evidence review supports recommendations 8.1.1 and the research recommendation on ketogenic diets.

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Appendices

Appendix A Review protocols

A.1 Review protocol for ketogenic diets in drug-resistant epilepsy

ID	Field	Content
1.	Review title	Ketogenic diets for drug-resistant epilepsy
2.	Review question	What is the effectiveness of ketogenic diets in drug-resistant epilepsy?
3.	Objective	The aim of the review is to determine if a ketogenic diet is effective in adults and children with drug-resistant epilepsy. The ketogenic diet is high in fat and low in carbohydrate, and it has been suggested that this diet reduces seizure frequency. This diet is used mainly as an adjunctive treatment for children who continue to have seizures despite treatment with antiepileptic drugs. Recently, there has been interest in less restrictive ketogenic diets such as the modified Atkins diet, and the use of these diets has been extended into adult practice.
4.	Searches	The following databases will be searched: • Cochrane Epilepsy Group Specialized Register • Cochrane Central Register of Controlled Trials (CENTRAL) • Embase from 1980 to March 2003 • MEDLINE • ClinicalTrials.gov • World Health Organisation (WHO) International Clinical Trials Registry Platform There were no restrictions on date Other searches: • Reference lists from screened full text studies The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant.

		The full search strategies for MEDLINE and Cochrane Register of Studies (CRS Web) database will be published in the final review.
5.	Condition or domain being studied	Drug-resistant epilepsy Epilepsy is a common treatable condition, characterised by recurrent involuntary brain activity that manifests as seizures. Although the majority of people have a good response to antiepileptic drugs and become seizure free, approximately 30% continue to have seizures despite taking multiple antiepileptic drugs.
6.	Population	Inclusion: Children, young people and adults with drug-resistant epilepsy Strata: evidence in people with learning disabilities will be presented separately from evidence in people without learning disabilities Exclusion: New-born babies (under 28 days) with acute symptomatic seizures
7.	Intervention/Exposure/Test	Ketogenic diet (4:1 ratio of total energy from fat to carbohydrate and protein combined) Any diet that is designed to produce ketones: Classical KD Medium-chain triglyceride (MCT) KD Modified Atkins diet (MAD) Low glycaemic index treatment (LGIT)
8.	Comparator/Reference standard/Confounding factors	Placebo/Usual care/Sham One diet vs another diet
9.	Types of study to be included	RCTs with a minimum study period of 1 month Non-randomised studies will not be included Systematic reviews will not be included
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. RCT study period less than 1 month
11.	Context	The review will update the NICE guideline: Epilepsies: diagnosis and management, published in 2004.

12.	Primary outcomes (critical outcomes)	• seizure freedom (100% reduction in seizure frequency at study endpoint • seizure frequency (50% or greater reduction in seizure frequency at study endpoint • quality of life (as measured by validated scales) • adverse events (all e.g., diarrhoea / constipation / vomiting / renal stones (all GI heading)) at study endpoint • attrition rate
13.	Secondary outcomes (important outcomes)	Cognitive and behavioural outcomes (as measured by validated scales)
14.	Data extraction (selection and coding)	Reference manager will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion by 2 review authors independently, resolving disagreements through discussion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. The electronic Cochrane data collection form will be used that has been adapted to fit the scope of the review.
15.	Risk of bias (quality) assessment	Two review authors will independently assess risk of bias for each randomized trial using Cochrane's recommended domain-based evaluation tool for randomized trials, in which critical assessments are made separately for different domains, including selection bias (random sequence generation, allocation concealment), performance bias (blinding of personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other sources of bias. All outcomes reported in papers for selective outcome reporting will be examined. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness,

		inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. • The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects.	
17.	Analysis of sub-groups	Strata: evidence in people with learning disabilities will be presented separately from evidence in people without learning disabilities If possible, heterogeneity in meta-analyses will investigated according to the following subgroups: • Adults' vs children • One diet type vs another diet • Comparator for example active control vs placebo • Duration (< 12 weeks, > 3 months)	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	

21.	Anticipated or actual start date	Search completed April 2019		
22.	Anticipated completion date	End of 2019		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Epilepsies@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	Cochrane Collaboration Lead author: KJ Martin-McGill R Bresnahan R G Levy P N Cooper		

26.	Funding sources/sponsor	This systematic review is being completed by the Cochrane Epilepsy Group which receives funding from Cochrane Epilepsy Group.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators		
29.	Other registration details		
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol if there is one.]	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Ketogenic diets, epilepsy	
33.	Details of existing review of same topic by same authors	Published 7 November 2018 https://www.cochrane.org/CD001903/EPILEPSY_ketogenic-diets-drug-resistant-epilepsy	
34.	Current review status	☒	Ongoing
		☐	Completed but not published

		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information		
36.	Details of final publication	www.nice.org.uk	

1 # A.2 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2004 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[10] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with "Minor limitations" then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with "Very serious limitations" then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:*

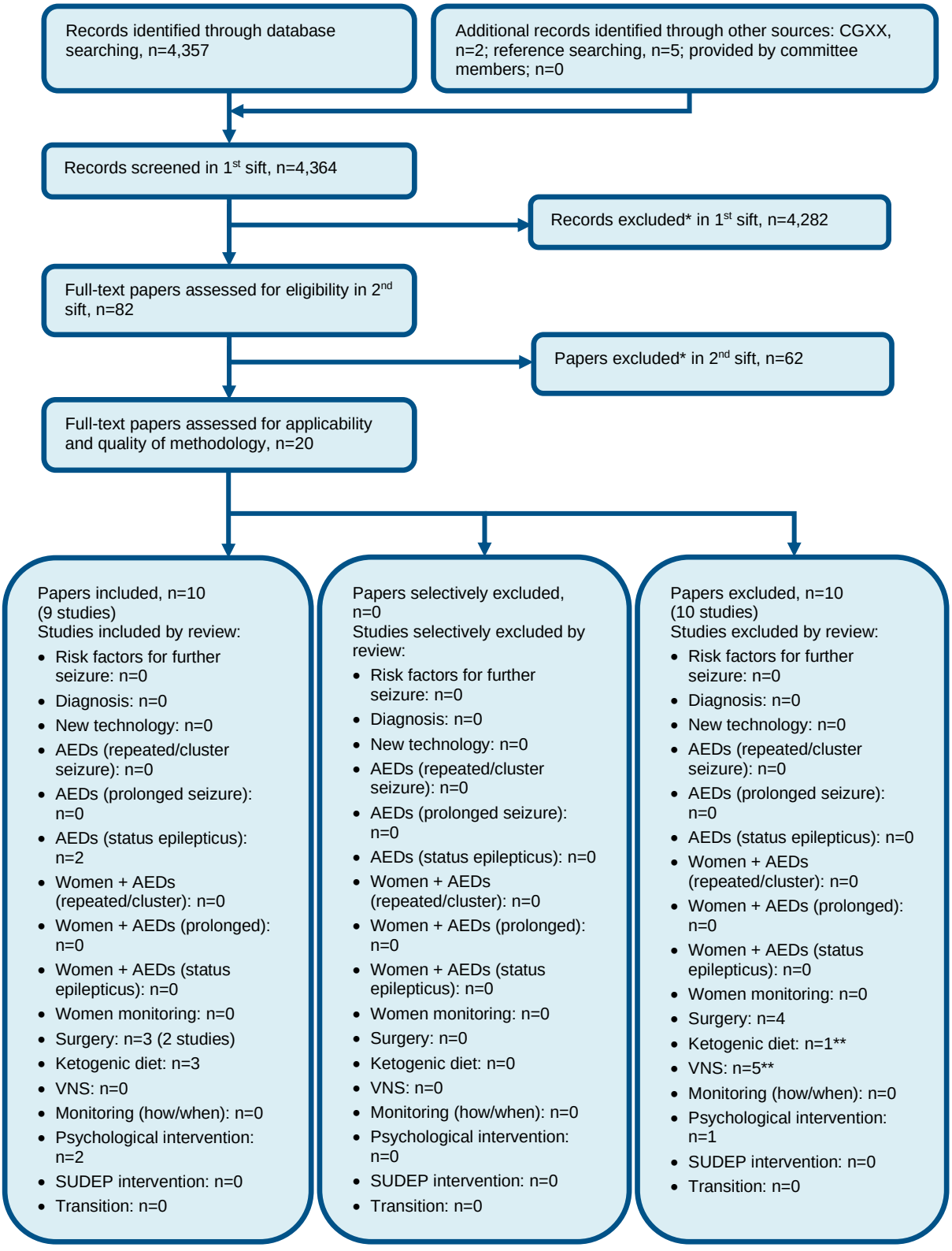
	• UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature Search Strategy

None.

Not applicable to Cochrane reviews.

Appendix C Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

**Please note that 1 article related to two questions. For this reason, the numbers listed for each review may not total the

Appendix D Economic evidence tables

Study	De Kinderen 2015 [3]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model. Children start on the treatments and after 3 months patients may have switched from active intervention (ketogenic diet) to usual care or have died. After the first cycle children enter one of these health states: seizure-free, improvement (50% or more seizure reduction), no improvement (less than 50% seizure reduction) or death (from SUDEP or other causes). 3-month cycle duration. **Perspective:** Dutch healthcare	**Population:** Children (1-18 years) with intractable epilepsy who have tried two or more drugs and are not eligible for resective surgery **Cohort settings:** Start age: NR Male: NR **Intervention 1:** Usual care **Intervention 2:** Ketogenic diet (80% medium chain triglyceride diet, 15% classic diet and 5% diet via tube feeding)	**Total costs (mean per patient):** 1 year Intervention 1: £2,880 Intervention 2: £12,226 Incremental (2−1): £9,346 (95% CI: NR; p=NR) 5 years Intervention 1: £13,091 Intervention 2: £26,946 Incremental (2−1): £13,855 (95% CI: NR; p=NR) **Currency & cost year:** 2013 Euros (presented here as 2013 UK pounds(b)) **Cost components incorporated:** Number of neurologist visits, number of seizure related hospitalisations (both linked to the health states of how seizure free	**QALYs (mean per patient):** 1 year Intervention 1: 0.662 Intervention 2: 0.693 Incremental (2−1): 0.031 (95% CI: NR; p=NR) 5 years Intervention 1: 3.153 Intervention 2: 3.338 Incremental (2−1): 0.185 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** 1 year £302,169 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost effective (€20K = circa £17.5K threshold): 0% 5 years £74,933 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost effective (€20K = circa £17.5K threshold): 0% **Analysis of uncertainty:** Deterministic sensitivity analyses undertaken to explore different types of ketogenic diet. The percentage of classic diet users was increased from 15% to 100% and simultaneously lowered the ketogenic diet initiation costs by assuming no hospitalisation required. This resulted in a higher probability ketogenic diet was cost effective at 5 years (26% at threshold of €20K = circa £17.5K).

Time horizon: 1 year and 5 years **Treatment effect duration:**(a) 24 months extrapolated to 5 years **Discounting:** Costs: 4%; Outcomes: 1.5%		someone is). Initiation costs of ketogenic diet, including 5-day admission to epilepsy centre, visits of neurologist, paediatrician, dietician and epilepsy nurse and laboratory costs. Costs related to the ketogenic diet were vitamin and diet supplements and keto sticks.		
Data sources				
Health outcomes: Baseline (usual care) and effectiveness data taken from two RCTs identified via literature search (Neal 2008[11] and Sharma 2013[16]). Pooled proportion analyses were used to calculate weighted average probabilities based on a random effects model. Annual age-specific all-cause mortality rates were based on Dutch life tables (2013) and transformed into 3-month mortality rates. SUDEP rates (Shorvon and Tomson 2011) added to all-cause mortality rates. **Quality-of-life weights:** Identified following a literature search and were based on utility values used in a health economic analysis by Messori 1998. Unclear if these utility values were EQ-5D but they appear to be elicited using a time trade-off. **Cost sources:** Resource use based on expert opinion and unit costs taken from Dutch guidelines for costing research. Note, cost of antiepileptic drugs and the cost of side-effects due to antiepileptic drugs were not taken into account; they were assumed to be equal in both arms.				
Comments				
Source of funding: The Netherlands Organization for Health Research and Development. **Limitations:** Dutch healthcare perspective. Incorrect discounting applied. Unclear if EQ5D or other utility measure used for estimating quality of life. Includes 2 of 4 included RCTs and so may not reflect full body of clinical evidence. Dutch costs. Children on ketogenic diet would follow the dietary treatment for a maximum of 24 months, after this period they were treated with usual care. Model assumed that a responder remains a responder and a non-responder remains a non-responder for the rest of the study period (i.e., patients do not switch between health states after 24months). Other complications, such as gastrointestinal complaints and hoarseness, were not incorporated in the model; there are many, with generally a limited or short-term impact on quality of life or costs. **Other:** A third comparator (vagus nerve stimulation) was included in this study but not reported here as it was not relevant to this review. Side-effects of antiepileptic drugs not included as assumed to be the same in both treatment arms.				
Overall applicability: Partially applicable(c)		**Overall quality:** Potentially serious limitations(d)		

Abbreviations: CCA= cost–consequences analysis; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; SUDEP= sudden unexpected death in epilepsy

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2013 purchasing power parities[12]

(c) Directly applicable / Partially applicable / Not applicable
(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**De Kinderen 2016[2] and Wijnen 2017[18]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Within trial analysis (associated RCT Lambrechts 2017[8]) **Approach to analysis:** Analysis of individual level data for health outcomes (seizure frequency and severity, side effects of anti-epileptic drugs, and quality of life) and resource use. Unit costs applied. **Perspective:** Dutch healthcare **Follow-up:** 4[2] and 16[18] months **Treatment effect duration:**[(a)] For 16-month analysis, usual care is extrapolated from 4-month data. **Discounting (for 16-month analysis only):**	**Population:** Children and adolescents (age 1 to 18 years) with intractable epilepsy not eligible for epilepsy surgery **Cohort settings:** Start age: Intervention 1: 8.1 Intervention 2: 7.8 Male: Intervention 1: 40.9% Intervention 2: 69.2% Number of participants: Intervention 1: 22 Intervention 2: 26 **Intervention 1:** Usual care (weekly telephone meeting with epilepsy nurse). **Intervention 2:** Ketogenic diet (admitted to tertiary epilepsy centre for a 5-day introduction to the	**Total costs (mean per patient):** <u>4 months</u> Intervention 1: £7,981 Intervention 2: £10,574 Incremental (2−1): £3,963 (95% CI: £414, £12,456; p=NR) <u>16 months</u> Intervention 1: £20,842 Intervention 2: £29,773 Incremental (2−1): £8,930 (95% CI: NR; p=NR) **Currency & cost year:** 2013 Euros (presented here as 2013 UK pounds[(b)]) **Cost components incorporated:** Healthcare costs (including but not limited to): visits (for example GP, nurse, specialist), hospitalisations, EEG and MRIs, other (for example social services) and	**QALYs (mean per patient):** <u>4 months (using TACQOL/TAPCOL)</u> Intervention 1: 0.250 Intervention 2: 0.253 Incremental (2−1): 0.003 (95% CI: NR; p=NR) <u>16 months (using TACQOL/TAPCOL)</u> Intervention 1: 0.998 Intervention 2: 0.996 Incremental (2−1): 0.002 fewer QALYs (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** 4 months £1,321,094 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost effective (€50K = circa £43.5K threshold): 3% **16 months** Usual care dominates ketogenic diet (more costly and less effective). **Analysis of uncertainty:** Bootstrapping undertaken, presented both from societal (4 months and 16 months) and healthcare perspective (4 months only). Healthcare perspective at 4 months presented above. Responder analysis presented (cost per responder) = £12,456 and £181,171 per responder for ketogenic diet compared to usual care at 4 and 16 months respectively. In addition, a hypothetical sensitivity analysis undertaken where intervention costs decreased and simultaneously increased classical diet from 32% to

Costs: 4%; Outcomes: 1.5%	diet. Dietician and parents decided what type of diet the child would receive. Ketogenic diets included the MCT diet, the classical ketogenic diet or a mixture of the two; 69.2%, 26.9% and 3.9% respectively. Separate weekly telephone meetings with epilepsy nurse and dietician.) For both visits at 6 weeks and 4 months with neurologist, paediatrician and epilepsy nurse (and dietician for in ketogenic diet arm only). Continue antiepileptic drugs. <u>From months 4 to 16</u>: Ketogenic diet group: dietician and epilepsy nurse continued patents on monthly basis via email. 3 monthly visit with neurologist, paediatrician, dietician and epilepsy nurse. Usual care group: extrapolated data from 4 months to 16 months.	medication. Intervention costs (including diet and ketosis check costs). Societal costs reported but not presented here.		100%. This resulted in an increased probability of ketogenic diet being cost effective (from 5% to 32% at a threshold of £43.5K). These results are from a societal perspective.
Data sources				
Health outcomes: Within trial analysis based on RCT (Lambrechts 2017[8]). Intention to treat analysis, no baseline adjustment deemed necessary. Cost per responder results also presented in the economic analyses, ketogenic diet responders n= 13/26 and usual care n=4/22. 1 or 5 trials comparing ketogenic diet to usual care in children. In the second analysis (Wijnen 2017[18]), a longer follow up is presented based on 16 months follow up data for the				

ketogenic diet comparator. For those receiving usual care, no follow up data was available and so this was an extrapolation from 4 months. **Quality-of-life weights:** TAPQOL and TACQOL age-dependent used derive QoL scores for children and parents (parent pro. These are not preference-based utilities. These were then converted to QALYs using the under the curve method. EQ-5D-Youth was included as an outcome in study was only possible in a minority study participants. **Cost sources:** Resource use cost based on trial costs. Differing protocols may result in different resource use costs. Cost diary used in trial for other health care costs. It was noted that, in some centres offering a ketogenic diet only the classical ketogenic diet may be available which is also cheaper. In addition, at other centres patients initiating ketogenic diet may not incur such high costs due to patients not being admitted to hospital for five days upon initiation of ketogenic diet. Unit costs based on standardised prices such as from the Dutch guidelines for cost research.
Comments
Source of funding: The Netherlands Organization for Health Research and Development. **Limitations:** Dutch healthcare perspective. Incorrect discounting applied. Does not use EQ5D to estimate quality of life, but rather a non-preference-based measure of quality of life: TAPQOL and TACQOL. Includes parent and child QoL in total QALYs. Includes 1 of 4 included RCTs and so may not reflect full body of clinical evidence. Dutch 2013 costs. The primary outcome measure of the trial was seizure reduction therefore, sample size possibly too small to detect QoL changes. Short time horizon for 4-month analysis. Extrapolation of usual care arm from 4 months to 16 months. It was noted that, in some centres offering a ketogenic diet only the classical ketogenic diet may be available which is also cheaper. In addition, at other centres patients initiating ketogenic diet may not incur such high costs due to patients not being admitted to hospital for five days upon initiation of ketogenic diet. **Other:**
Overall applicability: Partially applicable(c) **Overall quality: Potentially serious limitations**(d)

Abbreviations: CCA= cost–consequences analysis; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; MCT *= medium-chain triglyceride; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; TAPQOL= TNO-AZL Preschool Children's Quality of Life) for children aged between 1 and 5 years (parent proxy); TACQOL = TNO-AZL Children's Quality of Life for children aged between 6 and 16 years (parent proxy).*

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2013purchasing power parities[12]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix E Health economic model

No health economic undertaken.

Appendix F Excluded studies

F.1 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 3: Studies excluded from the health economic review

Reference	Reason for exclusion
Whiting 2017 [17]	Excluded due to a combination of applicability and methodological limitations. Canadian resource use and unit costs in part from pre 2004 and therefore may not reflect the current NHS context. This cost comparison analysis (resource utilisation only) is based on a before and after study which was not included in clinical review. No analyses of uncertainty.

Appendix G Research recommendations

What is the short-term and long-term clinical and cost-effectiveness of ketogenic diets in adults and children with drug-resistant epilepsy and what factors affect the long-term maintenance/tolerability of ketogenic diets?

Why this is important

Around a third of people with epilepsy will not respond to currently available anti-seizure medications. A proportion of this group will be suitable for resective epilepsy surgery. There are, however, people with drug resistant epilepsy who are not candidates for epilepsy surgery or in whom surgery is unsuccessful. In these individuals, alternative methods to control seizures should be considered, including neurostimulation or dietary treatments. While, for example, the ketogenic diet is indicated in certain conditions (for example GLUT 1 deficiency), the broader applicability of dietary treatment in people with drug-resistant epilepsy, especially in adults, is uncertain.

Rationale for research recommendation

Importance to 'patients' or the population	Treatment options for people with drug-resistant epilepsy, especially those not suitable for epilepsy surgery, can be limited. While novel anti-seizure medications continue to be developed, it is also important to consider non-pharmacological approaches to seizure management. While dietary treatment can offer benefits to certain individuals, it is important to better determine whether dietary treatment can be applied more widely to people with drug-resistant epilepsy and/or whether certain groups may derive specific benefits from such diets.
Relevance to NICE guidance	Ketogenic diet therapy has been considered in this guideline and there is a lack of data on long-term clinical and safety outcomes. Also, the economic data that were reviewed do not reflect practice in the United Kingdom where, for example, ketogenic diet can be initiated as an outpatient, making costs significantly lower.
Relevance to the NHS	A UK based study of ketogenic dietary treatment seems necessary to determine the long-term effectiveness of the treatment, the potential adverse effects and to calculate the cost of providing the treatment within the NHS. Identifying who may be most suitable for the diet would enable the diet to be offered earlier to target groups and as such could be cost saving (for example by avoiding unnecessary trials of anti-seizure medications, reducing hospital admissions)
National priorities	Moderate
Current evidence base	Minimal data for ketogenic diet is currently available, and data are particularly scarce in adults.
Equality considerations	Ketogenic diet tends to be considered in people with drug-resistant epilepsy who are not thought suitable for resective epilepsy surgery. Many of the people who are trialled on ketogenic diet

	have learning disabilities or epileptic encephalopathy. This research will therefore apply more specifically to people with learning disabilities and enable this population to participate in long-term prospective studies.

Modified PICO table

Population	People with drug resistant epilepsy who are considered suitable for ketogenic diet.
Intervention	Ketogenic diet (and variations of this diet including, but not limited to, modified Atkins diet, low glycaemic index diet), plus best medical care.
Comparator	Best medical care.
Outcome	Seizure frequency Seizure freedom Mortality Effect on mood Effect on cognition Quality of life (person with epilepsy and family/carers) Adverse diet related outcomes and discontinuation of diet Adherence to diet
Study design	Registry/ case control
Timeframe	Long term
Additional information	None