NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** **and** **final stakeholder list** are available on the NICE website.

1. **Company submission** from **GW Pharma**
   a. Company submission summary
   b. Revised economic assessment

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Epilepsy Action
   b. Association of British Neurologists
   c. NHS England

4. **Expert personal perspectives** from:
   a. Mrs Galia Wilson – patient expert, nominated by Dravet Syndrome UK
   b. Malcolm Qualie – commissioning expert, nominated by NHS England
   Malcolm Qualie has said that he wishes to support the NHS England statement

5. **Evidence Review Group report** prepared by **Kleijnen Systematic Reviews**
   The Evidence Review Group report was updated following the factual accuracy check

6. **Evidence Review Group – factual accuracy check**

7. **Technical engagement response** from **GW Pharma**
   a. Company engagement response
   b. Addendum
   c. Clinical Outcomes – On-Clobazam Population
   d. Company's Updated Base Case in the On-Clobazam Subpopulation

8. **Technical engagement response from consultees and commentators:**
   a. Association of British Neurologists
   b. NHS England

9. **Evidence Review Group critique of company response to technical engagement** prepared by **Kleijnen Systematic Reviews**

a. Evidence Review Group critique
b. ERG critique of company's validity checks

10. Final Technical Report

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

Document B

Company evidence submission

April 2019

File name	Version	Contains confidential information	Date
ID1211 CBD in DS evidence submission 12Apr2019	**1.0**	**Yes**	**12 Apr 2019**

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Abbreviations

AE	Adverse event
AED	Anti-epileptic drug
AWMSG	All Wales Medicines Strategy Group
BDI-II	Beck Depression Inventory-II
BI	Budget impact
BIM	Budget impact model
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CBD	Cannabidiol
CCM	Current clinical management
CG	Clinical Guideline
CGIC	Caregiver Global Impression of Change
CGICSD	Caregiver Global Impression of Change in Seizure Duration
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIC	Commercial in confidence
CSR	Clinical study report
CUA	Cost-utility analysis
d	Day(s)
DARE	Database of Abstracts of Reviews of Effects
DS	Dravet syndrome
DSA	Deterministic sensitivity analysis
ED, ER	Emergency department
EED	NHS Economic Evaluation Database
EEG	Electroencephalogram
EMA	European Medicines Agency
EMD	Estimated median difference
EQ-5D	European Quality of Life-5 Dimensions
EQ-VAS	EQ-5D visual analogue scale
FDA	U.S. Food and Drug Administration
GCSE	General Certificate of Secondary Education
GP	General Practitioner

HRQoL	Health-related quality of life
HS	Health state
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ILEA	International League Against Epilepsy
IMP	Investigational medicinal product
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IVRS	Interactive voice-response system
kg	Kilogram
KOL	Key opinion leader
LGS	Lennox-Gastaut syndrome
ml	Millilitre
MoA	Mechanism of Action
N, n	Number
NA or N/A	Not applicable
NAC	Not adequately controlled
NHS	National Health Service
NR	Not reported
NSF	Not seizure-free
OLE	Open-label extension
ONS	Office for National Statistics
OR	Odds ratio
PLD	Patient-level data
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QOL	Quality of life
QOLCE	Quality Of Life in Childhood Epilepsy

RCT	Randomised controlled trial
RR	Risk ratio
ScHARRHUD	The University of Sheffield Health Utilities Database
SD	Standard deviation
SE	Standard error
SF	Seizure-free
SF-36	36-Item Short Form Survey
SG	Standard gamble
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMEI	Severe myoclonic epilepsy in infancy
SmPC	Summary of product characteristics
SoC	Standard of care
SUDEP	Sudden unexpected death in epilepsy
TC	Tonic-clonic
TSC	Tuberous sclerosis complex
TEAE	Treatment emergent adverse event
TP	Transition probability
TTO	Time trade-off
Tx	Treatment
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
Wks	Weeks
WTP	Willingness to pay
Y, yr	Year(s)

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with Dravet syndrome whose seizures are inadequately controlled by established clinical management.	People with Dravet syndrome (DS) whose seizures are inadequately controlled by current or prior established clinical management. People with DS where current clinical management is unsuitable or not tolerated.	This is in line with recommendations in NICE Clinical guideline 137 (CG137)(1)
Intervention	Cannabidiol in addition to current clinical management	Cannabidiol in addition to current clinical management	Not applicable
Comparator(s)	Established clinical management without cannabidiol, which may include combinations of: • sodium valproate • topiramate • clobazam • stiripentol • levetiracetam • ketogenic diet • vagus nerve stimulation	Established clinical management without cannabidiol, which may include combinations of: • sodium valproate • topiramate • clobazam • stiripentol • levetiracetam • ketogenic diet • vagus nerve stimulation	Not applicable

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • seizure frequency (overall and by seizure type) • response rate (overall and by seizure type) • seizure severity • incidence of status epilepticus • mortality • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • seizure frequency (convulsive seizures and overall) • proportion of people convulsive seizure-free • number of people with episodes of status epilepticus • mortality • adverse effects of treatment • health-related quality of life • CGIC (Caregiver Global Impression of Change) • CGICSD (Caregiver Global Impression of Change in Seizure Duration)	The primary endpoint of the pivotal clinical trials was change in convulsive seizure frequency. A seizure severity proxy (duration of seizures) was measured through the caregiver surveys as an impression of seizure duration change rather than as a defined metric. The clinical trial patients were a highly refractory group of patients with status epilepticus as part of their disease. In the trials, the number of people with episodes of status epilepticus was reported, not the incidence.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope	Not applicable
Subgroups to be considered	Not applicable	Not applicable	Not applicable
Special considerations including issues related to equity or equality	Not applicable	Not applicable	Not applicable

B.1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Cannabidiol / Epidyolex®
Mechanism of action	The precise mechanisms by which cannabidiol exerts its anticonvulsant effects in humans are unknown. Cannabidiol reduces neuronal hyper-excitability and inflammation through modulation of intracellular calcium via G protein-coupled receptor 55 (GPR55) and transient receptor potential vanilloid 1 (TRPV-1) channels, as well as modulation of adenosine-mediated signalling through inhibition of adenosine cellular uptake via the equilibrative nucleoside transporter 1 (ENT-1).
Marketing authorisation/CE mark status	Awaiting marketing authorisation in the UK for Dravet syndrome (and Lennox-Gastaut syndrome). Submission of the marketing authorisation application to EMA was December 2017. CHMP positive opinion is expected on 31 January 2019. European Commission approval is anticipated in April 2019.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Epidyolex is indicated for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.
Method of administration and dosage	Oral administration. The recommended starting dose of Epidyolex is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day). Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 20 mg/kg/day, should be made considering individual benefit and risk.
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment	The price of cannabidiol is [redacted]
Patient access scheme (if applicable)	Not applicable

Summary

Epidyolex® (cannabidiol or CBD) is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.

DS and LGS are rare, devastating and life-threatening forms of epilepsy that present early in childhood. They are severe complex epilepsy syndromes that are associated with refractory seizures and poor outcomes. In addition to the high seizure burden, they result in progressive dysfunction of the brain with associated cognitive and behavioural difficulties that prevent children from achieving independence in adult life. This has a profound impact on the quality of life experienced not only by the patients but also by their families and carers. Mortality rates for patients with DS are much higher than in the general population.

This appraisal relates to cannabidiol in DS. A separate appraisal (ID1308) in LGS is also being undertaken by NICE.

Despite the availability of a broad range of anti-epileptic drugs (AEDs), complete seizure control in DS is typically unachievable in most patients: children with DS continue to have convulsive seizures and are at high risk of hospitalisation and death.

The value of CBD is in the treatment of patients with DS (and LGS) with uncontrolled seizures despite treatment with at least two AEDs.

CBD offers DS (and LGS) patients the opportunity of a long-term treatment with durable efficacy that reduces seizure severity (seizure frequency and duration), and, for some patients who had previously been inadequately controlled, the potential for seizure-freedom.

Cannabidiol in DS

Orphan designation (EU/3/14/1339) was granted by the European Commission on 15 October 2014 for cannabidiol for the treatment of Dravet syndrome.

DS is a very rare (orphan), lifelong, treatment-resistant form of epilepsy presenting in the first year of life in formerly developmentally normal infants. Children with DS experience severe symptoms including prolonged convulsive seizures with a high risk of SUDEP (Sudden Unexpected Death in Epilepsy).

With the current range of treatment options, complete seizure control is typically not achievable: patients with DS continue to have convulsive seizures and are at high risk of hospitalisation and death. High mortality rates (7% to 18%) are reported for children with DS. There is a clear and urgent need to treat these patients.

The majority of children with DS develop consequences/comorbidities, for example, autistic behaviour and developmental delays, and require constant care throughout their life. This poses a heavy burden on caregivers: 77% report having less than 1 hour per day for themselves.

Epidyolex is a highly purified, plant-derived pharmaceutical formulation of cannabidiol, administered as an oral solution. It is the first cannabinoid in class, with a novel, multi-modal mechanism of action (MoA) that is different to the MoA of other AEDs.

CBD has been rigorously evaluated in the largest global clinical trial programme in patients with orphan DS and orphan LGS, which included four blinded, randomised, controlled Phase 3 studies, an open-label extension study, and an early access programme.

As part of the largest Phase 3 clinical study programme in DS, CBD demonstrated a clinically and statistically significant median reduction in convulsive seizure frequency, of 49% (10 mg/kg/day dose) versus 27% with current clinical management (CCM) (p= 0.0095). A proportion of patients achieved further seizure reductions and [redacted] achieved complete convulsive seizure-freedom with a dose of 20 mg/kg/day, compared with [redacted] of patients on CCM, thereby offering the potential to transform the lives of those patients and their families.

A subset of 18 patients in the GWPCARE1 study had never experienced seizure reduction from any previous AEDs. Of these, 9 patients were on CBD (20 mg/kg/day)

and 9 were on current clinical management (CCM) + placebo. The patients on CBD saw a 70% median reduction in convulsive seizures while those on CCM saw a median increase in convulsive seizures of 11%.

In the Phase 3 studies, caregivers reported an overall improvement in the condition of patients receiving CBD more often than in CCM [redacted] versus [redacted] respectively, as measured on the Caregiver Global Impression of Change (CGIC) scale), an improvement that has been consistently maintained in an open-label extension (OLE) study to 48 weeks in >80% of patients.

Cannabidiol has a consistent, well-defined and manageable safety and tolerability profile. Most adverse events (AEs) were mild to moderate; the majority occurred during initiation of treatment (2-4 weeks), were transient and resolved within 4 weeks of onset. Real world observational data have demonstrated reductions of concomitant AEDs, with the potential to reduce the overall drug AE burden in these patients.

CBD is cost-effective in patients suffering from DS who are without further treatment options, reducing seizures and with the potential to reduce seizure-related injuries and mortality. CBD will have a predictable and limited budget impact due to the orphan nature of DS as well as cost offsets associated with disease management.

Following the largest Phase 3 study programme ever conducted in DS, Epidyolex offers patients with DS the opportunity of a long-term treatment with sustained efficacy, which reduces seizure severity (seizure frequency and duration) and, for some patients and their families, the potential for seizure-freedom.

B.1.3 Health condition and position of the technology in the treatment pathway

DS is a severely debilitating, lifelong and treatment-resistant form of epilepsy presenting in the first year of life in formerly developmentally normal infants. It is very rare, with a prevalence of 0.4 in 10,000 people (2).

Children with DS experience severe symptoms including prolonged convulsive seizures, resulting in emergency hospital visits. DS is also associated with many

consequences and co-morbidities that can result in lifelong impairment, so that patients are completely dependent upon caregivers for daily activities.

Around 70-85% of individuals with clinical features of DS test positive for mutations of the SCN1A gene that result in the dysfunction of voltage-gated sodium channels in neurones (3-5).

High seizure burden, hospitalisation and risk of injury

Patients with DS suffer from some of the most severe seizure subtypes that are associated with a high risk for status epilepticus, a state of continuous seizure requiring emergency medical care, and Sudden Unexpected Death in Epilepsy (SUDEP) (6).

DS typically starts in the first year of life with prolonged, repeated clonic or unilateral seizures in developmentally normal children, associated in many instances (estimates range from 39-72%) with a fever (7).

Over time, seizures become more frequent and of multiple types. Patients with DS present with different seizure patterns, but most include combinations of severe convulsive seizures, including generalised tonic-clonic and clonic seizures, as well as myoclonic, atypical absence and focal seizures (3, 6).

In adolescence and adulthood, patients with DS may suffer from brief nocturnal generalised convulsive seizures that are specifically associated with the greatest risk for SUDEP (3, 8, 9).

The prolonged convulsive seizures seen in DS often result in emergency hospital visits. In a survey of DS caregivers, 50% of patients required at least one emergency admission, and 46% required at least one ambulance call in the previous year (10).

Patients with DS are also at risk from injuries due to falls associated with convulsive seizures (11).

Cognitive impairment, functional impairment and neuromotor impairment

In addition to a high seizure burden, there are many consequences and co-morbidities associated with DS.

Some of these can cause lifelong cognitive impairment, functional impairment and neuromotor impairment, resulting in patients with DS relying on caregiver assistance for most daily activities and requiring adaptive medical equipment.

Following seizure onset, patients with DS suffer from stagnation in cognitive and motor development, affecting verbal language, general IQ, gait, balance and fine motor coordination (3, 9).

Children with DS usually develop cognitive and psychomotor retardation, with attention-deficit hyperactivity disorder, autistic behaviour, treatment resistant sleep disorder, and absent language skills common from the age of 2 years onwards (7, 12).

A higher seizure frequency is linked to a greater degree of cognitive and behavioural impairment, further underlining the importance of reducing seizures in DS (3).

DS is associated with many other comorbidities that can result in lifelong impairment and dependence upon family and caregivers. These include:

- Orthopaedic issues such as scoliosis, for which patients may require surgery.
- Arrhythmias and cardiac structural abnormalities. In the International Dravet Syndrome Epilepsy Action League (IDEAL) study, 9% of patients had heart rhythm irregularities, 14% had tachycardia, and 5% had bradycardia (13), compared with a prevalence of 1.2-2.3% of arrhythmias in school-age children (14). In addition, 4.6% of patients with DS showed structural abnormalities, including bicuspid aortic valve, tricuspid atresia, atrial septal defect and pulmonary stenosis, compared with 0.8 to 1.5% in the general paediatric population (15).
- Motor abnormalities, including hypotonia and crouch gait (3).

- Fine motor deficits, such as incoordination and impaired dexterity (3).

Mortality

DS is life-threatening. The risk of death is significantly elevated in patients with drug-resistant forms of epilepsy. DS-related mortality is estimated to be around 20%, with mortality rates ranging from 7 to 18% in patients under 18 years of age (13, 16).

Premature mortality is a major issue in DS (17), with most deaths occurring before 10 years of age.

High seizure frequency is a significant independent predictor of early death (18), with persistent seizures strongly related to excess mortality (19). Standardised mortality ratios are especially high among those with convulsive seizures (20).

Patients with DS are at high risk of SUDEP and status epilepticus, which cause around a half and a third of deaths in DS respectively (17).

Clinical opinion recommends that the most effective prevention strategy for death related to epilepsy, and especially SUDEP, is to reduce the frequency of seizures (21, 22). Early treatment may improve the outcomes for patients, with better seizure control potentially leading to reduced mortality.

The premature mortality in patients with DS underlines clearly the urgency to treat these patients.

High impact on the patient and the family/caregivers

DS has a severe impact not only on the patient but also on their families and caregivers. The burden of care and the effects of DS on the child necessitate adjustments in virtually all aspects of the lives of caregivers and family members.

Lifelong cognitive impairment, functional impairment and neuromotor impairment result in patients with DS requiring constant care throughout life, imposing a heavy burden on families and caregivers.

An extensive European-focused survey of caregivers of patients with DS, involving 584 respondents (92% from Europe), confirmed that quality of life for patients with DS is much lower than in the general population (10).

In a survey of DS caregivers, 77% reported they had less than 1 hour per day for themselves to relax or do any personal activity (23).

In addition to the psychological burden, there is also a significant financial burden on families affected by DS, in part because of the need for additional care, lifestyle and home modifications (24). In a European-focused DS caregiver survey, 80% of respondents reported that caring for a child with DS had influenced their career choices; more than a third of caregivers (34%) were unemployed, of whom 81% had given up their job due to their role as a caregiver (10, 25).

Clinical pathway of care

The following treatment guidance and algorithms have been identified for the diagnosis and treatment of DS:

- NICE guidance - Epilepsies: diagnosis and management Clinical guideline [CG137] Published date: January 2012 Last updated: April 2018 (1). A full update is underway (expected 2021).

- Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations from a North American Consensus Panel, published 2017 (3).

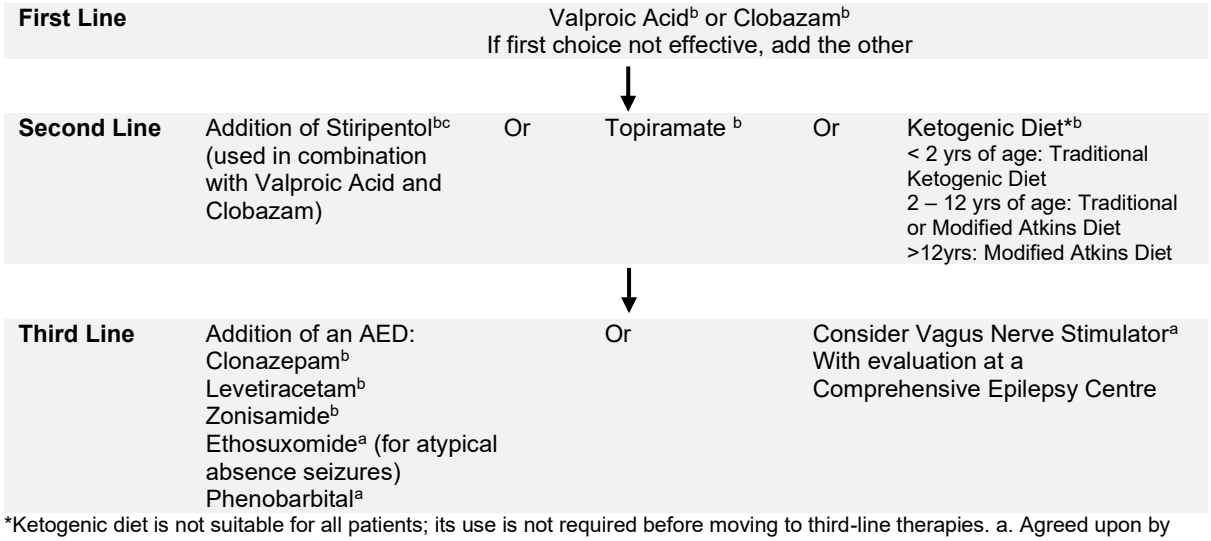
NICE Clinical guideline 137 recommends sodium valproate or topiramate as a first-line treatment option for DS and, if seizures are inadequately controlled, clobazam or stiripentol as an adjunctive treatment (1).

A number of AEDs (as shown in Table *3* below) should not be given to patients with DS as they may worsen seizures.

Table 3: NICE CG137 - treatment options for DS

First-line AEDs	Adjunctive AEDs	Do not offer AEDs (may worsen seizures)
Discuss with, or refer to, a paediatric epilepsy specialist Sodium valproate Topiramate	Clobazam Stiripentol	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin

A North American consensus panel, comprised of 13 epileptologists and 5 parents of children with DS, formulated recommendations for the diagnosis, treatment and management of children and adults with DS (3). The panel's proposed treatment algorithm is shown in Figure 1 below.



*Ketogenic diet is not suitable for all patients; its use is not required before moving to third-line therapies. a. Agreed upon by moderate consensus. b. Agreed upon by strong consensus. c. Stiripentol not approved for use in all jurisdictions.

Figure 1: Treatment algorithm for DS

Remaining unmet need

Despite the availability of a broad range of AEDs, non-pharmacological interventions and invasive surgery such as corpus callosotomy, seizure control in DS remains inadequate, with the majority of patients unresponsive to treatment or unable to tolerate current AEDs.

A study of real-world treatment patterns of patients with DS demonstrated that no single combination of current AEDs offered sustained control, with treatment largely empirical, and physicians having to balance seizure control effectiveness, adverse

event burden, and the side-effect profile of combinations as patients progressed (26).

There remains a significant unmet need for treatment that reduces seizure frequency and severity, and improves the overall condition of patients with DS:

- Current medications for DS are only partly effective and essentially all patients develop multiple comorbidities over time, which may be exacerbated by recurrent seizures and side-effects of polypharmacy (3).

- A number of AEDs (including carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin) should not be given to patients with DS as they may worsen seizures.

- Clinicians recommend that the highest priority should focus on avoiding prolonged convulsive seizures given their morbidity and impact on developmental outcome (3).

- Uncontrolled patients with DS who enter clinical trials typically experience numerous convulsive seizures each month, which causes significantly impaired quality of life, high mortality risk and distress in the patients and their caregivers and families, as well as adding substantial costs to healthcare providers.

Placement of cannabidiol within the care pathway

There is a substantial unmet need in DS for an intervention that can effectively reduce seizures in the long term, without markedly increasing adverse events.

Refractory epilepsy has been defined by the International League Against Epilepsy (ILAE) as failure of adequate trial of two tolerated and appropriately chosen and used AED regimens (as monotherapies or in combination) to achieve sustained freedom from seizures.

The value of CBD is in the treatment of patients with DS with uncontrolled seizures despite treatment with at least two AEDs.

For patients with DS considered for treatment with CBD, it will be an add-on treatment for refractory seizures in people aged 2 years of age and older once two other appropriate AEDs, trialled to a maximally tolerated dose, have failed to achieve seizure-freedom (see Figure 2).

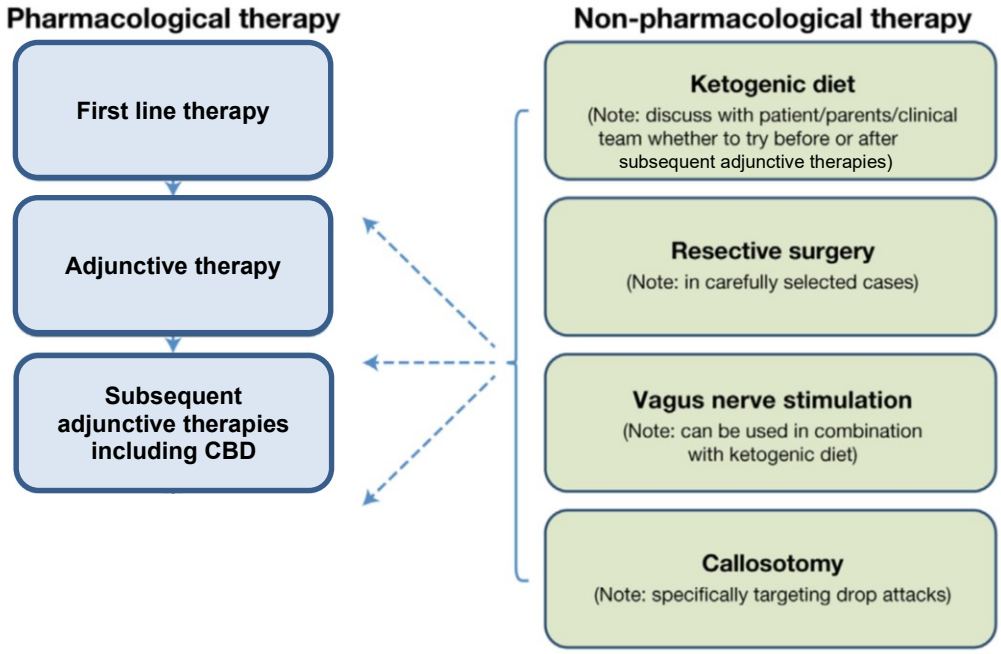


Figure 2: Clinical pathway for DS including CBD

CBD has been rigorously evaluated in the largest global clinical trial programme in patients with orphan DS, which included two global blinded, randomised, controlled Phase 3 studies, GWPCARE1 (27) and GWPCARE2 (28), and an ongoing open-label extension (OLE) study (GWPCARE5) (29).

CBD demonstrated a clinically and statistically significant median reduction in convulsive seizure frequency of 49% in the global GWPCARE2 study (10 mg/kg/day dose arm) versus 27% with current clinical management (CCM) (p=0.0095). The OLE study of CBD demonstrates the long-term consistency and reproducibility of its efficacy: reductions in convulsive and total seizure frequency were sustained over a 48-week period.

CBD increased the chance of achieving convulsive seizure-freedom and/or additional seizure-free days in the trials, with a proportion of patients potentially

benefiting from escalation to a higher dose of up to 20 mg/kg/day in order to achieve convulsive seizure-freedom at this dose: [redacted] of patients in GWPCARE1 and GWPCARE2 achieved complete convulsive seizure-freedom with a dose of 20 mg/kg/day, compared with [redacted] of patients on CCM. Patients receiving CBD also experienced a greater number of mean additional convulsive seizure-free days in a 28-day treatment period than those on CCM.

For patients with DS and their families, a period of seizure-free time (whether several hours in a day, or seizure-free days) has the potential to improve quality of life and may mean that patients and families can undertake everyday activities previously unimaginable, such as playing outside or going on holiday. A seizure-free period also gives patients the opportunity to learn and develop skills.

A subset of 18 patients in the GWPCARE1 study had **never experienced seizure reduction from any previous AEDs**. Of these, 9 patients were on CBD (20 mg/kg/day) and 9 were on current clinical management (CCM) + placebo. The patients on CBD saw a 70% median reduction in convulsive seizures while those on CCM saw a median increase in convulsive seizures of 11% (85).

In both Phase 3 DS studies, a greater improvement in the overall condition of patients with DS receiving CBD compared to those receiving CCM alone was reported by caregivers. This improvement has been consistently maintained in the OLE study to 48 weeks in >80% of patients.

The safety and tolerability profile of cannabidiol is consistent, well-defined and manageable. Most AEs were mild to moderate, transient and resolved within 4 weeks of onset.

Cannabidiol offers patients with DS the opportunity of a long-term treatment with durable efficacy that reduces seizure severity (seizure frequency and duration) and, for some patients who had previously been inadequately controlled, the potential for seizure-freedom.

The introduction of cannabidiol in the DS treatment pathway aligns with current clinical management. No service redesign will be required.

B.1.4 Equality considerations

The use of cannabidiol is unlikely to raise any equality issues.

Patient age is defined in the indication: Epidyolex is indicated for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

The clinical evidence included in this submission was identified from a rigorous systematic review of multiple data sources to identify all relevant publications for the efficacy, safety and development of economic models for the use of cannabidiol in Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS). This submission reports the findings that were relevant to DS. Full details of the methodology followed is reported in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Cannabidiol has been rigorously evaluated in the largest global clinical trial programme in patients with DS. The cannabidiol clinical trial programme in DS includes two RCTs, GWPCARE 1 (27) and GWPCARE2 (28).

Both DS Phase 3 studies were double-blind, randomised, placebo-controlled, multicentre trials carried out in children and adolescents between 2 and 18 years with DS, whose seizures were incompletely controlled with previous AEDs. The intervention was cannabidiol in addition to current clinical management (CCM) and the comparator was CCM without cannabidiol (i.e. CCM plus placebo).

GWPCARE1 is available as a full publication. GWPCARE2, which completed very recently, has published some preliminary findings in a press release in November 2018; additional information from GWPCARE2 is planned for publication in the near future. The two RCTs are summarised below in Table 4. An open-label extension study of RCTs in DS and LGS, GWPCARE5, has published some preliminary safety results as a conference abstract.

A list of all primary and secondary publications identified for these trials is reported in Table 44 in Appendix D.

Table 4. Clinical effectiveness evidence

Study	**GWPCARE1 (27)**					**GWPCARE2 (28)**				
Study design	Double-blind, placebo-controlled, multinational RCT					Double-blind, placebo-controlled, multinational RCT				
Population	Children and adolescents aged 2 to 18 years with DS, uncontrolled with current regimen with 4+ convulsive seizures in past 28 days					Children and adolescents aged 2 to 18 years with DS, uncontrolled with current regimen with 4+ convulsive seizures in past 28 days				
Intervention(s)	Cannabidiol					Cannabidiol				
Comparator(s)	Placebo					Placebo				
Indicate if trial supports application for marketing authorisation	Yes	*X*	**Indicate if trial used in the economic model**	Yes	*X*	**Indicate if trial supports application for marketing authorisation**	Yes	*X*	**Indicate if trial used in the economic model**	Yes	*X*
	No			No			No			No	
Rationale for use/non-use in the model	Pivotal Phase 3 study in DS					Pivotal Phase 3 study in DS				
Reported outcomes specified in the decision problem	• **Percentage change in convulsive seizure frequency from baseline/28 days** • Reduction in total seizure frequency and seizure subtypes; • Caregiver global impression of change using 7-point scale • Seizure duration assessed by Caregiver Global Impression of change in Seizure Duration 3-point scale					• **Percentage change in convulsive seizure frequency from baseline/28 days** • Reduction in total seizure frequency and seizure subtypes; • Caregiver global impression of change using 7-point scale • Seizure duration assessed by Caregiver Global Impression of change in Seizure Duration 3-point scale				
All other reported outcomes	• Number with ≥25%, ≥50%, ≥75%, 100% reduction in convulsive seizures; • Sleep disruption assessed with 0-10 numerical rating scale and Epworth Sleepiness Scale; • QOL using Quality of Life in Childhood Epilepsy scale; • Vineland Adaptive Behaviour Scale; • Hospitalisations due to epilepsy; • Emergence of new seizure types; • Use of rescue medication; • Safety, including Columbia Suicide Severity Rating Scale; • Palatability on 5-point scale.					• Number with ≥25%, ≥50%, ≥75%, 100% reduction in convulsive seizures; • Sleep disruption assessed with 0-10 numerical rating scale and Epworth Sleepiness Scale; • QOL using Quality of Life in Childhood Epilepsy scale; • Vineland Adaptive Behaviour Scale; • Hospitalisations due to epilepsy; • Emergence of new seizure types; • Use of rescue medication; • Safety, including Columbia Suicide Severity Rating Scale; • Palatability on 5-point scale.				

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The methodology followed in the GWPCARE1 (27) and GWPCARE2 (28) trials is summarised below in Table 5.

Table 5. Summary of study methodology for included trials

Trial number (acronym)	**GWPCARE1 (27) Study GWEP1332B**	**GWPCARE2 (28) Study GWEP1424**
Location	France, Poland, UK, USA	US, Spain, Poland, Australia, Israel, Netherlands
Trial design	Multinational, randomised, double-blind, placebo-controlled trial.	Multinational, randomised, double-blind, placebo-controlled trial.
Eligibility criteria for participants	Aged 2 to 18 years with established diagnosis of DS, taking ≥1 antiepileptic drugs and had ≥4 convulsive seizures in previous 28 days.	Aged 2 to 18 years with established diagnosis of DS, taking ≥1 antiepileptic drugs and had ≥4 convulsive seizures in previous 28 days.
Settings and locations where data were collected	Patients or caregivers recorded number and type of seizures daily via interactive voice-response system; Laboratory assessments conducted after 2, 4, 8 and 14 weeks and end of taper period; Safety endpoints assessed at every visit.	Patients or caregivers recorded number and type of seizures daily via interactive voice-response system; Laboratory assessments conducted after 2, 4, 8 and 14 weeks and end of taper period; Safety endpoints assessed at every visit.
Trial drugs (number in each group)	Cannabidiol oral solution 100 mg/ml (n=61); dose escalated up to 20 mg/kg/day over 14 days then maintained for 12 weeks, followed by 10-day tapering before cessation or entry into open-label extension study. Matching placebo (n=59).	Cannabidiol oral solution 100 mg/ml; dose escalated up to 10 mg/kg/day (n=67) over 7 days or 20 mg/kg/day (n=67) over 11 days then maintained for 12 weeks, followed by 10-day tapering before cessation or entry into open-label extension study. Matching placebo (n=65).
Permitted and disallowed concomitant medication	Other anti-epileptic therapies allowed if stable for 4 weeks prior to screening and unchanged throughout the study.	Other anti-epileptic therapies allowed if stable for 4 weeks prior to screening and unchanged throughout the study.
Primary outcomes	Percentage change in convulsive seizure frequency from baseline/28 days.	Percentage change in convulsive seizure frequency from baseline/28 days.
Other outcomes used in the economic model or specified in the scope	• Caregiver Global Impression of Change; • Number with ≥25%, ≥50%, ≥75%, 100% reduction in convulsive seizures; • Reduction in total seizure frequency and seizure subtypes; • Seizure duration assessed by Caregiver Global Impression of Change in Seizure Duration; • Sleep disruption assessed with 0-10 numerical rating scale and Epworth Sleepiness Scale;	• Caregiver Global Impression of Change; • Number with ≥25%, ≥50%, ≥75%, 100% reduction in convulsive seizures; • Reduction in total seizure frequency and seizure subtypes; • Seizure duration assessed by Caregiver Global Impression of Change in Seizure Duration; • Sleep disruption assessed with 0-10 numerical rating scale and Epworth Sleepiness Scale;

Trial number (acronym)	GWPCARE1 (27) Study GWEP1332B	GWPCARE2 (28) Study GWEP1424
	• QOL using Quality of Life in Childhood Epilepsy scale; • Vineland Adaptive Behaviour Scale; • Hospitalisations due to epilepsy; • Emergence of new seizure types; • Use of rescue medication; • Safety, including Columbia Suicide Severity Rating Scale; • Palatability.	• QOL using Quality of Life in Childhood Epilepsy scale; • Vineland Adaptive Behaviour Scale; • Hospitalisations due to epilepsy; • Emergence of new seizure types; • Use of rescue medication; • Safety, including Columbia Suicide Severity Rating Scale; • Palatability.
Pre-planned subgroups	None	None

GWPCARE2

GWPCARE2 assessed [redacted] patients with DS, who had a diagnosis that was established and confirmed by an independent panel under a standard protocol. Of these, [redacted] met the inclusion criteria and were randomised to receive either 10 mg/kg/day of cannabidiol, 20 mg/kg/day of cannabidiol or placebo in addition to CCM. All patients were observed for 28 days to establish baseline characteristics (Table 6) before initiating treatment. Treatment lasted 14 weeks and consisted of a 2-week initial titration period in which patients received their assigned intervention (placebo or cannabidiol) beginning at a low dose and working up to 10 mg/kg/day or 20 mg/kg/day, before entering the 12-week maintenance phase, where treatment was stable and continuous. Interventions were tapered by 10% each day over a period of 10 days at the end of the 12-week treatment period (28).

Table 6: Baseline characteristics of treatment groups in GWPCARE2 (safety analysis set)(28)

Baseline characteristic	Cannabidiol 10 mg/kg/day	Cannabidiol 20 mg/kg/day	Placebo + CCM
Number randomised	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]
Ethnicity/ location	[redacted]	[redacted]	[redacted]

Baseline characteristic	Cannabidiol 10 mg/kg/day	Cannabidiol 20 mg/kg/day	Placebo + CCM
Baseline seizure types	[redacted]	[redacted]	[redacted]
Baseline seizure frequency*	[redacted]	[redacted]	[redacted]
Prior AED use	[redacted]	[redacted]	[redacted]
Concurrent AED use	[redacted]	[redacted]	[redacted]

*From ITT dataset

GWPCARE1

GWPCARE1 assessed 177 patients with DS, who had a diagnosis that was established and confirmed by an independent panel under a standard protocol. Of these, 120 met the inclusion criteria and were randomised to receive either 20 mg/kg/day of cannabidiol or placebo in addition to CCM. All patients were observed for 28 days to establish baseline characteristics (Table 7) before initiating treatment. Treatment lasted 14 weeks and consisted of a 2-week initial titration period in which patients received their assigned intervention (placebo or cannabidiol) beginning at a low dose and working up to 20 mg/kg/day, before entering the 12-week maintenance phase, where treatment was stable and continuous. Interventions were tapered by 10% each day over a period of 10 days at the end of the 12-week treatment period (27).

Table 7: Baseline characteristics of treatment groups in GWPCARE1 (27)

Baseline characteristic	Cannabidiol 20 mg/kg/day	Placebo + CCM
Number randomised	61	59
Age	Mean 9.7 SD 4.7y Median 9.1y Range 2.5 to 18y	Mean 9.8 SD 4.8y Median 9.2y Range 2.3 to 18.4y

Baseline characteristic	Cannabidiol 20 mg/kg/day	Placebo + CCM
Gender	35 male	27 male
Ethnicity/ location*	White: 44 Other: 6 NA: 11 USA: 35 Rest of world: 26	White: 50 Other: 3 NA: 6 USA: 37 Rest of world: 22
Baseline seizure types*	Convulsive (tonic, clonic, tonic-clonic or atonic), myoclonic, partial, absence seizures	Convulsive (tonic, clonic, tonic-clonic or atonic), myoclonic, partial, absence seizures
Baseline seizure frequency*	All seizures: median 24.0 per 28 days Convulsive seizures: median 12.4/28d; range 3.9 to 1717	All seizures: median 41.5 per 28 days Convulsive seizures: median 14.9/28d; range 3.7 to 718
Prior AED use	Mean 4.6 AEDs; SD 4.3	Mean 4.6 AEDs; SD 3.3
Concurrent AED use	Mean AEDs: 3.0; SD 1.0 Clobazam: 40 Valproate: 37 Stiripentol: 30 Levetiracetam: 16 Topiramate: 16 Ketogenic diet: 6 Vagus nerve stimulation: 6	Mean AEDs: 2.9; SD 1.0 Clobazam: 38 Valproate: 34 Stiripentol: 21 Levetiracetam: 17 Topiramate: 15 Ketogenic diet: 4 Vagus nerve stimulation: 9
*From CSR		

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Analysis of the primary outcome in GWPCARE2 was based on an ITT analysis, which comprised all randomised patients who received at least 1 dose of Investigational Medicinal Product (cannabidiol or placebo) and who had at least one post-treatment efficacy outcome recorded. The calculated sample size of 186 participants in the trial was exceeded and 198 participants were randomised and included in the ITT set.

Analysis of the primary outcome in GWPCARE1 was based on an intention-to-treat (ITT) analysis, which comprised all patients in the safety set who had at least one post-treatment efficacy outcome recorded. The calculated sample size of 100 participants in the trial was exceeded and 120 participants were randomised and included in the ITT set.

The statistical approach is summarised in Table 8.

Table 8: Statistical methodology used in relevant trials

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
GWPCARE2 (28)	The null hypothesis for the primary efficacy endpoint in the double-blind phase was that the response rates to the primary efficacy analysis are equal between the placebo and CBD treatment groups.	Change in convulsive seizure frequency from baseline assessed with Wilcoxon rank-sum test; median difference calculated with Holmes-Lehmann approach; % with at least 25%, 50%, 75% and 100% reduction in seizures assessed with Cochran-Mantel-Haenszel test; change in CGIC used ordinal logistic-regression model.	For a Wilcoxon-Mann-Whitney test comparing 2 distributions with a 2-sided significance level of 0.05, a sample size of 62 per group (after pooling the placebo groups) was required to obtain a power of at least 80%. This was based on gamma distributions for the CBD and placebo groups with parameters estimated by maximum likelihood estimates using the Newton-Raphson approximation using data from the GWCARE1 trial	Two patients randomised to 10 mg/kg/day and 2 to placebo were given dosing schedules for 20 mg/kg/ day in error. Of 199 patients randomised, 190 (95.5%) completed the treatment period (64 on 10 mg/kg/day, 61 on 20 mg/ kg/day group, 65 on placebo). 9 patients (4.5%) were withdrawn during the treatment period (3 on 10 mg/kg/day [4.5%], 6 on 20 mg/kg/day [9.0%]). 1 patient on 10 mg/kg/day [1.5%] was withdrawn as they were randomised in error and did not receive investigational medicinal product.
GWPCARE1 (27)	The null hypothesis for the primary efficacy endpoint in the double-blind phase was that the response rates to the primary efficacy analysis are equal between the placebo and CBD treatment groups.	Change in convulsive seizure frequency from baseline assessed with Wilcoxon rank-sum test; median difference calculated with Holmes-Lehmann approach; % with at least 25%, 50%, 75% and 100% reduction in seizures assessed with Cochran-Mantel-Haenszel test; change in CGIC used ordinal logistic-regression model.	Sample of 100 patients would provide 80% power to detect 32% difference in primary outcome with a 2-sided significance of 5%.	No adjustment was made of secondary outcome assessment p values for multiple comparisons. Intention-to-treat analysis included all 120 randomised patients in safety set, all of whom had postbaseline efficacy data.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality of the trials was assessed and recorded, as shown in Table 9 below. Both trials were considered to be high quality, with low risk of bias. The full quality assessment is reported in Appendix D.

Table 9: Summary of quality assessment of included clinical efficacy trials

Trial acronym	**GWPCARE2** (28)	**GWPCARE1** (27)
Overall risk of bias	Low	Low

B.2.6 Clinical effectiveness results of the relevant trials

Both the GWPCARE1 and GWPCARE2 studies met their primary endpoint, demonstrating that CBD had a statistically significant effect compared with placebo (in addition to CCM) in the median percentage change from baseline in convulsive seizure frequency.

GWPCARE2

A summary of the outcomes of GWPCARE2 is reported in Table *10*. There was a statistically significant reduction in convulsive seizures in both the cannabidiol treatment groups (10 mg/kg/day and 20 mg/kg/day) compared with the placebo (in addition to CCM) group. In the 10 mg/kg/day cannabidiol treatment group, patients achieved a 49% reduction in convulsive seizures compared with a 27% reduction in patients taking placebo (p=0.0095). Patients taking cannabidiol 20 mg/kg/day demonstrated a 46% reduction in convulsive seizures (p=0.0299).

A reduction in convulsive seizure frequency of 50% or more from baseline occurred in [redacted] of patients in the 10 mg/kg/day cannabidiol group and in [redacted] of patients in the 20 mg/kg/day group, compared with [redacted] of patients taking placebo (p = [redacted] and p = [redacted], respectively).

Overall, [redacted] patients experienced complete convulsive seizure-freedom during the treatment period: [redacted] in the 10 mg/kg/day cannabidiol group, [redacted] in the 20mg/kg/day group and [redacted] in the placebo group.

There was also a [redacted] in both the 10 mg/kg/day and 20 mg/kg/day cannabidiol groups compared with the placebo group.

CBD does not have a detrimental effect on the quality of life of patients with DS. There were [redacted] between treatment groups.

Table 10: Outcomes from GWPCARE2

Treatment group (ITT)	Cannabidiol 10 mg/kg/day	Cannabidiol 20 mg/kg/day	CCM + Placebo
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

GWPCARE1

A summary of the outcomes of GWPCARE1 is reported in Table 11. In the cannabidiol treatment group, convulsive seizure frequency decreased from a median of 12.4 seizures per month at baseline to 5.9 over the entire treatment period, a median change of -38.9% (Interquartile range [IQR] -69.5 to -4.8) from baseline. In the placebo group, the median monthly convulsive seizure frequency decreased from 14.9 to 14.1, a median change of -13.3% (IQR -52.5 to 20.2). The adjusted mean difference in convulsive seizures between the two treatment groups was -22.8% (95%confidence interval [CI] -41.1 to -5.4, p = 0.01).

A reduction in seizure frequency of 50% or more occurred in 43% of patients in the cannabidiol group and 27% of patients in the placebo group (odds ratio [OR] 2.0, 95%CI 0.93 to 4.30, p = 0.08).

During treatment, 3 patients in the cannabidiol group were 100% seizure-free, but no participants in the placebo group achieved seizure-freedom (p = 0.08).

The median number of total seizures per month decreased from 24.0 to 13.7 in the cannabidiol group, compared with a decrease from 41.5 to 31.1 with placebo (adjusted mean difference between groups = -19.2%, p=0.03 (27).

CBD does not have a detrimental effect on the quality of life of patients with DS. There were no statistically significant differences in changes in sleep disruption and

Epworth Sleepiness Scale scores, Quality of Life in Childhood Epilepsy and Vineland II scale scores between treatment groups.

Table 11. Outcomes from GWPCARE1(27)

Treatment group	**Cannabidiol 20 mg/kg/day**	**CCM + Placebo**
Number randomised	61	59
Study duration	14 wks	14 wks
Baseline total seizure frequency	Median 24.0	Median 41.5
End of study total seizure frequency	Median 13.7	Median 31.1
Generalised convulsive seizure frequency, baseline	Median 12.4/28 day Range: 3.9 to 1717	Median 14.9/28 day Range: 3.7 to 718
Generalised convulsive seizure frequency, treatment end	Median 5.9 Range: 0 to 2159	Median 14.1 Range: 0.9 to 709
Number with ≥50% reduction in total seizures	26 (43%)	16 (27%)
Number with 100% reduction in total seizures during treatment period	3	0
Use of rescue medication	36	41
CGIC improvement in overall condition	37	20
Number with adverse events (all)	57	44
Withdrawals (all)	9	3

B.2.7 Subgroup analysis

No subgroup analyses were conducted.

B.2.8 Meta-analysis

No meta analyses were conducted.

Refractory epilepsy (also known as drug-resistant epilepsy) has been defined as failure of adequate trials of two tolerated and appropriately chosen and used AED regimens (as monotherapies or in combination) to achieve sustained freedom from seizures.

A high proportion of patients with DS are refractory despite taking a variety of AEDs, reflecting the complexity of the condition and the fact that patients often become resistant to or are unable to tolerate current AEDs.

In the Phase 3 clinical trials of cannabidiol, the intervention was cannabidiol oral solution in addition to current clinical management and the comparator was established clinical management without cannabidiol (i.e. CCM + placebo).

For patients considered for treatment with Epidyolex, it will be an add-on treatment for refractory seizures in people aged 2 years of age and older once two other appropriate AEDs, trialled to a maximally tolerated dose, have failed to achieve seizure-freedom.

Therefore, the only viable comparator is established clinical management.

B.2.9 Indirect and mixed treatment comparisons

No indirect treatment comparisons were conducted.

Refractory epilepsy (also known as drug-resistant epilepsy) has been defined as failure of adequate trials of two tolerated and appropriately chosen and used AED regimens (as monotherapies or in combination) to achieve sustained freedom from seizures.

A high proportion of patients with DS are refractory despite taking a variety of AEDs, reflecting the complexity of the condition and the fact that patients often become resistant to or are unable to tolerate current AEDs.

In the Phase 3 clinical trials of cannabidiol, the intervention was cannabidiol oral solution in addition to current clinical management and the comparator was established clinical management without cannabidiol (i.e. CCM + placebo).

For patients considered for treatment with Epidyolex, it will be an add-on treatment for refractory seizures in people aged 2 years of age and older once two other appropriate AEDs, trialled to a maximally tolerated dose, have failed to achieve seizure-freedom.

Therefore, the only viable comparator is established clinical management.

B.2.10 Adverse reactions

Cannabidiol has a consistent, well-defined and manageable safety and tolerability profile. Most AEs were mild to moderate. The majority occurred during initiation of treatment (2-4 weeks), were transient and resolved within 4 weeks of onset.

Both GWPCARE1 (27) and GWPCARE2 (28) recorded adverse reactions reported by the patients, the number of withdrawals from the study and whether these were due to adverse events.

The adverse events reported across the studies are summarised in Table 12 below and in Appendix F.

Table 12: Adverse events recorded in GWPCARE1 (27) and GWPCARE2 (28).

Trial Name	**GWPCARE1** (27)		**GWPCARE2 CSR** (28)		
Treatment group	**20mg CBD (n=61), n (%)**	**Placebo (n=59), n (%)**	**10mg CBD (n=64), n (%)**	**20mg CBD (n=69), n (%)**	**Placebo (n=65), n (%)**
Pyrexia	9 (15%)	5 (8%)	[redacted]	[redacted]	[redacted]
Somnolence	22 (36%)	6 (10%)	[redacted]	[redacted]	[redacted]
Decreased appetite	17 (28%)	3 (5%)	[redacted]	[redacted]	[redacted]
Sedation	NR	NR	[redacted]	[redacted]	[redacted]
Vomiting	9 (15%)	3 (5%)	[redacted]	[redacted]	[redacted]
Nasopharyngitis	NR	NR	[redacted]	[redacted]	[redacted]
Ataxia	NR	NR	[redacted]	[redacted]	[redacted]
Gastroenteritis	NR	NR	[redacted]	[redacted]	[redacted]
Fatigue	12 (20%)	2 (3%)	[redacted]	[redacted]	[redacted]
Convulsion	7 (11%)	3 (5%)	[redacted]	[redacted]	[redacted]
Abnormal behaviour	NR	NR	[redacted]	[redacted]	[redacted]
Abdominal pain	NR	NR	[redacted]	[redacted]	[redacted]
Pneumonia	NR	NR	[redacted]	[redacted]	[redacted]
Rash	NR	NR	[redacted]	[redacted]	[redacted]
Infection, upper respiratory/viral	7 (11%)	5 (8%)	[redacted]	[redacted]	[redacted]
Pharyngitis, streptococcal	NR	NR	[redacted]	[redacted]	[redacted]
Psychomotor hyperactivity	NR	NR	[redacted]	[redacted]	[redacted]
Diarrhoea	19 (31%)	6 (10%)	[redacted]	[redacted]	[redacted]
Lethargy	8 (13%)	3 (5%)	[redacted]	[redacted]	[redacted]
Total patients experiencing any TEAEs	**57 (93%)**	**44 (75%)**	[redacted]	[redacted]	[redacted]

GWPCARE2

In GWPCARE2 (28), adverse events were recorded in [redacted] of the cannabidiol 10 mg group, [redacted] of the cannabidiol 20mg group and [redacted] of the placebo group. In each of the treatment groups, most patients who had TEAEs experienced events that were of mild to moderate severity ([redacted] patients in the 20 mg/kg/day cannabidiol group, [redacted] patients in the 10 mg/kg/day cannabidiol group and [redacted] patients in the placebo group). TEAEs were considered related to treatment by the investigator in [redacted] patients in the 20 mg cannabidiol group, [redacted] patients in the 10 mg cannabidiol group and [redacted] patients in the placebo group. [redacted] patients in the 20 mg cannabidiol group withdrew from the trial due to adverse events, compared with [redacted] from the 10 mg/kg/day cannabidiol and placebo groups. The most common adverse event across all groups was [redacted], reported in [redacted] patients in the 10 mg cannabidiol group, [redacted] patients in the 20 mg cannabidiol group and [redacted] patients in the placebo group.

Serious adverse events were reported in all groups; in [redacted] patients in the 20 mg cannabidiol group, in [redacted] patients in the 10 mg cannabidiol group and in [redacted] patients in the placebo group.

Elevated aminotransferase levels were recorded in [redacted] patients in the 20 mg CBD group and [redacted] patients in the 10 mg CBD group, and led to treatment withdrawal in [redacted] patients taking the 20 mg cannabidiol dose. All these patients were also taking sodium valproate.

There were [redacted] during the trial.

GWPCARE1

In GWPCARE1 (27), adverse events were recorded in 93% of the cannabidiol 20mg group and 75% of the placebo group. Of all the adverse events that occurred, 84% of those experienced by the cannabidiol group and 95% of the placebo group were mild or moderate.

The proportion of adverse events that were considered to be treatment-related was 75% for the cannabidiol group and 36% for the placebo group. For both groups, it

was most common for an adverse event to occur during the first 14 days of dose escalation. In the cannabidiol group, eight patients withdrew from the trial due to adverse events, compared with one withdrawal from the placebo group. The most common adverse event across both groups was somnolence, reported in 22 (36%) patients in the cannabidiol group and 6 (10%) patients in the placebo group. This was often associated with the use of clobazam as a concomitant medication, as seen in 18 of the 22 cannabidiol group and 5 of the 6 placebo group patients with somnolence.

Serious adverse events were reported in both groups; 10 in the cannabidiol group and 3 in the placebo group. Status epilepticus was reported in 3 patients in the cannabidiol group and 3 in the placebo group. None of these events led to withdrawal from the trial, and none were deemed to be related to the trial agent.

Elevated aminotransferase levels were recorded in 12 patients in the CBD group and 1 in the placebo group and led to treatment withdrawal in 3 patients taking cannabidiol and 1 taking placebo. All these patients were also taking sodium valproate. Enzyme levels returned to normal during the trial in the 9 patients who continued with cannabidiol treatment.

There were no deaths during the trial, no significant differences in other clinical laboratory safety measures and no differences in Columbia Suicide Severity Rating Scale scores in the 77 patients who completed the questionnaire.

Status epilepticus

The cannabidiol clinical trial patients were a highly refractory group with status epilepticus as part of their disease. In the two Phase 3 DS studies, status epilepticus was reported in 10 patients receiving cannabidiol 20 mg/kg, 5 patients receiving cannabidiol 10 mg/kg and 11 patients receiving placebo in addition to CCM.

B.2.11 Ongoing studies

GWPCARE5 is an ongoing, open-label extension of GWPCARE1 (DS), GWPCARE2 (DS), GWPCARE3 (LGS) and GWPCARE4 (LGS), to investigate the safety of cannabidiol in children and adults with inadequately controlled DS or LGS who had previously participated in one of the four trials. The trial is estimated to complete in June 2019. The primary outcome measure is the incidence of adverse events and other measures of safety. Patients are being followed for a maximum of three years. Secondary outcome measures include: the mean change in quality of life and Caregiver Global Impression of Change scores; mean percentage change in frequency of seizures and sub-types of seizure including convulsive and non-convulsive seizures, drop and non-drop seizures; the number of subjects considered treatment-responders, defined by the percentage reduction in convulsive seizures or drop seizures; and percentage changes in the number of seizures defined by their subgroups. All secondary endpoints will be compared against baseline values in the core study in which the patient participated.

Interim efficacy results were published in a conference abstract based on 14% of the 278 participants with DS having completed the study after a median of 50 weeks (range 1 to 99 weeks), 52% with ongoing treatment and 34% withdrawn.

There was a median 44% to 57% reduction in convulsive seizures from a baseline of 12 per 28 days, and a median 49% to 67% reduction in total seizures from a baseline frequency of 32 per 28 days with cannabidiol (29).

Preliminary safety results from this study have also been published as conference abstracts (29-31) and are reported in Appendix F.

B.2.12 Innovation

DS is a life-threatening orphan disease with very high unmet need

DS is a severe, lifelong, treatment-resistant form of epilepsy affecting children from 2 years of age, characterised by convulsive seizures that frequently lead to injuries, hospitalisation and premature death. DS is associated with many consequences/co-morbidities that can result in lifelong intellectual and physical impairment, and

complete dependence upon caregivers for daily activities. Patients with DS are also at high risk of SUDEP and status epilepticus. High mortality rates (7% to 18%) are reported for DS children.

Current guidelines recommend the use of AEDs developed more than 20 years ago

With the current range of AED options, many of which were developed more than 20 years ago, seizure control in DS remains inadequate: most children with DS remain uncontrolled or are intolerant to currently available AEDs.

It is also important to consider that, for some patients with DS, their quality of life may be impaired as much by the side-effects of current treatments and polypharmacy as by the seizures themselves. For those patients who respond to CBD, there may be an opportunity to reduce their concomitant drug burden over time. This may be achieved either through a reduction in dose or through complete elimination of concomitant AEDs, thereby potentially reducing the overall drug-related adverse event burden in these patients.

High patient and caregiver burden

DS places a significant long-term burden on patients and their families/carers. Specific high-risk seizures experienced by patients with DS predispose them to status epilepticus, SUDEP and injury. Parents/caregivers must live with the fear and anxiety of knowing that their child is at risk of injury, cognitive/physical decline or death, and that current treatment options are limited.

First cannabidiol medicine under review by EMA for DS

Epidyolex was granted orphan designation (EU/3/14/1339) by the European Commission in October 2014 for the treatment of DS. It is the first cannabidiol medicine approved by FDA (25 June 2018) in the USA and under review by EMA for the treatment of patients with DS whose seizures are not adequately controlled with current AED treatment.

Epidyolex is a highly purified, plant-derived pharmaceutical formulation of cannabidiol, administered as an oral solution. It is the first cannabinoid in class, with a novel, multi-modal mechanism of action, different to that of other AEDs.

Efficacy and safety of cannabidiol

As outlined in more detail above, as part of the largest Phase 3 clinical study programme in DS, CBD has demonstrated clinically and statistically significant reductions in convulsive seizure frequency and overall seizure frequency and has a consistent, well-defined and manageable safety and tolerability profile.

Seizure reduction in patients with DS with no other treatment options

A subset of 18 patients in the GWPCARE1 study had never experienced seizure reduction from any previous AEDs. Of these, 9 patients were on CBD and 9 were on CCM + placebo. The patients on CBD saw a 70% median reduction in convulsive seizures while those on CCM saw a median increase in convulsive seizures of 11%.

Importance of seizure-free periods to patients/caregivers

In addition to demonstrating reductions in seizure frequency, CBD has also demonstrated convulsive seizure-freedom and/or additional seizure-free days.

For patients with DS and their families/caregivers, a period of seizure-free time (whether several hours in a day, or seizure-free days) has the potential to improve quality of life in ways that it is challenging to demonstrate fully in the context of a clinical trial or in a QALY calculation. For example:

- A period of seizure-free time may give patients with DS the opportunity to learn, play and develop new skills.
- A seizure-free period may also mean that patients and families can undertake ‘everyday’ activities previously considered unthinkable, such as playing outside, visiting relatives or going on holiday.

- Parents/caregivers may feel less anxious about the potential for injury or death of the child with DS and more able to focus on their own lives and on the child's siblings.
- The DS patient may be able to live at home with family rather than needing to be cared for in a specialist institution, which reduces the burden on society as a whole.

Cannabidiol represents a step-change in the treatment of DS

There are currently only a small number of treatments approved for DS, and no drugs that are effective or well-tolerated in the majority of patients.

Given the lack of emerging therapeutic options specifically for DS, a variety of other treatments have been tried in these patients. However, limited efficacy has been observed and a large proportion of patients with DS remain refractory.

Cannabidiol is a novel, innovative therapy for patients with DS.

It offers a unique therapeutic modality and has been shown to be clinically effective with a favourable safety and tolerability profile in patients with DS who live with the constant risk of life-threatening seizures and who otherwise have extremely limited treatment options.

B.2.13 Interpretation of clinical effectiveness and safety evidence

DS accounts for approximately 1% of childhood epilepsies, with an estimated prevalence of 1 to 2 per 40,000 population (32).

Extrapolating statistics for the United Kingdom from the Office for National Statistics in 2017 (33), we can calculate that the likely number of patients with DS will be as shown in Table 13:

Table 13. Expected number of patients with DS and new cases in children aged 0-14 years across UK, 2017

	England	**Wales**	**Scotland**	**Northern Ireland**
Total population 2017	55,619,430	3,125,165	5,424,800	1,870,834
Population aged 0-14 years 2017	10,048,365	526,634	864,154	368,420
Prevalence of DS	1390 to 2781	78 to 156	136 to 271	47 to 94

As part of the largest Phase 3 clinical study programme in DS, CBD has demonstrated clinically and statistically significant reductions in convulsive seizure frequency and total seizure frequency and has a consistent, well-defined and manageable safety and tolerability profile.

The two RCTs of cannabidiol in DS (GWPCARE1 (27) and GWPCARE2 (28)) recruited patients who were uncontrolled despite a mean of 3 current AEDs, and having previously tried or failed a mean of 4 other AEDs.

There remains considerable unmet need for additional effective treatments to control seizures in DS which is reflected in the fact that these RCTs included more than the required statistical sample size of patients.

Despite the recruited population being difficult to manage, CBD adjunctive therapy reduced convulsive- and total-seizure rates compared with current clinical management and significantly more patients/caregivers reported that the patient's overall condition had improved with CBD.

Cannabidiol was generally well-tolerated, with the majority of patients experiencing only mild or moderate adverse events. Common adverse events (occurring in more than 1 in 10 people) across both Phase 3 DS trials with cannabidiol were decreased appetite, diarrhoea, somnolence, pyrexia, fatigue and vomiting. In GWPCARE1 patients also commonly experienced upper respiratory tract infection, convulsion and lethargy, whilst in GWPCARE2 [redacted] was commonly reported. Raised liver aminotransferases were reported with CBD and were seen more often with the higher dose of CBD (20 mg/kg/day), when the patient had elevated transaminases at baseline, or when CBD was taken with concomitant valproate or clobazam. Cases of raised liver transaminases resolved either spontaneously (without dose reduction or interruption of CBD treatment during the studies) or with dose adjustments of CBD or concomitant AEDs. Liver function monitoring is recommended before commencing CBD, with escalation of dose beyond 10 mg/kg/day and periodically during treatment with CBD. This does not affect current clinical practice as liver function is commonly monitored for other AEDs.

The two cannabidiol RCTs were well-designed, multinational multicentre studies, even though DS is an orphan disease. All participants, researchers and assessors were blind to treatment allocations, and patients and caregivers submitted data daily on the primary outcome via an interactive voice-response system and were trained to identify different seizure types before the start of the study. The results were clinically meaningful and statistically significant and show that adding adjunctive cannabidiol to existing anti-epileptic medication can significantly improve outcomes in this hard-to-treat population.

The randomised treatment phase in the RCTs was 14 weeks (2-week titration phase followed by 12-week maintenance phase). The open-label extension study will follow patients for a further three years to reduce uncertainty about longer-term efficacy and safety outcomes. Interim data up to 48 weeks have already reported from this study, demonstrating durability of outcomes in these patients.

The baseline characteristics of participants in the cannabidiol RCTs showed that, as is typical in RCTs of DS and other orphan diseases, they were somewhat heterogeneous in terms of baseline seizure frequency and concomitant/prior anti-

epileptic therapies. This increases the relevance of the clinical trials to the real-world, heterogeneous population of patients with DS.

DS is a severely debilitating, lifelong and treatment-resistant form of epilepsy, with a high risk of mortality. Even with current clinical management, there remains a significant unmet need in this life-threatening disease for treatments that reduce seizure frequency and severity, improve the overall condition of patients with DS and reduce carer burden, without further increasing adverse events.

The value of CBD is in the treatment of patients with DS with uncontrolled seizures despite treatment with at least two AEDs.

Cannabidiol offers patients with DS the opportunity of a long-term treatment with durable efficacy that reduces seizure severity (seizure frequency and duration) and, for some patients who had previously been inadequately controlled, the potential for seizure-freedom.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

Identification of the studies

A systematic literature review was conducted to identify cost-effectiveness studies from the published literature relevant to Dravet syndrome (DS).

The following databases were searched for relevant publications: Medline® via PubMed, EMBASE via ProQuest, Heoro.com, The Cochrane library, the American Epilepsy Society, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), The All Wales Medicines Strategy Group (AWMSG), The Scottish Medicines Consortium (SMC), The National Institute for Health and Care Excellence (NICE), clinicaltrials.gov, NHS Economic Evaluation Database (EED), Health Technology Assessment (HTA), Database of Abstracts of Reviews of Effects (DARE), The University of Sheffield Health Utilities Database (ScHARRHUD) and EuroQol Database.

Database searches were supplemented by hand searching the following sources: LGS Foundation Conference 2016-17, International Epilepsy Congress 2015-17 and European Congress on Epileptology 2016-18.

The database searches were run on 19th November 2018 and the grey literature sites were searched on 19th November and 3rd December using the search strategies outlined in Appendix D.

In total, 11,255 papers were identified through the searches (10,163 through database search and 1,092 through hand search). After removing 2,432 duplicated papers, 8,823 titles and abstracts were reviewed. Full text articles were obtained for 292 records of which 246 were excluded for various reasons (irrelevant topic, irrelevant population, irrelevant intervention/comparator, full text not in English, insufficient data or old abstract, systematic review or irretrievable, duplicate, relevant to Lennox-Gastaut Syndrome only or not reporting utility values). A total of 46 records were included in the submission (see Appendix D).

The full details of the search and the PRISMA flowchart are presented in Appendix D.

Description of the identified studies

Five economic modelling publications were identified, including four analyses of HTA submissions of stiripentol with relatively few details reported of the underlying models: a budget impact model based on a simplistic cost-listing for children aged 3 to 18 years submitted to the AWMSG (32), a cost-utility plus budget-impact model used in a resubmission of stiripentol with clobazam and valproate as adjunctive therapy for children at least 3 years old with uncontrolled DS in Wales (34) and what is presumably the same cost-utility model submitted to Scotland (35), and a cost-utility Markov model for patients with uncontrolled DS in Canada submitted to CADTH (36). The fifth economic modelling publication was an economic evaluation reporting a cost-utility Markov model of stiripentol for the treatment of patients with DS who have been unresponsive to concomitant treatment with clobazam and valproate, for the Canadian jurisdiction (37).

The AWMSG did not recommend stiripentol in DS in 2008 (32), but the revised submissions in 2017 to AWMSG and the SMC both approved stiripentol for use in combination with clobazam and valproate as adjunctive therapy for refractory DS (34, 35). CADTH also recommended its use in combination with clobazam and valproate as adjunctive therapy for refractory DS provided that the patient is under the care of a neurologist and the price of stiripentol was reduced to make it cost-effective (36). The Canadian cost-utility analysis found that adjunctive stiripentol had a 20.7% chance of being cost-effective at a willingness-to-pay threshold of CAN$100,000 with an ICER of CAN$151,310/QALY gained, and concluded that stiripentol was only likely to be cost-effective if its cost were reduced by 61.4% (37).

As no cost-effectiveness studies appraising cannabidiol were identified from the search, the summary of the studies assessing other treatment alternatives for DS is presented in Appendix G.

B.3.2 Economic analysis

As confirmed by the systematic literature review presented in Section B.3.1, no cost-effectiveness studies appraising cannabidiol for the treatment of seizures associated with DS were published prior to this submission. Therefore, a *de novo* analysis was required. Details of the model and the analysis are presented in the sections below.

Patient population

The target population for the cost-effectiveness analysis consists of patients with DS who are aged 2 years or older and in whom the condition is inadequately controlled by the established current clinical management (CCM) in the UK. This patient population is also consistent with the therapeutic indication proposed in the marketing authorisation application for cannabidiol to the European Medicines Agency (EMA).

Cannabidiol does not yet have a UK marketing authorisation for the indication detailed in this submission. However, the Committee for Medicinal Products for Human Use (CHMP) opinion is expected on 31 January 2019 on the marketing authorisation of Epidyolex® (cannabidiol), and the target population for this cost-effectiveness analysis has been defined in anticipation of the final approval from the EMA for the expected licensed indication (i.e. for the adjunctive treatment of DS in patients aged 2 years or older).

The study population of the two pivotal Phase 3 trials for DS (GWEP1332 Part B and GWEP1424) included patients aged 2 to 18 years whose disease was not completely controlled by their current AEDs. Despite this restriction on the age of the patients included in the trial, clinical evidence from this study may be considered appropriate for patients older than 18 years of age as, in DS, the onset of seizures occurs within the first year of the patient's life and becomes more frequent and persistent during the second year of life (38). After the fourth year of life, patients are in a "sequelae phase" where seizures may reach a plateau (39).

The target population is also consistent with the final scope published by NICE for the health technology appraisal of cannabidiol in DS (40).

Model structure

A Markov state-transition cohort model that captures the major characteristics and the natural history of the disease was developed in Microsoft *Excel*®. The Markov cohort model structure was preferred to a micro-simulation, as analysis of the patient-level data from the pivotal Phase 3 trials for DS showed that the treatment effect was not significantly different across the patient subgroups stratified by age, gender, number of AEDs previously taken and use of specific AED (such as clobazam or valproate).

Furthermore, all cost-effectiveness analyses conducted for DS to date have also been based on the Markov cohort model structure (see Section B.3.1).

Definition of health states

As DS is characterised by multiple, treatment-resistant convulsive seizures, the model has been designed to capture the costs and consequences associated with the number of convulsive seizures patients experience in a month. The model structure used for DS is shown in Figure 3.

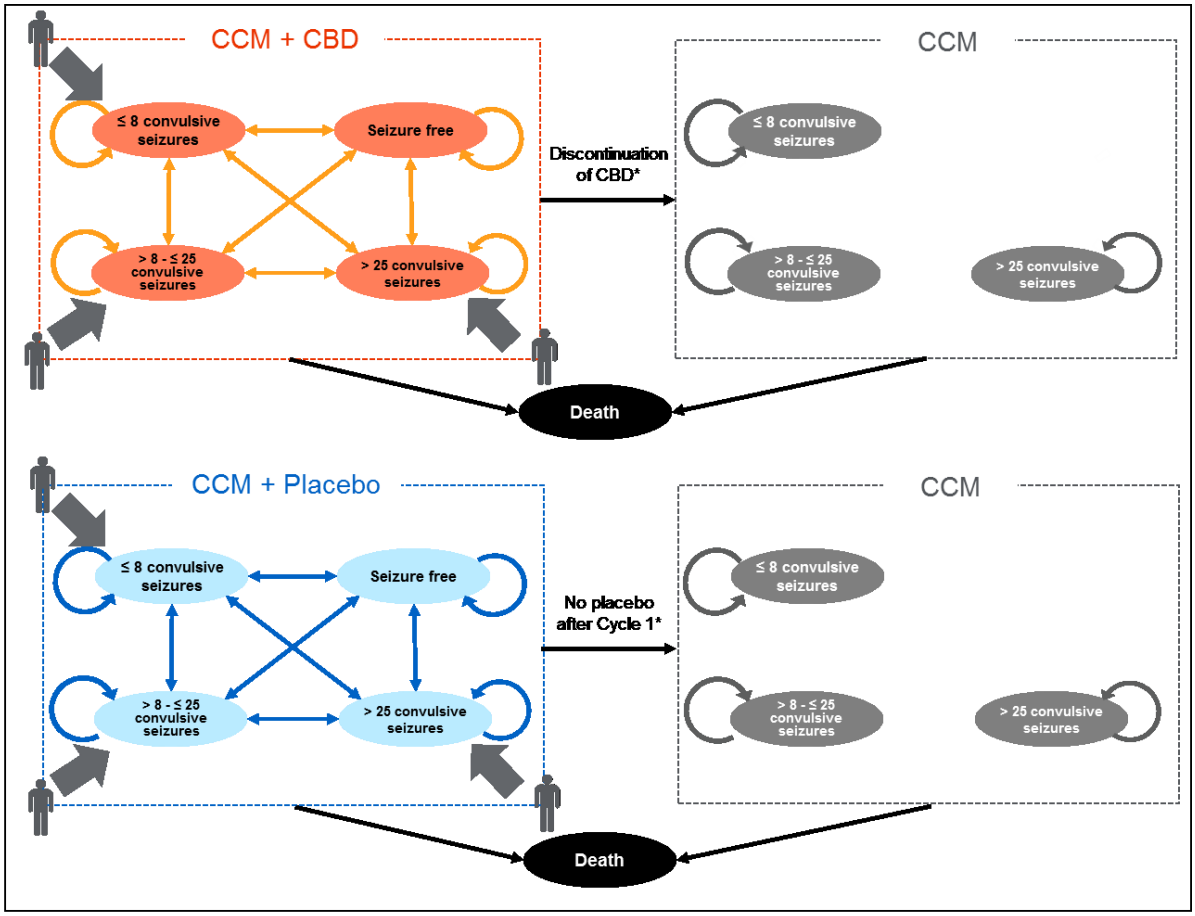
Seizure frequency is known to vary widely among individual patients with DS. Previous models assessing treatment alternatives for DS defined the model health states based on the percentage reduction in convulsive seizures from baseline. However, this approach may not accurately capture the costs and quality of life as patients with similar percentage reduction in convulsive seizures would be grouped together irrespective of the total number of seizures experienced at baseline. For example, patient A experiences 24 convulsive seizures a month, while patient B experiences 8 convulsive seizures a month. Following treatment, both experience a 50% reduction in their seizures. Patient A continues to experience a relatively high number of seizures i.e. 12 per month, while the number of seizures for patient B has dropped to 4 per month and yet both patients would be applied the same costs and QALYs.

Therefore, the health states in the current analysis were defined based on the total number of convulsive seizures per month. The model includes mutually exclusive health states that are based on the following four categories of seizure frequency

(seizure categories were determined to ensure that that patients enrolled in the Phase 3 trials were split into three equal groups and the analyses could be based on sufficient statistical power; refer to Section B.3.3 for further details), and an all absorbing health state for death:

1. Seizure-Free
2. ≤ 8 convulsive seizures per month
3. > 8 - ≤ 25 convulsive seizures per month
4. > 25 convulsive seizures per month.

Figure 3: Markov Model Schematic



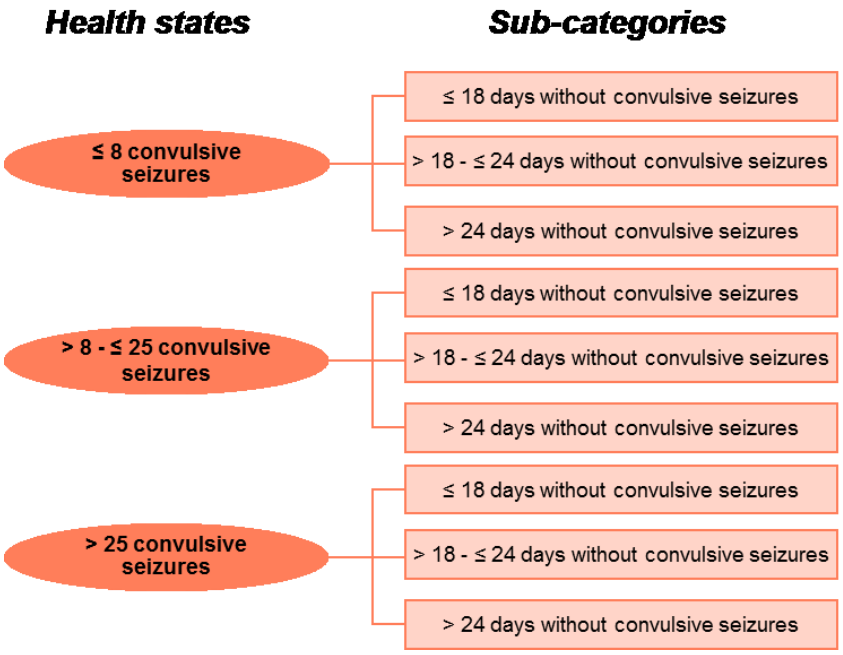
Abbreviations: CBD: cannabidiol; CCM; current clinical management
*Revert to baseline seizure frequency rates

Health state sub-categories

As improvements in quality of life and patient wellbeing can be linked to both the reduction in the total number of convulsive seizures and an increase in the number of seizure-free days, each health state for patients experiencing seizures (active

treatment and treatment discontinued) was categorised into three sub-categories based on the number of seizure-free days experienced in the corresponding health state (Figure 4).

Figure 4: Heath state sub-categories



Compared to patients with a high number of seizures, patients with a low number of convulsive seizures are more likely to experience a high number of seizure-free days. These sub-categories help in assigning different utility scores for patients in a specific seizure group based on the number of seizure-free days they experience.

1. ≤18 seizure-free days
2. >18 - ≤ 24 seizure-free days
3. > 24 seizure-free days.

Patient transitions between health states

Patients in the treatment and comparator arm can enter the model via any one of the three health states with convulsive seizures (≤ 8, >8 - ≤ 25 and >25 convulsive seizures).

The model was based on a cycle length of 3 months as the clinical outcomes in the Phase 3 trials for DS (GWEP1332 Part B and GWEP1424) and the open-label extension study (GWEP1415) were reported at 12-week intervals.

At each cycle, patients in the treatment arm (i.e. cannabidiol in addition to CCM) can continue to receive treatment, discontinue or die:

- If they continue to receive the treatment, patients can move to another health state (better or worse seizure group) or stay in the same health state.
- Discontinuation rates were applied to only the treatment arm (i.e. cannabidiol in addition to CCM).
    - The discontinuation rate for the first cycle in the model was estimated from the Phase 3 trials for DS (GWEP1332 Part B and GWEP1424).
    - Discontinuation rates for subsequent cycles were based on estimates from the open-label extension study (GWEP1415).
- When patients discontinue their treatment, they go back to baseline and remain in their baseline state until the end of the analysis.
- Once patients have discontinued their treatment, they cannot receive the active treatment again (i.e. they receive only CCM).

Similar to the treatment arm, patients in the comparator arm can move to another health state (better or worse seizure group) or stay in the same health state. However, unlike in the treatment arm, patients in the comparator arm cannot discontinue treatment (as they do not receive the active drug [i.e. cannabidiol]). Patients in the comparator arm receive CCM for the duration of the analysis, or until death.

Patients with DS who experience seizures (active treatment and discontinued treatment) were assumed to be at risk of SUDEP as well as death from other non-SUDEP causes such as status epilepticus, drowning and asphyxia. The rates of SUDEP and non-SUDEP were obtained from the published literature (8, 13).

There is evidence that epilepsy-related deaths may be related to the frequency of seizures. Furthermore, clinical experts have indicated that the additional risk of mortality due to their underlying condition is minimal in patients who are seizure-free

(41, 42). Therefore, additional risk of disease-specific mortality was not applied to patients in the seizure-free health state (refer to section B.3.3 for further information).

Features of the economic analysis are presented in Table 14. No NICE technology appraisal for the same indication was identified.

Table 14: Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Perspective	NHS/PSS	NICE recommendation (43)
Time horizon	15 years	Long enough to reflect all expected consequences in costs and health effects between cannabidiol and CCM.
Discount for utilities and costs	3.5% QALYs and Costs	NICE recommendation (43)
Source of utilities	Health states: utilities based on VAS from online survey conducted by GW	VAS data collection in line with guidance in NICE reference case (43)
Source of costs	NHS reference costs PSSRU BNF Published literature Expert opinion	NICE recommendation (43)
Mortality rates	ONS life table for England Published literature	Latest available published data were used (8, 13)
Abbreviations: BNF, British National Formulary; DS, Dravet syndrome; NHS, National Health Service; ONS, Office for National Statistics; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; VAS, visual analogue scale		

Intervention technology and comparators

The model evaluates the incremental cost-effectiveness of cannabidiol in addition to CCM compared to CCM without cannabidiol (i.e. CCM plus placebo).

The following concomitant therapies: valproate, clobazam, stiripentol, topiramate and levetiracetam were selected to constitute the established CCM. The CCM was determined based on primary research on AED prescription patterns in the UK and the Final NICE scope for cannabidiol in DS (40, 44).

Although the NICE scope for cannabidiol in DS includes ketogenic diet and vagus nerve stimulation as potential comparators, these treatments were not considered within this economic analysis (40):

- Although non-pharmacological options such as ketogenic diet and vagus nerve stimulation maybe used as second/third-line treatments alongside AEDs for DS, they are not recommended for all patients due to issues concerning adherence, adverse effects and long term complications such as bone fractures, kidney stones and decreased growth (ketogenic diet) and low efficacy (vagus nerve stimulation) (17, 45).

As patients in both the treatment and the comparator arm are assumed to receive the same established clinical management, the exclusion of these interventions from the current analysis will have no impact on the incremental cost-effectiveness ratios (ICERs).

Cannabidiol oral solution is administered as per the dosage specified for the proposed licensed indication: recommended starting dose of 2.5 mg/kg twice daily increased to a maintenance dose of 10 mg/kg/day (46). Refer to section B.3.3 for the CBD dosage used in the model.

B.3.3 Clinical parameters and variables

The primary data sources for the economic model are the Phase 3 pivotal clinical trials, GWEP1332 Part B and GWEP1424 and the open-label extension study, GWEP1415 (Section B.2.3). These studies are the source for demographic characteristics, clinical outcomes (frequency of convulsive seizures, number of days without convulsive seizures, discontinuation rates) and adverse events for both the comparator (established CCM without cannabidiol) and intervention (cannabidiol in addition to CCM) arms.

Baseline characteristics of patients

Baseline demographic characteristics such as mean age, weight and disease severity (i.e. frequency of convulsive seizures and the number of days without convulsive seizures) were obtained from patient-level data (PLD) analysis of the Phase 3 clinical trials, GWEP1332 Part B and GWEP1424, and were assumed to be the same for the cohort of patients entering the model in the treatment arm and the comparator arm (Table 15).

As the treatment dosages for CBD and some other AEDs are weight-based, the trial populations were split into four age groups (2-5 years, 6-11 years, 12-17 years and 18-55 years) in order to ensure more precise estimation of the treatment dosages. The age groups were amalgamated into two groups for the cost-effectiveness analysis in order to improve statistical power: <12 years and ≥12 years. Therefore, demographic characteristics and all clinical efficacy and safety outcomes were obtained from the PLD analysis of the GWEP1414 and GWEP1423 studies for these two age-groups. The proportion of patients, their mean age and weight were determined for the following age-groups: 2-5 years, 6-11 years, 12-17 years and 18-55 years.

Patients entering the model get older over time and the mean body weight used to estimate the treatment dosage changes when they enter a higher age category (for example, a patient enters the model at 5 years of age and the following year when the patient is 6 years old, the treatment dosages are calculated based on the mean weight of the 6-11 years age group; i.e. 31.04 kg). Similarly, clinical outcomes, costs and resource use change for patients when they move from the <12 years category to the ≥12 years category.

As mentioned in Section.B.3.2, three distinct severity groups (i.e. ≤ 8, > 8 - ≤ 25, > 25 convulsive seizures per month) based on the number of convulsive seizures that patients experienced in a month were included as mutually-exclusive health states in the model. The upper and lower bounds of these severity groups were determined in such a way so as to ensure the patients enrolled in GWEP1332 Part B and GWEP1424 trials were split into three equal groups. This approach was used to ensure that the three different severity groups had equal numbers of patients and sufficient statistical power. A similar approach was used to determine the three distinct categories for the seizure-free days.

The baseline demographic characteristics and clinical data were validated by clinical experts and were considered to be appropriate and representative of the UK population. The three distinct severity groups determined for the number of seizures and seizure-free days were also validated by clinical experts.

Table 15: Baseline characteristics per age group used in the model

Demographic characteristics at baseline	<12 years			≥12 years	
	2-5 years	6-11 years		12-17 years	18-55 years
% of patients	[redacted]				
Mean age	[redacted]				
Mean weight	[redacted]				
Frequency of convulsive seizures at baseline					
≤ 8 convulsive seizures per 28 days	[redacted]				
> 8 - ≤ 25 convulsive seizures per 28 days	[redacted]				
> 25 convulsive seizures per 28 days	[redacted]				
Number of days without convulsive seizures (per 28 days) at baseline					
≤ 8 convulsive seizures per 28 days					
≤ 18 days	[redacted]				
> 18 - ≤ 24 days	[redacted]				
> 24 days	[redacted]				
> 8 - ≤ 25 convulsive seizures per 28 days					
≤ 18 days	[redacted]				
> 18 - ≤ 24 days	[redacted]				
> 24 days	[redacted]				
> 25 convulsive seizures per 28 days					
≤ 18 days	[redacted]				
> 18 - ≤ 24 days	[redacted]				
> 24 days	[redacted]				
Reference: GW 2018 Data on file (47)					

Cannabidiol dosage

Epidyolex is presented as an oral solution containing 100 mg/ml cannabidiol. The recommended starting dose of cannabidiol is 2.5 mg/kg taken twice daily for one week (46). After one week, the dose is increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, the dose can be further increased in weekly increments of 2.5 mg/kg twice daily to a recommended maximum recommended dose of 10 mg/kg twice daily (i.e. 20 mg/kg/day) (46).

The base case analysis utilises the maintenance dose of 10 mg/kg/day, as the majority of patients will receive this dose in clinical practice. A limited number of patients may be treated with a maximum dose of up to 20 mg/kg/day based on individual clinical response and tolerability, as detailed in the scenario analysis.

Current Clinical Management Basket

Pharmacological treatment options are limited and patients with DS are largely resistant to current anti-epileptic treatments. In its clinical guideline CG137, NICE recommends sodium valproate or topiramate as a first-line treatment option for DS

and, if seizures are inadequately controlled, clobazam or stiripentol as an adjunctive treatment (1).

As mentioned in Section B.3.2, the CCM was determined based on primary research on AED prescription patterns in the UK and the Final NICE scope for DS (40, 44). The primary market research consisted of a 30-40 minute online survey by 40 UK physicians who fulfilled the following criteria: firstly, it was required that the physician currently manage and treat at least one patient with DS, LGS or tuberous sclerosis complex (TSC), and secondly that they review a minimum of 100 paediatric or 200 adult epilepsy cases per year.

The CCM considered in the current analysis is in line with published evidence on current clinical practice and the final scope published by NICE and has also been validated by clinical experts to be appropriate and representative of the UK clinical setting.

Table 16: CCM basket by age group

	<12 years	≥12 years
Valproate	[redacted]	[redacted]
Clobazam	[redacted]	[redacted]
Stiripentol	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]
Levetiracetam	[redacted]	[redacted]
Source: GW 2018 market research (44)		

Transition probabilities

As explained in Section B.3.2 and illustrated in Figure 3, patients can enter the model via any one of the three health states with seizures (≤ 8, >8 - ≤ 25 and >25 convulsive seizures). At each cycle, patients receiving the active treatment can continue to experience the same number of seizures, or move to better or worse health states.

For both the treatment and the comparator arms, the transition probabilities for the first cycle were derived from the GWEP1332 Part B and GWEP1424 Phase 3 trials. For cycles two to nine, time-dependent transition probabilities for the treatment arm (cannabidiol in addition to CCM) were estimated using the open-label extension study, GWEP1415. The base case analysis assumed that, after cycle nine, patients stay in the same health state for the remaining duration of the analysis. This

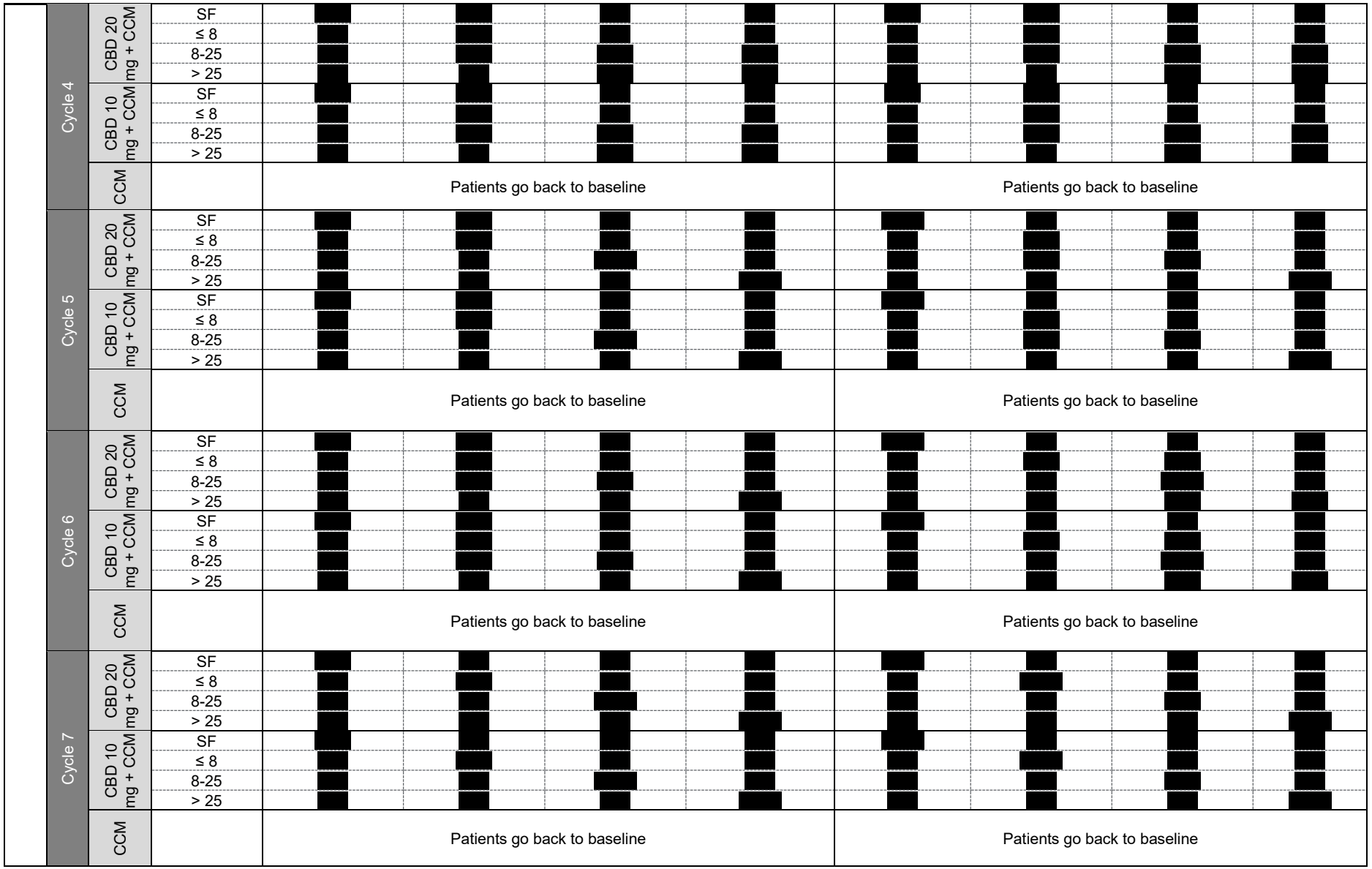
assumption was considered to be appropriate given that no decline in treatment efficacy was observed among patients enrolled in the open-label extension study, GWEP1415 (Section B.2.3).

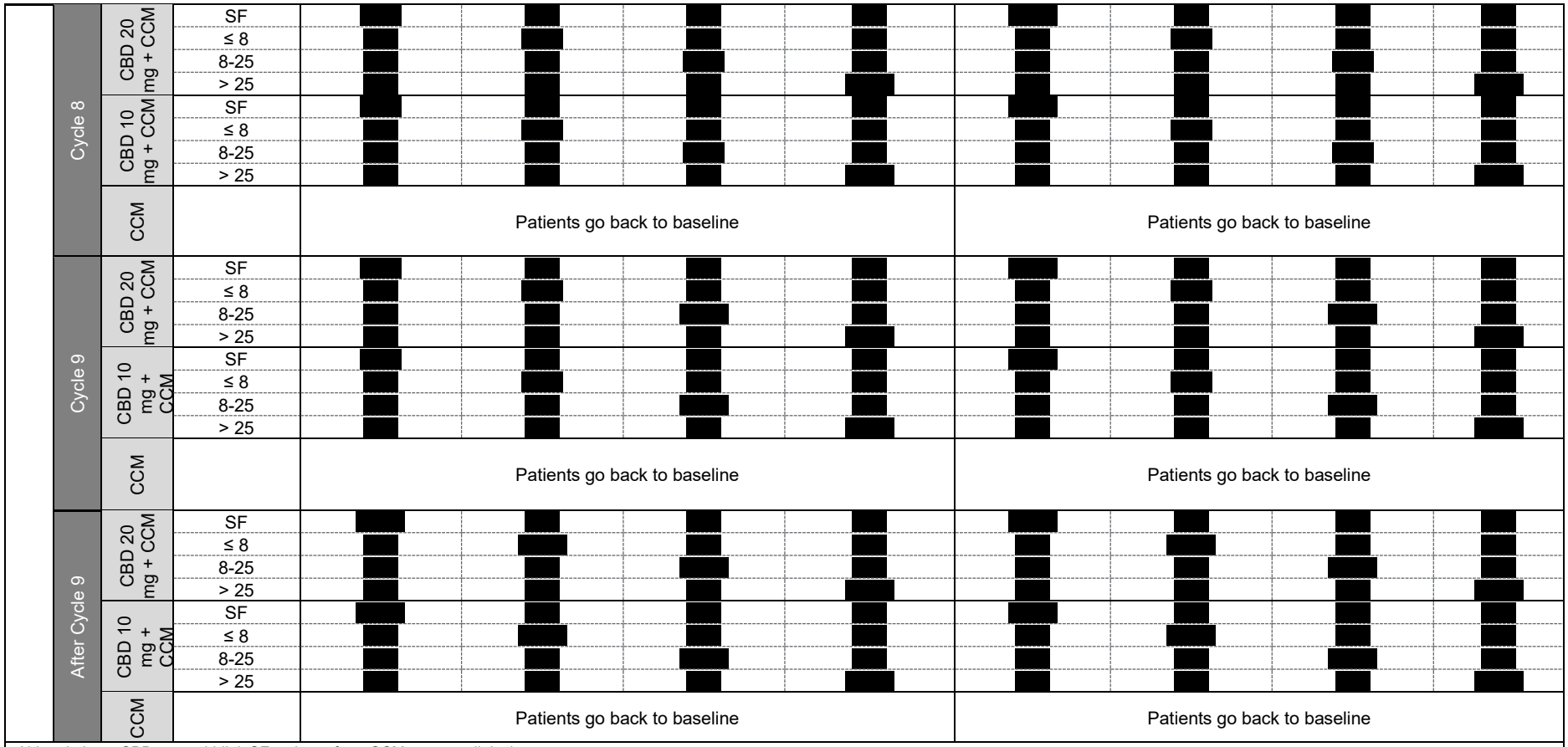
As efficacy data for the control arms were available only for the duration of the GWEP1332 Part B and GWEP1424 Phase 3 trials (i.e. 14 weeks, see Section B.2.3), any change to seizure rates was assumed to apply for one cycle only (i.e. for the duration that patients were receiving placebo + CCM in the Phase 3 trials). In subsequent cycles, patients were assumed to revert to baseline efficacy rates (Table 17).

This assumption was considered appropriate as patients in the GWEP1332 Part B and GWEP1424 Phase 3 trials were already receiving treatment with CCM at baseline, which was continued in both study arms, thus the baseline seizure rates could be assumed to be representative of the efficacy associated with CCM without placebo. This assumption has also been validated by clinical experts in the UK.

Table 17: Transition probabilities

Transition from				<12 years				≥12 years			
				SF	≤ 8	8-25	> 25	SF	≤ 8	8-25	> 25
Cycle 1	CBD 20 mg + CCM	SF		[redacted]							
		≤ 8		[redacted]							
		8-25		[redacted]							
		> 25		[redacted]							
	CBD 10 mg + CCM	SF		[redacted]							
		≤ 8		[redacted]							
		8-25		[redacted]							
		> 25		[redacted]							
	CCM	SF		[redacted]							
		≤ 8		[redacted]							
		8-25		[redacted]							
		> 25		[redacted]							
Cycle 2	CBD 20 mg + CCM	SF		[redacted]							
		≤ 8		[redacted]							
		8-25		[redacted]							
		> 25		[redacted]							
	CBD 10 mg + CCM	SF		[redacted]							
		≤ 8		[redacted]							
		8-25		[redacted]							
		> 25		[redacted]							
	CCM			Patients go back to baseline				Patients go back to baseline			
Cycle 3	CBD 20 mg + CCM	SF		[redacted]							
		≤ 8		[redacted]							
		8-25		[redacted]							
		> 25		[redacted]							
	CBD 10 mg + CCM	SF		[redacted]							
		≤ 8		[redacted]							
		8-25		[redacted]							
		> 25		[redacted]							
	CCM			Patients go back to baseline				Patients go back to baseline			





Abbreviations: CBD, cannabidiol; SF. seizure-free; CCM, current clinical management
Note: CBD dosage is per kilogram and per day
Reference: GW 2018 Data on file (48)

Health state sub-categories distribution

As explained in Section B.3.2, improvements in quality of life and patient wellbeing could also be linked to an increase in the number of seizure-free days. Therefore, the health states for patients experiencing seizures (active treatment and treatment discontinued) were categorised into three groups based on the number of seizure-free days experienced in the corresponding health state (Figure 4).

The proportion of patients in each of the 'seizure-free days' categories were determined from the PLD analysis of the GWEP1332 Part B and GWEP1424 Phase 3 trials for both the treatment and the comparator arm. The number of seizure-free days in the subsequent cycles was assumed to be constant for patients who continue to receive the active treatment (i.e. CBD). Patients who discontinue CBD are assumed to revert to the baseline seizure-free day rates and remain in the same sub-health state for the remaining duration of the analysis.

Table 18: Number of days without seizures

		<12 years			≥12 years		
		≤ 18 days	> 18 - ≤ 24 days	> 24 days	≤ 18 days	> 18 - ≤ 24 days	> 24 days
CBD 20 mg + CCM	SF						
	≤ 8						
	8-25						
	> 25						
CBD 10 mg + CCM	SF						
	≤ 8						
	8-25						
	> 25						
CCM	SF						
	≤ 8						
	8-25						
	> 25						

Abbreviations: CBD, cannabidiol; SF, seizure-free; CCM, current clinical management
Reference: GW 2018 Data on file (49)

Treatment discontinuation

The analysis considered an all-inclusive discontinuation rate that considered patients withdrawing from treatment due to adverse events or loss of efficacy. As explained in Section B.3.2, patients who discontinue their treatment transition to the discontinuation pathway. In the base case, patients who withdraw from cannabidiol stop benefiting from the treatment effect immediately and are assumed to revert to baseline seizure rates and seizure-free day rates, and remain in the same health state for the remaining duration of the analysis (i.e. in the following cycle, the

proportion of patients in each of the health states was determined based on the initial baseline proportions).

Discontinuation rates were applied only for patients entering the model in the treatment arm (i.e. cannabidiol in addition to CCM). The discontinuation probabilities for the first cycle were derived from the GWEP1332 Part B and GWEP1424 trials (Table 19). For cycles two to nine, time-dependent treatment discontinuation probabilities were estimated using the open-label extension study, GWEP1415. The discontinuation rates estimated for cycle nine were assumed to remain constant over time, for the remaining duration of the analysis.

Table 19: Treatment discontinuation per age group

		<12 years		**≥12 years**	
		Cycle 1	Subsequent Cycles	Cycle 1	Subsequent Cycles
CBD 20 mg + CCM	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 8 seizures	[redacted]	[redacted]	[redacted]	[redacted]
	>8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]
	> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]
CBD 10 mg + CCM	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 8 seizures	[redacted]	[redacted]	[redacted]	[redacted]
	>8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]
	> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CBD, cannabidiol; CCM, current clinical management
Note: CBD dosage is per kilogram and per day
Reference: GW 2018 Data on file (50)

Mortality

The risk of death, especially SUDEP, is significantly elevated in patients with drug-resistant forms of epilepsy (19-21, 51, 52).

In the base case analysis, in addition to the all-cause age-dependent probabilities of death derived from the national life tables for England (53), the additional risk associated with DS-specific mortality was also considered. The latter was only applied for patients experiencing seizures.

The rates of SUDEP and non-SUDEP deaths were obtained from the published literature (8, 13) and were only applied to the health states where patients experienced seizures. Therefore, only the all-cause mortality based on the life tables was applied to patients in the seizure-free health state.

The 10-year mortality rate published in Cooper *et al.* (2016) (8) was converted to a 3-month probability and was applied to the >8 - ≤ 25 seizure frequency category (per cycle probability: 0.23%). As it is likely that patients with a higher number of seizures are at a greater risk of death compared to those with fewer seizures (also validated by clinical experts), a 3-month risk ratio, relative to the >8 - ≤ 25 seizure frequency category, was estimated for the <8 seizure frequency category (annual risk ratio: 0.6) and the >25 seizure frequency category (annual risk ratio: 1.4).

The calculated risk ratios ensured that the annual SUDEP rate for the >25 seizure frequency category was 1.3%; i.e. consistent with the upper limit of published SUDEP death rates (13). The reduced risk of SUDEP in the <8 seizure frequency category was assumed to be proportionally similar to the increased risk in the >25 seizure frequency category.

Table 20: Epilepsy-related mortality rates

	<12 years		**≥12 years**	
	SUDEP	Non-SUDEP	SUDEP	Non-SUDEP
Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]
≤ 8 seizures	[redacted]	[redacted]	[redacted]	[redacted]
>8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]
> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: SUDEP, Sudden unexpected death in epilepsy.
Reference: estimated based on Cooper 2016, Skluzacek 2011 (8, 13)

Adverse events

The most frequently occurring (events reported in ≥3% of patients treated with CBD and ≥1% of patients in the placebo arm) treatment-emergent adverse events of special interest were included in the base case analysis. Incidence rates were estimated from a pooled analysis of the Phase 3 trials for DS and LGS (GWEP1332B, GWEP1424, GWEP1414 and GWEP1423). The incidence rates estimated for the first cycle were assumed to remain the same for the duration of the analyses (see Table 21).

Table 21: Incidence rate of adverse events

	Rash	Somnolence	Fatigue	Lethargy	Sedation	Diarrhoea	Decreased appetite	Aggression	Irritability
CBD 10mg + CCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CBD 20 mg + CCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + CCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CBD, cannabidiol; CCM, current clinical management
Note: CBD dosage is per kilogram and per day
Selected AEs: Incidence of Common TEAEs (≥ 3% of Patients in the All CBD-OS Group) in Controlled DS and LGS Trials (Pool DS/LGS)
Reference: GW 2018 Summary of Clinical Safety (54)

Validation of clinical inputs in the model

A panel interview via phone and Webex was held with two clinical experts: Dr Dipak Ram and Dr Jeen Tan, consultant paediatric neurologists at the Royal Manchester Children's Hospital in the UK. In addition to this panel interview, a teleconference interview with Dr Richard Appleton, a consultant in paediatric neurology at Alder Hey Children's NHS Foundation in Liverpool in the UK, was also conducted. The experts were selected based on their extensive experience in treating patients with DS.

Dr Dipak Ram has declared no conflicts of interest. Dr Jeen Tan has declared no conflicts of interest. Dr Richard Appleton was the Principal Investigator at Alder Hey for studies GWEP1332 and GWEP1415 and has also participated in a GW LGS advisory board meeting.

Clinical experts were asked for inputs regarding current clinical practice for DS in the UK and to validate the model structure and inputs. The key clinical parameter values and assumptions validated or estimated by the experts included:

- Model target population;
- Model characteristics (Markov model structure, cycle length, time horizon);
- Patient characteristics;
- Definition of CCM;
- Treatment dosage, frequency and administration for drugs included in CCM;

- Long-term efficacy response in the treatment arm;
- Long-term discontinuation rates in the treatment arm;
- Resource use for treatment and control arm (e.g. GP and specialist visits, hospitalisations, adverse events);
- Additional risk of mortality;
- Costs associated with SUDEP and non-SUDEP.

Clinical experts were also asked to validate assumptions on the possibility of sustained benefits from placebo effect, beyond the trial period.

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

For patients with DS, in both the pivotal Phase 3 studies (GWEP1332B and GWEP1424), and the open-label extension study (OLE, GWEP1415), patients on cannabidiol or their caregivers were more likely to report an improvement in overall condition as measured on the caregiver global impression of change (CGIC) scale.

In GWEP1332B, compared to the placebo group, caregivers were significantly more likely to report an improvement in overall condition for patients receiving CBD as measured on the CGIC scale (odds ratio [OR] = 2.29, p = 0.0155). Similarly, in GWEP1424, caregivers reported an improvement in [redacted] of patients receiving CBD (CBD 20 mg/kg/day: [redacted]; CBD 10 mg/kg/day: [redacted]) compared to [redacted] in the placebo group (p = [redacted] [10 mg CBD vs. placebo]; p = [redacted] [20 mg CBD vs. placebo]).

This improvement has been consistently maintained. In the GWEP1415 OLE study, 88% of patients or their caregivers were reporting an improvement after 24 and 48 weeks of exposure to CBD (55).

CBD does not have a detrimental effect on the QoL of patients with DS. The GWEP1332B and GWEP1424 trials assessed patient-reported outcomes, and found no significant differences between cannabidiol and current clinical management in Quality of Life in Childhood Epilepsy (QOLCE), sleep disruption, Epworth Sleepiness Scale or Vineland II score (Table 22) (27).

Table 22: Differences between PRO outcome scores between CBD and placebo groups in GWP1332B (27) and GWEP1424 (28)

PRO instrument	GWP1332B	GWEP1424	
	Difference between cannabidiol and placebo groups at study end	Difference between cannabidiol 10 mg/kg/day and placebo groups at study end	Difference between cannabidiol 20mg/kg/day and placebo groups at study end
Sleep disruption score (negative value favours cannabidiol)	-0.4 (95%CI -1.5 to 0.7)	[redacted]	[redacted]
Epworth Sleepiness Scale (negative value favours cannabidiol)	1.5 (95%CI -0.2 to 3.2)	[redacted]	[redacted]
Vineland II score (negative value favours cannabidiol)	-2.6 (95%CI -6.8 to 1.6)	[redacted]	[redacted]
Quality of Life in Childhood Epilepsy (QOLCE) score (positive value favours cannabidiol)	1.5 (95%CI -3.8 to 6.8)	[redacted]	[redacted]

There are a number of challenges in collecting HRQoL data in patients with refractory epilepsies such as DS. There are no validated disease-specific instruments. The patients with DS in the cannabidiol clinical trials were children and young adults with a broad spectrum of abilities, many of whom were unable to communicate effectively, so many patients were not able to complete the questionnaires. The PRO measures used in the clinical trials were not considered appropriate for inclusion in the cost-utility analysis.

Mapping

Not applicable.

Health-related quality-of-life studies

The systematic literature review identified six publications that were relevant to the reference case of patients with DS who were either receiving a drug therapy of interest or were reporting on quality of life regardless of treatments. None of the studies estimated utilities for health states defined by number of seizures and seizure-free days.

The studies are summarised in Table 53 in Appendix H. Detailed descriptions of the search strategy and extraction methods are also provided in Appendix H.

Adverse reactions

No studies reported utility values associated with adverse reactions to cannabidiol. The SMC 2017 cost-utility model (35) reported utility values for a maintenance health state where the patient had discontinued due to adverse events (utility value of 0.516), but the HTA appraisal report did not report utility values for specific adverse events.

In the model, adverse events were associated with a cost. No disutility was considered for any of the adverse events used in the model as it is unlikely to have a significant impact on the ICERs.

Health-related quality-of-life data used in the cost-effectiveness analysis

As mentioned previously, no relevant utility values were identified from the systematic literature review. Therefore, an online study was conducted whereby patients and/or carers of DS or epilepsy patients were asked to complete a quality of life questionnaire and score patient vignettes (representing the health states used in the cost-utility model) using a VAS scale. A similar study was conducted for LGS.

Vignette study overview

The quality of life questionnaire included patient vignettes that were based on the health states included in the cost-utility model (Table 23) and on the clinical/ demographic characteristics of patients from the cannabidiol Phase 3 pivotal trials. As mentioned in Section.B.3.2, the *de novo* cost-utility model included heath states based on three distinct severity groups (i.e. ≤ 8, > 8 - ≤ 25, > 25 convulsive seizures per month) and each severity group was further categorised into three subgroups based on the number of seizure-free days experienced (i.e. ≤ 18 days, > 18 - ≤ 24 days, > 24 days seizure-free per month). The upper and lower bounds of the severity groups and the seizure-free categories were selected to ensure that the clinical outcomes for the different severity groups were estimated with sufficient statistical power.

However, as the quality of life of individuals along each range may vary, it was considered important to include additional health states to account for the mid-point

of the range, for each severity group and for the three ‘seizure-free days’ subgroups. In total, 23 health states were developed.

In addition to the health states of patients, vignettes assessing the quality of life of caregivers were also included in the questionnaire. Three additional vignettes for carers of patients with a moderately severe health state (32 convulsive seizures per month and 18 seizure-free days), a less severe health state (16 convulsive seizures per month and 21 seizure-free days) and a convulsive seizure-free state were included to determine the impact of disease severity on caregiver quality of life.

Table 23: Health states included in the survey

	Health state	Number of seizures in an average month*	Number of seizure-free days in an average month
Hypothetical patient QoL assessment	DS_32_4	32 seizures	4 seizure-free days
	DS_32_8	32 seizures	8 seizure-free days
	DS_32_12	32 seizures	12 seizure-free days
	DS_32_18	32 seizures	18 seizure-free days
	DS_32_21	32 seizures	21 seizure-free days
	DS_32_24	32 seizures	24 seizure-free days
	DS_32_28	32 seizures	28 seizure-free days
	DS_25_8	25 seizures	8 seizure-free days
	DS_25_12	25 seizures	12 seizure-free days
	DS_25_18	25 seizures	18 seizure-free days
	DS_25_21	25 seizures	21 seizure-free days
	DS_25_24	25 seizures	24 seizure-free days
	DS_25_28	25 seizures	28 seizure-free days
	DS_16_18	16 seizures	18 seizure-free days
	DS_16_21	16 seizures	21 seizure-free days
	DS_16_24	16 seizures	24 seizure-free days
	DS_16_28	16 seizures	28 seizure-free days
	DS_8_24	8 seizures	24 seizure-free days
	DS_8_28	8 seizures	28 seizure-free days
	DS_6_24	6 seizures	24 seizure-free days
	DS_6_28	6 seizures	28 seizure-free days
	DS_4_28	4 seizures	28 seizure-free days
	DS_no_seizures	No seizures	30 seizure-free days
Hypothetical caregiver QoL assessment	DS_CG_32_18	32 seizures	18 seizure-free days
	DS_CG_16_21	16 seizures	21 seizure-free days
	DS_CG_no_seizures	No seizures	30 seizure-free days

*All seizures refer to convulsive seizures
Abbreviations: CG, caregiver; DS, Dravet syndrome; QoL, quality of life

The visual analogue scale (VAS) was considered the most appropriate method to measure quality of life, due to the respondent burden of evaluating so many health states using EQ-5D questionnaires.

The NICE Decision Support Unit states that alternative methods to elicit utility values, including VAS, are accepted when there are no data based on validated measures and as long as the QoL values are generated based on the full health-death scale (56).

Study Methodology

The following sections present the study methods and approach in detail:

1. Vignettes development

Vignettes for the questionnaire were developed based on the clinical and demographic characteristics of patients included in the Phase 3 pivotal trial, GWEP1332B (data from the GWEP1424 were not available at the time this study was undertaken).

Given the large number of health states, it was considered appropriate to develop vignettes that were easy to understand and highlighted the main clinical features of a patient with DS. The questionnaire included a main narrative vignette to provide the background on a hypothetical patient with DS, and included information on the following dimensions: age, number of convulsive seizures in a month, number of seizure-free days in a month, number of previous and current treatments, and current health condition. Different scenarios were then presented using that same patient (one for each health state), and these included a short description on the number of convulsive seizures and seizure-free days that the hypothetical patient experienced in an average month (30 days). Respondents were asked to score these health states on a VAS from 0 (worst health) to 100 (best health).

A similar approach was used to develop the caregiver vignettes. Refer to the questionnaire in Appendix H.

2. Survey development

The survey was developed using an online platform, Survey Monkey®, and was structured as below (the full questionnaire is included in Appendix H):

- Consent form;
- Screening: the survey was completed by patients with epilepsy (LGS, DS and other epilepsy conditions) and caregivers (details on sample selection are presented below). The screener allowed only these respondents to complete the survey;

- Personal characteristics: questions on personal characteristics were included (such as gender, age, occupation, education level etc.);
- Disease-specific questions: respondents were asked about their own health condition or that of the patient for whom the caregiver is responsible;
- Own QoL assessment;
- Survey instructions: respondents were provided with a set of instructions on what the survey is assessing and how the respondent is to perform the QoL assessment;
- Hypothetical QoL assessment of a DS patient: respondents were provided with a narrative vignette and were asked to evaluate 23 health states;
- Hypothetical QoL assessment of a caregiver of a patient with DS: respondents were provided with a narrative vignette for a caregiver and were asked to evaluate three health states.

3. Survey respondents

As DS is a rare condition, and most patients are not able to participate in surveys due to the nature of their illness or because of their age, it was considered appropriate for caregivers and patients with epilepsy to provide QoL evaluations. Members of the general public were not recruited as patients with epilepsy and caregivers are more likely to have a better understanding of the impact of seizures and seizure-free days on QoL and wellbeing.

The survey was shared with two UK patient associations who advertised the questionnaire in their monthly newsletter, on their website or shared it with their members by word-of-mouth. The eligibility criteria for participation included:

- Individuals with DS or any epilepsy condition;
- Caregivers of individuals with DS or any epilepsy condition;
- UK residents only.

Participation and completion of the survey was voluntary, and no payments or rewards were paid to individuals who completed the survey. All responses were anonymous.

To ensure a sufficient number of completed responses, respondents who met the eligibility criteria were also identified through a vendor specialising in patient surveys.

4. Pilot test

The questionnaire was tested by four individuals: one caregiver of a patient with DS and one adult with epilepsy in the UK and one caregiver of a patient with DS and one epilepsy patient association representative in France. As the d*e novo* cost-utility model considers two age-groups: <12 years and ≥12 years, two versions of the survey were developed for the pilot, to investigate if the VAS scores were substantially influenced by the patient's age.

As patients with DS experience the highest burden in childhood and early adulthood, it was considered appropriate to compare the differences in the VAS scores for a hypothetical DS patient aged 11 and a DS patient aged 15 years old. Therefore, two surveys, one for an 11-year-old patient and a second for a patient aged 15 years, were developed and tested. With the exception of the age of the hypothetical individual presented in the main descriptive vignette, the two surveys were identical.

Each participant completed the survey for either the patient with DS aged 11 or the patient with DS aged 15 years old. To determine whether age had a significant impact on the QoL valuations, the VAS scores reported for the two surveys were compared (i.e. 11 years old vs. 15 years old) and the absolute difference in the VAS scores for each health state was calculated. Significant differences in the valuations (i.e. greater 30% variation) were observed for only 8 health states out of 23.

Following the pilot test, all participants were requested to participate in a follow-up interview. Of the four individuals that completed the pilot survey, three individuals took part in the follow-up discussions. When asked if they would have evaluated the health states differently for a younger or older patient with DS (depending on the survey they completed), all participants confirmed that age as such would not impact their QoL scores and that, in general, QoL is similar in younger and older

children with DS. Based on these valuations and feedback, it was decided to proceed with the survey for the patient with DS aged 11 years old.

Further linguistic and design improvements were made on the survey based on caregivers' feedback. The results of the pilot tests are presented in Appendix H.

Study Results

A total of [redacted] patients and [redacted] caregivers completed the questionnaire on Survey Monkey®. An additional [redacted] respondents were recruited through a vendor ([redacted] patients and [redacted] caregivers). In total, there were [redacted] respondents; [redacted] caregivers and [redacted] patients. Recruitment for the survey started in October 2018 and closed in November 2018. Most of the respondents were aged between 30 and 50 years, and 80% were women. [redacted] out of [redacted] respondents were either patients with DS or caregivers responsible for a patient with DS. Detailed responses on patient and caregiver characteristics are presented in Appendix H.

The average VAS scores increased as the number of convulsive seizures experienced per month decreased, highlighting that a higher seizure frequency has a negative impact on QoL in patients with DS. For example, the average VAS score for the health state defined by 32 convulsive seizures and 8 seizure-free days in an average month was [redacted], while the VAS score for 25 convulsive seizures and 8 seizure-free days was [redacted]. Similarly, higher number of seizure-free days per month was associated with higher VAS scores. The average VAS scores for all health states are presented in Appendix H.

Caregivers were also asked to evaluate three additional health states to investigate the impact DS has on caregivers' QoL. The results show that caregivers' QoL is also impacted by the frequency of convulsive seizures and number of seizure-free days; health states with higher seizure frequency and a lower number of seizure-free days were associated with lower VAS scores and vice versa.

VAS scores conversion to utility values

The average VAS scores obtained in the survey were converted to values between 0 and 1 for base-case analysis:

$$U_{HS_i} = VAS_{HS_i}/100$$

where U_{HS_i}represents the value associated with health state (HS) *i* and $VAS_{HS_i}$is the average score obtained in the survey for *HS i*.

Existing literature provides a number of conversions from VAS scores to time trade-off (TTO) and standard gamble (SG); however, there is no consensus on which is the most appropriate mapping formula. For this reason, the VAS scores (converted to a 0 to 1 scale) were considered for the base-case analysis and the mapped standard gamble utility values were included in the sensitivity analysis. VAS scores have been used in cost-utility studies; for example, Cheng *et al*. (57) used VAS scores converted into values ranging from 0 to 1 in a cost-utility analysis of cochlear implants in children.

Published studies also confirm that VAS scores provide a conservative estimation of QoL, compared to TTO, EQ-5D and SG (57-60). Furthermore, utilities mapped from VAS scores are lower than utility values elicited with EQ-5D, TTO and SG.

The conversion formulas were taken from Torrance *et al*. 2001 (61) who reported eight algorithms to convert VAS scores into SG utility values. The conversion formulas from VAS to SG are presented in Table 24.

Table 24: Mapping algorithms: VAS to SG utilities

Conversion	Formula
VAS	Survey score / 100
SG1	$VAS^{0.599}$
SG2	$VAS^{0.47}$
SG3	$1-(1-VAS)^{2.9}$
SG4	$1-(1-VAS)^{2.7}$
SG5	$1-(1-VAS)^{2.4}$
SG6	$1-(1-VAS)^{2.3}$
SG7	$1-(1-VAS)^{2.2}$
SG8	$1-(1-VAS)^{1.6}$
Assumptions: Death score = 0. full health state = 'No seizures' state. Reference: Torrance 2001 (61)	

Estimates included in the base case analysis

The mean VAS scores for the 23 health states were used to calculate the QoL values associated with the nine health states in the cost-effectiveness model.

The VAS scores of the health states corresponding to each severity range were averaged to obtain the score associated with each of the nine health states. For example, the VAS score for the health state ≤8 convulsive seizures per month and between 18 and 24 seizure-free days was obtained by averaging the VAS scores for 8 convulsive seizures and 24 seizure-free days per month and 6 convulsive seizures and 24 seizure-free days per month.

For the 'No seizures' health state, the mean VAS score estimated from the survey was included in the model (Table 25).

Table 25: Summary of mean VAS scores for cost-effectiveness analysis

Health state	State	VAS scores Mean (SE)	Justification (average of HS in utility study)
No seizures*	No seizures	[redacted]	'No seizure'
≤ 8 seizures	≤ 18 seizure-free days†	[redacted]	NA
	> 18 - ≤ 24 seizure-free days	[redacted]	DS_8_24. DS_6_24
	> 24 seizure-free days	[redacted]	DS_8_28. DS_6_28. DS_4_28
>8 - ≤ 25 seizures	≤ 18 seizure-free days	[redacted]	(DS_25_8. DS_25_12. DS_25_18). DS_16_18
	> 18 - ≤ 24 seizure-free days	[redacted]	(DS_25_21. DS_25_24). (DS_16_21. DS_16_24)
	> 24 seizure-free days	[redacted]	DS_25_28. DS_16_28
> 25 seizures	≤ 18 seizure-free days	[redacted]	DS_32_4. DS_32_8. DS_32_12
	> 18 - ≤ 24 seizure-free days	[redacted]	DS_32_18. DS_32_21
	> 24 seizure-free days	[redacted]	DS_32_24. DS_32_28

*All seizures refer to convulsive seizures
†This health state is included for completeness; no values were obtained as this is not a possible state
Abbreviations: DS, Dravet syndrome; HS, health state; NA, not applicable; SE, standard error

Strengths and Limitations

To our knowledge, this is the first study to measure QoL in relation to the number of seizures and seizure-free days in patients with DS. Publication of this methodology, analysis and results is planned.

Our analysis has shown that both seizure frequency and seizure-free days have a substantial impact on the QoL for patients with DS and caregivers.

The main limitation of this study is that the analyses are based on [redacted] responses. This is due to the fact that DS is a rare condition and it was difficult to identify and recruit patients with DS or any epilepsy condition. The survey vendors also had access to a limited number of patients with epilepsy in the UK ([redacted] individuals).

Despite this, the study found the number of seizure-free days to have a substantial impact on QoL, with both patients and caregivers reporting higher VAS scores when a patient experienced more seizure-free days per month. This methodology was also conducted in France for DS with comparable results.

Although the study could have included more health states to accommodate the full range of seizure and seizure-free days, this would have substantially increased respondent burden. Therefore, only the mid-point of the range for each severity group and for the three 'seizure-free days' subgroups was considered.

The VAS was used to elicit QoL data. Although VAS scores are not considered to be the most appropriate estimates for cost-utility analyses as they are not based on choice theory, SG and TTO outcomes would have required face-to-face interviews and would have proved extremely challenging to implement given the difficulty in recruiting patients with DS and caregivers and due to the large number of health states (62). In addition, the EQ-5D questionnaire is often not sensitive enough to measure subtle differences in health (58-60). For similar reasons, the generic EQ-5D questionnaire was also not considered appropriate.

To test the external validity of our results, the VAS scores for the seizure-free health state were compared with the utility values reported in a cost-utility study by Elliot *et al.* 2018 (37) and included in an SMC submission (35) (refer to HRQoL SLR

summary and Appendix H). This study obtained QoL estimates from Verdian *et al.* (2008) (63) and assumed a utility of 0.70 for the seizure-free health state as the original study did not elicit utility values for this health state. However, the utility values obtained in the original study were measured from LGS patients and not DS.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The systematic literature review identified eighteen publications that reported cost or resource use data for patients with DS. Those studies are summarised in Table 63 and Table 64 in Appendix I. Detailed descriptions of the search strategy and extraction methods are also provided in Appendix I.

None of the studies identified reported resource use or costs for health states defined by number of seizures and seizure-free days and therefore could not be included in the cost-utility analysis.

Intervention and comparators' costs and resource use

Drug resource use

Dosages for all AEDs and cannabidiol are presented in Table 26, and are based on the approved licensed dose for DS (46, 64-68).

For drugs where the approved licensed dose varied for adults and children, the paediatric dose was used to estimate the drug resource use for the proportion of patients aged <12 years and the adult dose was used to estimate the drug use for the proportion of patients aged >12 years.

As all drugs considered for this analysis (cannabidiol and the AEDs included as part of CCM) are administered orally, treatment administration costs were not considered. Furthermore, as monitoring requirements are similar for cannabidiol and the AEDs considered as part of the CCM, resource use and costs associated with routine patient monitoring were not considered. These assumptions were also validated by clinical experts.

Table 26: Drug dose - CBD and concomitant therapies

Drug	<12 years				≥12 years				Reference
	Average dose (mg/kg/day)	Lower bound	Upper bound	Comments from SmPC	Average dose (mg/kg/day)	Lower bound	Upper bound	Comments from SmPC	
Cannabidiol	10.00	N/A[ǂ]	N/A[ǂ]	"the dose should be increased to a therapeutic dose of 5 mg/kg twice daily (10 mg/kg/day). […] based on individual clinical response and tolerability, each dose can be further increased to a recommended maximum therapeutic dose of 10 mg/kg twice daily (20 mg/kg/day)."	10.00	N/A[ǂ]	N/A[ǂ]	"the dose should be increased to a therapeutic dose of 5 mg/kg twice daily (10 mg/kg/day). […] based on individual clinical response and tolerability, each dose can be further increased to a recommended maximum therapeutic dose of 10 mg/kg twice daily (20 mg/kg/day)."	GW 2018 SmPC (46)
Clobazam	0.65	0.30	1.00	"Paediatric patients aged 6 years and above: A maintenance dose of **0.3 to 1mg/kg body** weight daily is usually sufficient".	0.45	0.36** (20/55)	0.55** (30/55)	"Adults: In epilepsy a starting dose of **20-30mg daily** is recommended. increasing as necessary up to a maximum of 60mg daily."	Auden McKenzie. 2008 (65)
Stiripentol	30.00	10.00	50.00	"For Child 3–17 years Initially **10 mg/kg** daily in 2–3 divided doses. increased to up to **50 mg/kg daily** in 2–3 divided doses. titrated over minimum of 3 days."	50.00	50.00	50.00	"For Child 3–17 years Initially 10 mg/kg daily in 2–3 divided doses. increased to up to **50 mg/kg daily** in 2–3 divided doses. titrated over minimum of 3 days."	Biocodex 2017 (68)
Valproate	27.50	20.00	35.00	"Children **over 20 kg** […] usually within the range **20 – 30 mg/kg body weight per day**. […]this range the dose may be increased to **35 mg/kg body weight per day"**	25.00	20.00	30.00	"Adults: […] This is generally within the dosage range 1000 – 2000 mg per day. i.e. **20 – 30 mg/kg/day** body weight."	Sanofi 2006 (64)
Topiramate	7.00	5.00	9.00	Paediatric population (children aged 2 years and above) The recommended total daily dose of Topamax (topiramate) as adjunctive therapy is approximately **5 to 9 mg/kg/day**	5.45	3.64** (200/55)	7.27** (400/55)	"Adults In clinical trials as adjunctive therapy. 200 mg was the lowest effective dose. The usual daily dose is **200-400 mg** in two divided doses."	Janssen-Cilag 2010 (66)

Drug	<12 years				≥12 years				Reference
	Average dose (mg/kg/day)	**Lower bound**	**Upper bound**	**Comments from SmPC**	**Average dose (mg/kg/day)**	**Lower bound**	**Upper bound**	**Comments from SmPC**	
Levetiracetam	40.00	20.00	60.00	"Dosing adjustment for infants. children and adolescent patients weighing less than 50 kg with impaired renal function: Group Normal renal function : 10 **to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily"**	36.36	18.18** (500*2/55)	54.55** (1500*2/55)	"Monotherapy for adults and adolescents from 16 years of age The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of **500 mg twice daily** after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. **The maximum dose is 1500 mg twice daily**."	UCB Pharma 2015 (67)

*Assuming an average weight of 25 kg
** Assuming an average weight of 55 kg
[Ŧ] The average dose is estimated as explained in section B.3.3
Abbreviations: CBD, cannabidiol; SmPC, summary of product characteristics

Evidence suggests that some patients receiving cannabidiol may also benefit from a reduction in the dose of adjuvant concomitant AEDs. The proportion of patients receiving a dose reduction was obtained from Laux *et al.* (2017) (69) and the percentage reduction in the dose of the AEDs was based on clinical opinion and was assumed to be 33%.

Table 27: Dose reduction of concomitant therapies

Drug	<12 years		≥12 years		Reference
	% of patients	% of dose	% of patients	% of dose	
Clobazam	46.00%	-33.33%	46.00%	-33.33%	Laux et al. 2017 (69) and clinical opinion
Stiripentol	0.00%	N/A	0.00%	N/A	Clinical opinion
Valproate	52.00%	-33.33%	52.00%	-33.33%	Laux et al. 2017 (69) and clinical opinion
Levetiracetam	16.00%	-33.33%	16.00%	-33.33%	Laux et al. 2017 (69) and clinical opinion
Topiramate	0.00%	N/A	0.00%	N/A	Clinical opinion

Abbreviations: N/A, Not applicable

Drug acquisition costs

Costs for the AEDs were obtained from the NHS Electronic Drug Tariff 2018 (70). As the AEDs are available in different formulations, a weighted average based on prescribing proportions obtained from the Prescription Cost Analysis (71) was estimated to determine the cost per mg. The price of cannabidiol is [redacted].

Table 28: Drug acquisition costs - CBD and concomitant therapies

Drug	Formulation	Pack size	Cost per Pack Drug tariff price	Dose	Cost per mg	Prescription share	Average cost per mg
Cannabidiol	Oral solution	100 ml	[redacted]	100 mg/ml	[redacted]	[redacted]	[redacted]
Clobazam	Oral suspension	150 ml	£90.00	1mg / ml	£0.6000	5.56%	£0.0559
		150 ml	£95.00	2 mg/ ml	£0.3167	3.64%	
	Tablet	30	£3.64	10 mg	£0.0121	90.77%	
Stiripentol	Capsules	60	£284.00	250 mg	£0.0189	17.46%	£0.0180
		60	£493.00	500 mg	£ 0.0164	11.28%	
Valproate	Gastro resistant capsule	100	£3.68	150	£0.0002	8.97%	£0.0002
		100	£7.35	300	£0.0002	23.08%	
		100	£12.25	500	£0.0002	67.95%	
		90	£17.08	250	£0.0008	0.00%	

Drug	Formulation	Pack size	Cost per Pack Drug tariff price	Dose	Cost per mg	Prescription share	Average cost per mg
	Gastro resistant tablet	90	£34.11	500	£0.0008	0.00%	
Levetiracetam	Granules sachet	60	£22.41	250 mg	£0.0015	0.02%	£0.0002
		60	£39.46	500 mg	£0.0013	0.02%	
		60	£76.27	1000 mg	£0.0013	0.01%	
	Tablet	60	£3.19	250 mg	£0.0002	29.38%	
		60	£4.77	500 mg	£0.0002	38.81%	
		60	£6.66	750 mg	£0.0001	8.01%	
		60	£8.38	1000 mg	£0.0001	16.40%	
	Solution for infusion	10 vials	£127.31	500 mg/ 5 ml	£0.12731	0.02%	
	Oral solution	300 ml	£7.78	100 mg/ ml	£0.0013	0.02%	
Topiramate	Tablet	60	£5.53	25 mg	£0.0037	35.60%	£0.0044
		60	£9.06	50 mg	£0.0030	29.49%	
		60	£13.88	100 mg	£0.0023	20.13%	
		60	£47.50	200 mg	£0.0040	4.48%	
	Capsule	60	£26.28	15 mg	£0.0292	1.79%	
		60	£12.54	25 mg	£0.0084	4.90%	
		60	£55.02	50 mg	£0.0183	3.60%	

Abbreviation: CBD, cannabidiol.
References: SmPC, BNF 2018 (46, 72)

Health-state unit costs and resource use

In the absence of any published data on the annual resource use based on the severity of seizures, health-state specific resource use estimates for physician visits and hospitalisations were obtained from UK clinical experts.

Clinical experts indicated that older patients were more likely to be institutionalised as parents find it increasingly difficult to cope with behavioural disturbances and impaired cognitive development and functioning. Therefore, a conservative approach was taken: the probability of being institutionalised and the associated costs were applied only to patients aged 18 years and older. Evidence from the literature suggests that the decline in cognitive functioning is likely to be associated with the symptomatic level of epileptic activity in early age (73-75), so the risk of being institutionalised was not applied to patients in the seizure-free group.

Table 29 summarises the annual health-state specific resource use for the two age groups considered in the analysis.

Table 29: Annual resource use associated to each health state by age group

		<12 years	≥12 years	Reference
Visit Costs				
Nurse Visit	Seizure-Free	2.00	2.00	Clinical opinion
	≤ 8 seizures	4.00	2.00	Clinical opinion
	> 8 - ≤ 25 seizures	8.00	4.80	Clinical opinion
	> 25 seizures	12.00	12.00	Clinical opinion
Paediatric Epileptologist (<12 years) / Neurologist (≥12 years) Visit	Seizure-Free	1.00	0.50	Clinical opinion
	≤ 8 seizures	2.00	0.50	Clinical opinion
	> 8 - ≤ 25 seizures	4.00	0.50	Clinical opinion
	> 25 seizures	6.00	3.00	Clinical opinion
Paediatrician Visit	Seizure-Free	2.00	0.00	Clinical opinion
	≤ 8 seizures	4.00	0.00	Clinical opinion
	> 8 - ≤ 25 seizures	8.00	0.00	Clinical opinion
	> 25 seizures	12.00	0.00	Clinical opinion
Emergency department	Seizure-Free	0.00	0.00	Clinical opinion
	≤ 8 seizures	6.00	3.00	Clinical opinion
	> 8 - ≤ 25 seizures	12.00	6.00	Clinical opinion
	> 25 seizures	24.00	12.00	Clinical opinion
Phone Call Follow-up	Seizure-Free	0.00	0.00	Clinical opinion
	≤ 8 seizures	2.00	1.00	Clinical opinion
	> 8 - ≤ 25 seizures	6.00	2.5	Clinical opinion
	> 25 seizures	12.00	6.00	Clinical opinion
Orthopaedic surgeon	Seizure-Free	0.00	0.00	Clinical opinion
	≤ 8 seizures	0.00	0.00	Clinical opinion
	> 8 - ≤ 25 seizures	0.00	0.00	Clinical opinion
	> 25 seizures	0.00	0.00	Clinical opinion
Dentist	Seizure-Free	2.00	2.00	Clinical opinion
	≤ 8 seizures	2.00	2.00	Clinical opinion
	> 8 - ≤ 25 seizures	2.00	2.00	Clinical opinion
	> 25 seizures	2.00	2.00	Clinical opinion
Hospitalisation*				
Hospitalisation	Seizure-Free	0.00	0.00	Clinical opinion
	≤ 8 seizures	3.00	1.50	Clinical opinion
	> 8 - ≤ 25 seizures	6.00	3.00	Clinical opinion
	> 25 seizures	12.00	6.00	Clinical opinion
Institutionalisation**				
Institutionalisation	Seizure-Free	0.00%	0.00%	Clinical opinion
	≤ 8 seizures	0.00%	10.00%	Clinical opinion
	> 8 - ≤ 25 seizures	0.00%	10.00%	Clinical opinion
	> 25 seizures	0.00%	10.00%	Clinical opinion
Disease Management - Rescue Medication				
Rescue Medication by intake	Seizure-Free	0.00	0.00	Clinical opinion
	≤ 8 seizures	12.00	6.00	Clinical opinion
	> 8 - ≤ 25 seizures	24.00	12.00	Clinical opinion
	> 25 seizures	48.00	24.00	Clinical opinion

*Hospitalisation: according to the UK KOLs interviewed, 95% of the patients hospitalised will be admitted to a general ward, the rest (5%) will go to the Intensive Care Unit.
** Only patients over 18 are assumed to be institutionalised

The costs associated with physician visits and inpatient hospitalisation are summarised in Table 30 and were obtained from the PSSRU 2017 (76) and the NHS reference cost schedule 2016–2017 (77).

Table 30: Costs of resource use per age category

	<12 years	≥12 years	Reference
Visit Costs			
Nurse Visit	£44.00	£44.00	PSSRU 2017 (76) Epilepsy nurse specialist visit: 10.1 Nurses - Band 6 (page 159)
Paediatric Epileptologist (<12 years) / Neurologist (≥12 years) Visit	£366.00	£167.00	NHS Reference Costs 2016-17 (77) 1) All NHS trusts and NHS foundation trusts - Outpatient Attendances Data. Service code: 421 - Paediatric Neurology TOTAL COST 2) All NHS trusts and NHS foundation trusts - Outpatient Attendances Data. Service code: 400 – Neurology Total Cost
Paediatrician Visit	£196.00	£0.00	PSSRU 2017 (76) 6. Services for children and their families – 6.1 NHS reference costs for children's health services – Paediatric consultant-led outpatient attendances: £196 (page 83)
Emergency department	£237.00	£237.00	NHS Reference Costs 2016-17 (77) All NHS trusts and NHS foundation trusts - Outpatient Attendances Data. Service code: 421 - Paediatric Neurology Total Cost
Phone Call Follow-up (Paediatric Epileptologist [<12 years] / Neurologist [≥12 years] Visit)	£258.00	£107.00	NHS Reference Costs 2016-17 (77) 1) Consultant Led / Service Code 421: Paediatric Neurology / Code WF01C: Non-Admitted Non-Face-to-Face Attendance. Follow-up 2) Consultant Led / Service Code 400: Neurology / Code WF01C: Non-Admitted Non-Face-to-Face Attendance. Follow-up
Orthopaedic surgeon	£128.00	£119.00	NHS Reference Costs 2016-17 (77) 1) Outpatient Attendances Data - Service Code 214 "Paediatric Trauma and Orthopaedics" 2) Outpatient Attendances Data - Service Code 110 "Trauma & Orthopaedics"
Dentist	£127.00	£127.00	PSSRU 2017 (76) 10.5 NHS Dentist - Performer only. £127 per hour of patient contact (page 165)
Hospitalisation Costs			
Hospitalisation in general ward	£597.00	£460.00	NHS Reference Costs 2016-17 (77) 1) Non Elective Short Stay - Code PR02A/PR02B/PR02C: Paediatric Epilepsy Syndrome with CC Score 0 / Score 1-5 / Score 6+ 2) Non Elective Short Stay - Code [AA26C < > AA26H] : Muscular. Balance. Cranial or Peripheral Nerve Disorders. Epilepsy or Head Injury. with CC [Score 0-2 < > Score 15+]
Hospitalisation in ICU	£1,583.38	£1,299.32	NHS Reference Costs 2016-17 (77) 1) Critical Care - PD Paediatric - Code [XB01Z < > XB09Z] 2) Critical Care - CCU05 Neurosciences adult patients predominate - Code [XC01Z < > XC07Z]
Institutionalisation Costs			
Institutionalisation	£0.00	£1,337.00	PSSRU 2017 (76) 4.3 Residential care homes for adults requiring.
Disease Management - Rescue Medication			
Cost of Rescue Medication by intake (Rescue medication consists of buccal midazolam - given to all patients across all ages)	£34	£34	BNF 2018 (72) Midazolam. Average of: For Child 1–4 years / For Child 5–9 years / For Child 10–17 years / For Adult

Abbreviations: BNF, British National Formulary; ICU, Intensive Care Unit; NHS, National Health Service; PSSRU, Personal Social Services Research Unit

Mortality cost

Due to the lack of published evidence on the costs associated with death due to DS, the resource use associated with SUDEP and non-SUDEP deaths were based on clinical opinion. Costs associated with emergency department visits and intensive care unit were obtained from the NHS reference cost schedule 2016-2017 (77).

Table 31: Mortality costs - SUDEP and non-SUDEP causes

	<12 years		≥12 years		Reference
	Resource use	Cost	Resource use	Cost	
SUDEP	None	£0	None	£0	Clinical opinion
Non-SUDEP	1 visit to the ED	£237.00	1 visit to the ED	£237.00	Clinical opinion and NHS Reference Costs 2016-17 (77) All NHS trusts and NHS foundation trusts - Outpatient Attendances Data. Service code: 421 - Paediatric Neurology TOTAL COST
	7 days in ICU	£11,084.00 (7 x £1,583.00)	7 days in ICU	£9,095.00 (7 x £1,299.00)	Clinical opinion and NHS Reference Costs 2016-17 (77) 1) Critical Care - PD Paediatric - Code [XB01Z < > XB09Z] 2) Critical Care - CCU05 Neurosciences adult patients predominate - Code [XC01Z < > XC07Z]

Abbreviation: ED, Emergency Department; ICU, Intensive Care Unit, SUDEP, Sudden unexpected death in epilepsy.

Adverse reaction unit costs and resource use

Clinical experts indicated that the commonly identified treatment emergent adverse events (TEAEs) were unlikely to be resource intensive and recommended including in the analysis one visit to a specialised nurse following an AE. The cost of a specialised nurse is £44 per visit and was taken from the PSSRU 2017 (76).

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

Table 32: Summary of base-case variables applied in the economic model

Variable				Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Global settings						
Time horizon				15 years	N/A	B.3.2. Based on NICE recommend-ations (Table 14)
Cycle length				3 months	N/A	
Discount rate - efficacy				3.5%	[0-6%]	
Discount rate - costs				3.5%	[0-6%]	
Cohort definition						
Age groups						
Age group <12 years		2-5 years		[redacted]	N/A	B.3.3. Based on the PLD analysis of the GWEP1332 Part B and GWEP 1424 studies (Table 15)
		6-11 years		[redacted]	N/A	
Age group ≥12 years		12-17 years		[redacted]	N/A	
		18-55 years		[redacted]	N/A	
Demographic characteristics						
Age group <12 years		2-5 years	Mean age	[redacted]	[redacted]	B.3.3. Based on the PLD analysis of the GWEP1332 Part B and GWEP 1424 studies (Table 15)
			Mean weight	[redacted]	[redacted]	
		6-11 years	Mean age	[redacted]	[redacted]	
			Mean weight	[redacted]	[redacted]	
Age group ≥12 years		12-17 years	Mean age	[redacted]	[redacted]	
			Mean weight	[redacted]	[redacted]	
		18-55 years	Mean age	[redacted]	[redacted]	
			Mean weight	[redacted]	[redacted]	
Disease characteristics						
Age group <12 years	Frequency of seizures per 28 days	≤ 8 convulsive seizures		[redacted]	N/A	B.3.3. Based on the PLD analysis of the GWEP1332 Part B and GWEP 1424 studies (Table 15)
		> 8 - ≤ 25 convulsive seizures		[redacted]	N/A	
		> 25 convulsive seizures		[redacted]	N/A	
	Frequency of number of days without seizures	≤ 8 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 8 - ≤ 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	

Variable				Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
			> 24 seizure free days	[redacted]	N/A	
Age group ≥12 years	Frequency of seizures per 28 days	≤ 8 convulsive seizures		[redacted]	N/A	
		> 8 - ≤ 25 convulsive seizures		[redacted]	N/A	
		> 25 convulsive seizures		[redacted]	N/A	
	Frequency of number of days without seizures	≤ 8 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 8 - ≤ 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
Treatments used						
Age group <12 years	Cannabidiol dosage		10 mg	[redacted]	N/A	B.3.3. GW market research (Table 16) (44)
			20 mg	[redacted]	N/A	
	Concomitant therapies		Valproate	[redacted]	N/A	
			Clobazam	[redacted]	N/A	
			Stiripentol	[redacted]	N/A	
			Topiramate	[redacted]	N/A	
			Levetiracetam	[redacted]	N/A	
Age group ≥12 years	Cannabidiol dosage		10 mg	[redacted]	N/A	
			20 mg	[redacted]	N/A	
	Concomitant therapies		Valproate	[redacted]	N/A	
			Clobazam	[redacted]	N/A	
			Stiripentol	[redacted]	N/A	
			Topiramate	[redacted]	N/A	
			Levetiracetam	[redacted]	N/A	
Transition probabilities						
CCM – Back to baseline after the end of the trial period				After 1 cycle	N/A	B.3.3.
Cannabidiol – Back to baseline following discontinuation				Immediately	N/A	
Age group <12 years	Transition probabilities for cycle 1			Based on the PLD of the GWEP1332 Part B and GWEP 1424 (Table 17)	N/A	B.3.3. Based on the PLD analysis of the GWEP1332 Part B, GWEP 1424 and GWEP1415 studies (Table 17)
	Transition probabilities for cycle 2 to cycle 9			Based on the PLD of the OLE study 1415 (Table 17)	N/A	
	Transition probabilities beyond cycle 9			Assumed to return to baseline (Table 17)	N/A	
Age group ≥12 years	Transition probabilities for cycle 1			Based on the PLD of the GWEP1332 Part B and GWEP 1424 (Table 17)	N/A	
	Transition probabilities for cycle 2 to cycle 9			Based on the PLD of the OLE study 1415 (Table 17)	N/A	

Variable				Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	Transition probabilities beyond cycle 9			Assumed to return to baseline (Table 17)	N/A	
Number of days without seizures						
Age group <12 years	CBD 20 mg + CCM	Seizure-Free	≤ 18 seizure free days	[redacted]	N/A	B.3.3. Based on the PLD analysis of the GWEP1332 Part B and GWEP 1424 studies (Table 18)
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		≤ 8 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 8 - ≤ 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
	CBD 10 mg + CCM	Seizure-Free	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		≤ 8 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 8 - ≤ 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
	CCM	Seizure-Free	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		≤ 8 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 8 - ≤ 25 convulsive	≤ 18 seizure free days	[redacted]	N/A	

Variable				Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
		seizures	> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
Age group ≥12 years	CBD 20 mg + CCM	Seizure-Free	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		≤ 8 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 8 - ≤ 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
	CBD 10 mg + CCM	Seizure-Free	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		≤ 8 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 8 - ≤ 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
	CCM	Seizure-Free	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		≤ 8 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	

Variable				Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
			> 24 seizure free days	[redacted]	N/A	
		> 8 - ≤ 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		> 25 convulsive seizures	≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
Active treatment discontinuation						
Age group <12 years	Discontinuation during cycle 1	CBD 20 mg + CCM	Seizure-Free	[redacted]	N/A	B.3.3. Based on the PLD analysis of the GWEP1332 Part B and GWEP 1424 studies (Table 19)
			≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		CBD 10 mg + CCM	Seizure-Free	[redacted]	N/A	
			≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
	Discontinuation after cycle 1	CBD 20 mg + CCM	Seizure-Free	[redacted]	N/A	B.3.3. Based on the PLD analysis of the OLE study 1415 (Table 19)
			≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		CBD 10 mg + CCM	Seizure-Free	[redacted]	N/A	
			≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
Age group ≥12 years	Discontinuation during cycle 1	CBD 20 mg + CCM	Seizure-Free	[redacted]	N/A	B.3.3. Based on the PLD analysis of the GWEP1332 Part B and GWEP 1424 studies (Table 19)
			≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		CBD 10 mg + CCM	Seizure-Free	[redacted]	N/A	
			≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
	Discontinuation after cycle 1	CBD 20 mg + CCM	Seizure-Free	[redacted]	N/A	B.3.3. Based on the PLD analysis of the OLE study 1415 (Table 19)
			≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	
		CBD 10 mg + CCM	Seizure-Free	[redacted]	N/A	
			≤ 18 seizure free days	[redacted]	N/A	
			> 18 - ≤ 24 seizure free days	[redacted]	N/A	
			> 24 seizure free days	[redacted]	N/A	

Variable			Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Additional mortality risk					
Age group <12 years	SUDEP	Seizure-Free	[redacted]	N/A	B.3.3. Values based on Cooper *et al*. (2016) and Skluzacek 2011 (8, 13) (Table 20)
		≤ 18 seizure free days	[redacted]	N/A	
		> 18 - ≤ 24 seizure free days	[redacted]	N/A	
		> 24 seizure free days	[redacted]	N/A	
	Non-SUDEP	Seizure-Free	[redacted]	N/A	
		≤ 18 seizure free days	[redacted]	N/A	
		> 18 - ≤ 24 seizure free days	[redacted]	N/A	
		> 24 seizure free days	[redacted]	N/A	
Age group ≥12 years	SUDEP	Seizure-Free	[redacted]	N/A	
		≤ 8 seizures	[redacted]	N/A	
		>8 - ≤ 25 seizures	[redacted]	N/A	
		> 25 seizures	[redacted]	N/A	
	Non-SUDEP	Seizure-Free	[redacted]	N/A	
		≤ 8 seizures	[redacted]	N/A	
		>8 - ≤ 25 seizures	[redacted]	N/A	
		> 25 seizures	[redacted]	N/A	
Adverse events incidence rate					
CBD 20 mg + CCM		Rash	[redacted]	N/A	B.3.3. Phase 3 placebo-controlled trials for DS and LGS (Table 21)
		Somnolence	[redacted]	N/A	
		Fatigue	[redacted]	N/A	
		Lethargy	[redacted]	N/A	
		Sedation	[redacted]	N/A	
		Diarrhoea	[redacted]	N/A	
		Decreased appetite	[redacted]	N/A	
		Aggression	[redacted]	N/A	
		Irritability	[redacted]	N/A	
CBD 10 mg + CCM		Rash	[redacted]	N/A	
		Somnolence	[redacted]	N/A	
		Fatigue	[redacted]	N/A	
		Lethargy	[redacted]	N/A	
		Sedation	[redacted]	N/A	
		Diarrhoea	[redacted]	N/A	
		Decreased appetite	[redacted]	N/A	
		Aggression	[redacted]	N/A	
		Irritability	[redacted]	N/A	
CCM		Rash	[redacted]	N/A	
		Somnolence	[redacted]	N/A	
		Fatigue	[redacted]	N/A	
		Lethargy	[redacted]	N/A	
		Sedation	[redacted]	N/A	
		Diarrhoea	[redacted]	N/A	
		Decreased appetite	[redacted]	N/A	
		Aggression	[redacted]	N/A	
		Irritability	[redacted]	N/A	

Costs			
Treatment acquisition costs per pack (unit costs at list price per mg per kg per day)			
Cannabidiol	[redacted]	N/A	B.3.5. Based on the average and minimum and maximum values based on NHS drug tariff and prescription cost analysis (70, 71)
Clobazam	£0.0559	[£0.0121 - £0.6000]	
Stiripentol	£0.0180	[£0.0164 - £0.0189]	
Valproate	£0.0002	[£0.0002-£0.0008]	
Levetiracetam	£0.0002	[£0.0001-£0.0255]	
Topiramate	£0.0044	[£0.0023-£0.0292]	

Variable			Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Management Costs					
Age group <12 years	Visit Costs	Nurse Visit	£44.00	N/A	B.3.5. Based on PSSRU 2017 and NHS reference cost schedule 2016-2017 (76, 77)(Table 30)
		Paediatric Epileptologist	£366.00	[£363 - £410]	
		Paediatrician Visit	£196.00	N/A	
		Emergency department	£237.00	[£56 - £838]	
		Phone Call Follow-up	£258.00	[£55 - £234]	
		Orthopaedic surgeon	£128.00	[£117 - £129]	
		Dentist	£127.00	N/A	
	Hospitalisation Costs	General ward	£597.00	[£560 - £760]	
		ICU	£1,583.38	[£784 - £5,867]	
	Institutionalisation	Institutionalisation	£0.00	N/A	
	Disease Management - Rescue Medication	Cost of Rescue Medication by intake	£34.00	N/A	
Age group ≥12 years	Visit Costs	Nurse Visit	£44.00	N/A	
		Neurologist	£167.00	[£119 - £172]	
		Paediatrician Visit	£0.00	N/A	
		Emergency department	£237.00	[£56 - £838]	
		Phone Call Follow-up	£107.00	[£57 - £153]	
		Orthopaedic surgeon	£119.00	[£98 - £121]	
		Dentist	£127.00	N/A	
	Hospitalisation Costs	General ward	£460.00	[£402 - £807]	
		ICU	£1,299.32	[£643 - £4,482]	
	Institutionalisation	Institutionalisation	£1,337.00	N/A	
	Disease Management - Rescue Medication	Cost of Rescue Medication by intake	£34.00	N/A	
Mortality costs					
Age group <12 years	SUDEP	No cost	£0.00	N/A	B.3.5. Based on clinical opinion and NHS reference cost schedule 2016–2017(77) (Table 31)
	Non-SUDEP	1 visit to the ED	£237.00	[£56 - £838]	
		7 days in ICU	£11,084.00	[£5,491 - £41,068]	
Age group ≥12 years	SUDEP	No cost	£0.00	N/A	
	Non-SUDEP	1 visit to the ED	£237.00	[£56 - £838]	
		7 days in ICU	£9,095.00	[£4,499-£31,376]	
Adverse events costs (Management Unit Cost)					
Rash			£44.00	N/A	B.3.5. Based on PSSRU 2017 (76) (assumed one nurse visit)
Somnolence			£44.00	N/A	
Fatigue			£44.00	N/A	
Lethargy			£44.00	N/A	
Sedation			£44.00	N/A	
Diarrhoea			£44.00	N/A	
Decreased appetite			£44.00	N/A	
Aggression			£44.00	N/A	
Irritability			£44.00	N/A	
Resource use					
Concomitant therapy use (mg/kg/day)					
Age group <12 years	Clobazam		[redacted]	[redacted]	B.3.5. Base case and minimum /maximum
	Stiripentol		[redacted]	[redacted]	
	Valproate		[redacted]	[redacted]	

Variable			Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	Topiramate		[redacted]	[redacted]	values based on the SmPC of each drug (46, 64-68, 78, 79) (Table 26)
	Levetiracetam		[redacted]	[redacted]	
Age group ≥12 years	Clobazam		[redacted]	[redacted]	
	Stiripentol		[redacted]	[redacted]	
	Valproate		[redacted]	[redacted]	
	Topiramate		[redacted]	[redacted]	
	Levetiracetam		[redacted]	[redacted]	
Dose reduction of concomitant therapies					
% of patients	Clobazam		[redacted]	N/A	B.3.5. Based on Laux et al. 2017 (69) (Table 27)
	Stiripentol		[redacted]	N/A	
	Valproate		[redacted]	N/A	
	Topiramate		[redacted]	N/A	
	Levetiracetam		[redacted]	N/A	
% of dose	Clobazam		[redacted]	N/A	B.3.5. Based on clinical opinion (Table 27)
	Stiripentol		[redacted]	N/A	
	Valproate		[redacted]	N/A	
	Topiramate		[redacted]	N/A	
	Levetiracetam		[redacted]	N/A	
Management					
Age group <12 years	Nurse Visit	Seizure-Free	2.00	N/A	B.3.5. Based on clinical opinion (Table 29)
		≤ 8 seizures	4.00	N/A	
		> 8 - ≤ 25 seizures	8.00	N/A	
		> 25 seizures	12.00	N/A	
	Paediatric Epileptologist	Seizure-Free	1.00	N/A	
		≤ 8 seizures	2.00	N/A	
		> 8 - ≤ 25 seizures	4.00	N/A	
		> 25 seizures	6.00	N/A	
	Paediatrician Visit	Seizure-Free	2.00	N/A	
		≤ 8 seizures	4.00	N/A	
		> 8 - ≤ 25 seizures	8.00	N/A	
		> 25 seizures	12.00	N/A	
	Emergency department	Seizure-Free	0.00	N/A	
		≤ 8 seizures	6.00	N/A	
		> 8 - ≤ 25 seizures	12.00	N/A	
		> 25 seizures	24.00	N/A	
	Phone Call Follow-up (Paediatric Epileptologist0	Seizure-Free	0.00	N/A	
		≤ 8 seizures	2.00	N/A	
		> 8 - ≤ 25 seizures	6.00	N/A	
		> 25 seizures	12.00	N/A	
	Orthopaedic surgeon	Seizure-Free	0.00	N/A	
		≤ 8 seizures	0.00	N/A	
		> 8 - ≤ 25 seizures	0.00	N/A	
		> 25 seizures	0.00	N/A	
	Dentist	Seizure-Free	2.00	N/A	
		≤ 8 seizures	2.00	N/A	
		> 8 - ≤ 25 seizures	2.00	N/A	
		> 25 seizures	2.00	N/A	
	Hospitalisation (95% in general ward / 5% in ICU)	Seizure-Free	0.00	N/A	
		≤ 8 seizures	3.00	N/A	
		> 8 - ≤ 25 seizures	6.00	N/A	
		> 25 seizures	12.00	N/A	
	Institutionalisation	Seizure-Free	0.00%	N/A	
		≤ 8 seizures	0.00%	N/A	
		> 8 - ≤ 25 seizures	0.00%	N/A	
		> 25 seizures	0.00%	N/A	
	Rescue Medication by intake	Seizure-Free	0.00	N/A	
		≤ 8 seizures	12.00	N/A	
		> 8 - ≤ 25 seizures	24.00	N/A	
		> 25 seizures	48.00	N/A	

Variable			Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Age group ≥12 years	Nurse Visit	Seizure-Free	2.00	N/A	
		≤ 8 seizures	2.00	N/A	
		> 8 - ≤ 25 seizures	4.80	N/A	
		> 25 seizures	12.00	N/A	
	Neurologist	Seizure-Free	0.50	N/A	
		≤ 8 seizures	0.50	N/A	
		> 8 - ≤ 25 seizures	0.50	N/A	
		> 25 seizures	3.00	N/A	
	Paediatrician Visit	Seizure-Free	0.00	N/A	
		≤ 8 seizures	0.00	N/A	
		> 8 - ≤ 25 seizures	0.00	N/A	
		> 25 seizures	0.00	N/A	
	Emergency department	Seizure-Free	0.00	N/A	
		≤ 8 seizures	3.00	N/A	
		> 8 - ≤ 25 seizures	6.00	N/A	
		> 25 seizures	12.00	N/A	
	Phone Call Follow-up (Neurologist)	Seizure-Free	0.00	N/A	
		≤ 8 seizures	1.00	N/A	
		> 8 - ≤ 25 seizures	2.50	N/A	
		> 25 seizures	6.00	N/A	
	Orthopaedic surgeon	Seizure-Free	0.00	N/A	
		≤ 8 seizures	0.00	N/A	
		> 8 - ≤ 25 seizures	0.00	N/A	
		> 25 seizures	0.00	N/A	
	Dentist	Seizure-Free	2.00	N/A	
		≤ 8 seizures	2.00	N/A	
		> 8 - ≤ 25 seizures	2.00	N/A	
		> 25 seizures	2.00	N/A	
	Hospitalisation (95% in general ward / 5% in ICU)	Seizure-Free	0.00	N/A	
		≤ 8 seizures	1.50	N/A	
		> 8 - ≤ 25 seizures	3.00	N/A	
		> 25 seizures	6.00	N/A	
	Institutionalisation (only for patients over 18)	Seizure-Free	0.00%	N/A	
		≤ 8 seizures	10.00%	N/A	
		> 8 - ≤ 25 seizures	10.00%	N/A	
		> 25 seizures	10.00%	N/A	
	Rescue Medication by intake	Seizure-Free	0.00	N/A	
		≤ 8 seizures	6.00	N/A	
		> 8 - ≤ 25 seizures	12.00	N/A	
		> 25 seizures	24.00	N/A	
Adverse events					
Rash			1 nurse visit	N/A	B.3.5. Assumed 1 visit to a specialised nurse
Somnolence			1 nurse visit	N/A	
Fatigue			1 nurse visit	N/A	
Lethargy			1 nurse visit	N/A	
Sedation			1 nurse visit	N/A	
Diarrhoea			1 nurse visit	N/A	
Decreased appetite			1 nurse visit	N/A	
Aggression			1 nurse visit	N/A	
Irritability			1 nurse visit	N/A	
Utilities					
Patient utilities					
No seizures		No seizures	[redacted]	[redacted]	B.3.4 Mean and SE based on GW survey (80) (Table 25)
≤ 8 seizures		≤ 18 seizure-free days	[redacted]	[redacted]	
		> 18 - ≤ 24 seizure-free days	[redacted]	[redacted]	
		> 24 seizure-free days	[redacted]	[redacted]	
>8 - ≤25 seizures		≤ 18 seizure-free days	[redacted]	[redacted]	
		> 18 - ≤ 24 seizure-free days	[redacted]	[redacted]	
		> 24 seizure-free days	[redacted]	[redacted]	

Variable		Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
>25 seizures	≤ 18 seizure-free days	[redacted]	[redacted]	
	> 18 - ≤ 24 seizure-free days	[redacted]	[redacted]	
	> 24 seizure-free days	[redacted]	[redacted]	

Assumptions

Table 33: Key assumptions used in the economic model (base case)

Parameter	Assumption	Rationale
Time horizon	15 years.	Appropriate timeline to assess costs and benefits associated with the intervention. Consistent with previous published CE studies in DS (Section B.3.1).
Active treatment dosage	All patients receive 10 mg/kg/day.	This is the maintenance dose from the Epidyolex® SmPC.
Treatment efficacy	The base case analysis assumed that after cycle nine patients stay in the same health state for the remaining duration of the analysis.	This assumption was considered to be appropriate given that no decline in treatment efficacy was observed among patients enrolled in the open-label extension study GWEP1415.
	For the comparator arm, any change to seizure rates was assumed to apply for one cycle only (i.e. for the duration that patients were receiving placebo + CCM in the Phase 3 trials). In subsequent cycles, patients were assumed to revert to baseline efficacy rates and stay in the same health states for the remaining duration of the analysis.	This assumption was considered appropriate as patients in the GWEP1332B and GWEP1424 Phase 3 trials received prior treatment with AEDs and the baseline rates could be assumed to be representative of the efficacy associated with CCM without placebo. This assumption has also been validated by clinical experts in the UK.
Discontinuation rates	Discontinuation rates were applied only for patients entering the model in the treatment arm (i.e. cannabidiol in addition to CCM). Once patients have discontinued their treatment. they cannot receive the active treatment again (i.e. they receive only CCM).	This is a reasonable assumption. As patients in the comparator arm do not receive an active treatment, they are assumed to receive CCM for the duration of the analysis, or until death.
	The rates estimated for cycle nine were assumed to remain constant over time, for the remaining duration of the analysis.	This assumption was validated by expert opinion.
	In the base case analysis, patients discontinuing cannabidiol were assumed to stop benefiting from the treatment effect (they revert to baseline seizure rates).	This assumption was validated by expert opinion.
CCM basket	The model assumes the same CCM basket for the treatment and comparator arm (i.e. same drugs and dosage).	This is a conservative assumption as it is likely that patients receiving cannabidiol may receive lower doses of other AEDs.
	The patients receiving cannabidiol are also assumed to benefit from a reduction in the dose of concomitant AEDs.	Published evidence and clinical opinion.
Quality of life	Based on VAS data collected by GW.	The SLR did not retrieve any published studies that estimated utilities for health states defined by number of seizures and seizure-free days. Therefore, QoL data estimated using VAS was used in the economic model.
Mortality	Patients with a higher number of seizures were assumed to be at greater risk of	Published evidence and clinical opinion.

Parameter	Assumption	Rationale
	death compared to those with fewer seizures.	
Resource use associated with disease management	Patients with a higher number of seizures were assumed to be associated with higher levels of resource use compared to those with fewer seizures.	Clinical opinion.
Institutionalisation	The probability of being institutionalised and the associated costs were applied only to patients aged 18 years and older. With the exception of the seizure-free health states, the risk of being institutionalised was applied to all other seizure categories and was assumed to be the same (i.e. 10%).	Published evidence and clinical opinion.

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

The base-case results of the economic model are presented in Table 34.

Over a time horizon of 15 years, cannabidiol in addition to CCM was associated with a QALY gain of [redacted] and a total overall cost of [redacted]. In contrast, CCM alone was associated with a QALY gain of [redacted] and a total overall cost of [redacted]. Therefore, the resulting Incremental Cost-Effectiveness Ratio (ICER) versus CCM alone is [redacted] per QALY gained.

Refer to Appendix J for disaggregated results of the base-case incremental cost-effectiveness analysis (QALYs and costs).

Table 34: Base-case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM + placebo	[redacted]	[redacted]	-	-	-
CCM + CBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: CBD, cannabidiol; CCM, current clinical management; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Cannabidiol in addition to CCM is associated with an incremental QALY of [redacted] and an incremental cost of [redacted]. Table 35 details the overall costs (15-year time horizon) by cost categories. The introduction of cannabidiol as an add-on therapy to CCM resulted in lower management costs and non-SUDEP costs [redacted] and [redacted], respectively). Cannabidiol was associated with a marginal increase in the cost of management of AEs [redacted]. The difference in treatment costs between cannabidiol with CCM and CCM alone is [redacted].

Table 35: Total costs by category of cost with 15-year time horizon

Cost categories	CCM + CBD	CCM	Difference
Total costs per patient	[redacted]	[redacted]	[redacted]
Treatment costs per patient	[redacted]	[redacted]	[redacted]
Adverse events costs per patient	[redacted]	[redacted]	[redacted]
Management costs per patient	[redacted]	[redacted]	[redacted]
SUDEP cost per patient	[redacted]	[redacted]	[redacted]
Non-SUDEP cost per patient	[redacted]	[redacted]	[redacted]
Abbreviations: CBD, cannabidiol; CCM, current clinical management; SUDEP, Sudden unexpected death in epilepsy.			

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

The parameters included in the probabilistic sensitivity analysis (PSA) were determined based on the results of the one-way deterministic sensitivity analyses (DSA).

Nonetheless, the PSA included key parameters such as the transition probabilities, patient characteristics (weight), SUDEP rates, utilities and disease management costs and only inputs that were unlikely to have a significant impact on the ICERs were not considered. This approach was considered appropriate due to the complexity of the model.

The parameters included in the PSA and the corresponding distributions are presented in Table 36.

Table 36: Parameter values for multivariate probabilistic analysis

Parameters		Base case	Min	Max	SE	Alpha	Beta	Distribution
Transition probabilities								
Transition probabilities		Table 17	Bootstrap from trial data					
Weight								
2 - 5 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
6 - 11 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
12 - 17 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
18 - 55 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Management Unit Costs								
Visits Costs								
2 - 11 years	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	≤ 8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
12 - 55 years	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	≤ 8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Hospitalisation Costs								
2 - 11 years	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	≤ 8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
12 - 55 years	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	≤ 8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Rescue Med Costs								
2 - 11 years	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	≤ 8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma

Parameters		Base case	Min	Max	SE	Alpha	Beta	Distribution
	> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
12 - 55 years	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	≤ 8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Institutionalization Costs								
18 - 55 years	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	≤ 8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
	> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Daily Cost ICU								
Adults		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Paediatric		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Daily Cost General Ward								
Adults		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Paediatric		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Emergency Department Visit		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Epilepsy-related Mortality – SUDEP								
2 – 11 years	> 8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
12 – 55 years	> 8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Utilities								
No seizures	> 15 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
≤ 8 seizures	≤ 18 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	> 18 - ≤ 24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	> 24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
> 8 - ≤ 25 seizures	≤ 18 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	> 18 - ≤ 24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	> 24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
> 25 seizures	≤ 18 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	> 18 - ≤ 24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	> 24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta

Abbreviation: ICU, Intensive care unit; N/A, Not applicable; SE, Standard Error; SUDEP, Sudden unexpected death in epilepsy

As the transition probabilities associated with the movement of patients between the different seizure categories are interdependent, the uncertainty around this parameter was estimated by resampling the patients included in the Phase 3 trials and the OLE study. [redacted] bootstrap samples (the same sample size as the trials) were drawn independently from the Phase 3 trials to estimate the transition probabilities for the first cycle and a similar number of random samples were independently drawn from the OLE study to estimate the probabilities for the subsequent cycles.

The transition probabilities obtained from each bootstrap sample were run one at a time while varying the other parameters included in the PSA simultaneously. This was considered to be the most appropriate approach as individual patient-level data were available from the Phase 3 trials and the OLE study.

Results from the PSA are presented in Figure 5 and Table 37 compares the results to the base case estimates.

Table 37: PSA results compared to base-case

	Costs		**QALYs**		**ICERs**	
	Base case	**PSA**	**Base case**	**PSA**	**Base case**	**PSA**
CCM + CBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCM	[redacted]	[redacted]	[redacted]	[redacted]	-	-

Abbreviations: CBD, cannabidiol; CCM, current clinical management; ICER, incremental cost-effectiveness ratio; PSA, Probabilistic sensitivity analysis; QALY, quality-adjusted life year

Figure 5: Cost-effectiveness plane

The incremental cost-effectiveness acceptability curve (Figure 6) shows that there is [redacted] likelihood that cannabidiol + CCM is cost effective when compared to CCM alone at a willingness to pay (WTP) threshold of [redacted]/QALY.

Figure 6: Cost-effectiveness acceptability curve

Deterministic sensitivity analysis

The parameters included in the DSA are presented in Table 38. The lower and upper values for each parameter included in the DSA were either obtained from the literature, were based on clinical opinion or varied across a specified range (e.g. +/- 10%). The DSA did not include transition probabilities as the movement of patients between the different health states at the end of each cycle in the model are interdependent, and all the TPs would have to be changed simultaneously in order to ensure clinically meaningful results. Therefore, transition probabilities were tested only in the PSA using the bootstrapping method.

Table 38: Parameter values for univariate sensitivity analysis

Parameter	Base Case	Lower Bound	Upper Bound	References
Discount Rates				
Costs	3.5%	0.0%	6.0%	NICE recommendation (43)
Outcomes	3.5%	0.0%	6.0%	
Weight				
2 - 5 years	[redacted]	[redacted]	[redacted]	Based on the PLD analysis of the GWEP1332 Part B and GWEP 1424 studies
6 - 11 years				
12 - 17 years				
18 - 55 years				
Discontinuation				
Discontinuation	Table 19	-10%	+10%	Assumption
Management Unit Costs				
Visits Costs	Table 29, Table 30	-20%	+20%	Assumption
Hospitalisation Costs	Table 29, Table 30	-20%	+20%	Assumption
Rescue Med Costs	Table 29, Table 30	-20%	+20%	Assumption
Institutionalisation Costs	Table 29, Table 30	-20%	+20%	Assumption
Daily Cost ICU				
Adults	£1,299	£643	£4,482	Table 32
Paediatric	£1,583	£784	£5,867	
Daily Cost General Ward				
Adults	£460	£402	£807	Table 32
Paediatric	£597	£560	£760	
Phone Call Follow-up				
Neurologist	£107	£57	£153	Table 32
Paediatric neurologist	£258	£55	£234	
Emergency Department Visit				
Emergency Department Visit	£237	£56	£838	Table 30
Non-SUDEP costs, n days in ICU				
2 - 11 years	7.00	5.60	8.40	Assumption
12 - 55 years	7.00	5.60	8.40	
% of institutionalisation				
Seizure-Free	0.00%	0.00%	0.00%	Assumption
≤ 8 seizures	10.00%	0.00%	20.00%	
> 8 - ≤ 25 seizures	10.00%	0.00%	20.00%	
> 25 seizures	10.00%	0.00%	20.00%	
Epilepsy-related Mortality				
SUDEP – RR				
≤ 8 seizures				
2 - 11 years	0.60	-10%	+10%	Assumption
12 - 55 years	0.60	-10%	+10%	
> 25 seizures				
2 - 11 years	1.40	-10%	+10%	Assumption
12 - 55 years	1.40	-10%	+10%	

Parameter	Base Case	Lower Bound	Upper Bound	References
SUDEP – Probabilities				
> 8 - ≤ 25 seizures				
2 - 11 years	0.23%	0.11%	0.49%	Cooper et al. (2016) (8)
12 - 55 years	0.23%	0.11%	0.49%	
Non-SUDEP – RR				
≤ 8 seizures				
2 - 11 years	0.60	-10%	+10%	Assumption
12 - 55 years	0.60	-10%	+10%	
> 25 seizures				
2 - 11 years	1.40	-10%	+10%	Assumption
12 - 55 years	1.40	-10%	+10%	
Non-SUDEP – Probabilities				
> 8 - ≤ 25 seizures				
2 - 11 years	0.16%	0.11%	0.21%	Assumption
12 - 55 years	0.16%	0.11%	0.21%	
Utilities				
Lower and upper values estimated based on SE				
Seizure-Free; > 24 days	[redacted]	[redacted]	[redacted]	Based on survey estimates (Table 25)
≤ 8 seizures; > 18 - ≤ 24 days	[redacted]	[redacted]	[redacted]	
≤ 8 seizures; > 24 days	[redacted]	[redacted]	[redacted]	
>8 - ≤ 25 seizures; ≤ 18 days	[redacted]	[redacted]	[redacted]	
>8 - ≤ 25 seizures; > 18 - ≤ 24 days	[redacted]	[redacted]	[redacted]	
>8 - ≤ 25 seizures; > 24 days	[redacted]	[redacted]	[redacted]	
> 25 seizures; ≤ 18 days	[redacted]	[redacted]	[redacted]	
> 25 seizures; > 18 - ≤ 24 days	[redacted]	[redacted]	[redacted]	
> 25 seizures; > 24 days	[redacted]	[redacted]	[redacted]	

Abbreviations: kg, kilogram; ICU, intensive care unit; n, number; PLD, patient level data; RR, risk ratio; SE, standard error; SUDEP, sudden unexpected death in epilepsy

presents a tornado diagram showing the parameters with the greatest impact on the ICER, with descending ICER sensitivity. Results from the DSA are also presented in a tabulated format in Appendix J.

Figure 7: Tornado diagram

Scenario analysis

Uncertainty around the following structural and parametric assumptions has been tested in the scenario analyses:

- **Time horizon:** alternative horizons of 10 and 20 years were considered.
- **Age groups:** as the base case presents results for all age groups, ICERs were estimated separately for the two age groups considered in the model, i.e. <12 years and ≥12 years.
- **Dose reduction of drugs included in CCM:** in the base case, the percentage reduction in the dose of the concomitant AEDs was assumed to be 33%. However, clinical experts have indicated that, in view of the adverse side effects associated with clobazam and valproate, they would consider a 100% reduction in the dosages of these drugs for patients responding to cannabidiol treatment.
- **Utilities:** existing literature provides a number of conversions from VAS scores to TTO and standard gamble (SG); however, there is no consensus on which is the most appropriate mapping formula Therefore, the conversion algorithms that resulted in the lowest (obtained using the SG8 transformation function) and the highest SG utility values (obtained using the SG3 transformation function) were selected for the scenario analysis (Appendix H;

- Table *61*).

Table 39: Utilities for scenario analysis

Number of Seizures	Algorithm 1 (SG3)			Algorithm 2 (SG8)		
	Number of Days Without Seizures			Number of Days Without Seizures		
	≤ 18 days	> 18 - ≤ 24 days	> 24 days	≤ 18 days	> 18 - ≤ 24 days	> 24 days
Seizure-Free	-	-	[redacted]	-	-	[redacted]
≤ 8 seizures	-	[redacted]	[redacted]	-	[redacted]	[redacted]
>8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: SG, standard gamble						

- **Cannabidiol dosage:** as the dosage for CBD is patient-specific (i.e. based on patient weight and individual clinical response), an alternative mean dosage of CBD was tested in the scenario analysis. The maximum recommended dose of 20 mg/kg/day is most likely to be received only by a small proportion of patients who have the potential to achieve further seizure reductions and/or seizure-freedom. Therefore, the mean dose of CBD was estimated by assuming that patients who achieve ≥75% reduction in convulsive seizures receive 20 mg/kg/day, while patients experiencing <75% reduction in convulsive seizures receive 10 mg/kg/day. The proportion of responders with ≥75% and <75% reduction in convulsive seizures was obtained from the Phase 3 clinical trial (28).

Table 40: Cannabidiol dosage by age group

	<12 years	≥12 years
Patients receiving 10 mg/kg/day of cannabidiol (i.e. <75% response)	[redacted]	[redacted]
Patients receiving 20 mg/kg/day of cannabidiol (i.e. ≥75% response)	[redacted]	[redacted]
Average dose per mg/kg/day	[redacted]	[redacted]
Reference: GW Pharma 2018 Data on File (28)		

- **No variation in healthcare resource use across seizure groups:** based on clinical opinion, disease management resource use was linked to the severity of seizures. As most patients receiving CBD experience improvement in seizure severity, disease management resource use and consequently costs are lower for cannabidiol. However, due to a lack of published evidence on

the relationship between resource use and disease severity, a scenario assuming no variation in the resource use (i.e. visits and hospitalisations) across different seizure groups was implemented.

- **Long-term discontinuation:** due to limited long-term data, in the base case the discontinuation rates estimated for each seizure category at cycle nine were assumed to remain constant for the remaining duration of the analysis. Therefore, a scenario analysis assuming the same long-term discontinuation rate for all seizure groups was implemented. An overall rate of the discontinuations estimated in the OLE study was used in this analysis.

- **Mortality:** in the base case, patients with a higher number of seizures were assumed to be at a greater risk of death compared to those with fewer seizures. An alternative scenario where patients at the same risk of mortality, irrespective of their seizure severity, was implemented.

- **Hospitalisations:** based on clinical opinion, the majority of the patients (95%) were assumed to be hospitalised in the general ward and only 5% in the intensive care unit (ICU). An alternative analysis assuming a higher proportion of ICU admissions (10%) was conducted.

The scenarios tested and the results are shown in Table 41.**Error! Reference source not found.**

Table 41: Scenario analyses (CBD+CCM vs CCM)

			CCM + CBD		CCM		
Parameter	**Base case**	**Scenario analyses**	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the time horizon							
Time horizon	15 years	10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the target population							
Target population	All age groups	2-11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		12-55 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the dose reduction of other drugs included in the CCM							
Dose reduction when patients have clobazam reduced	Clobazam dose reduced by a third (-33%)	Patients completely discontinue clobazam (-100%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduction when patients have clobazam and valproate reduced	Clobazam and valproate dose reduced by a third (-33%)	Patients completely discontinue clobazam and valproate (-100%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the approach to modelling utilities							
Utilities	Table 25	Algorithm 1 (SG 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Algorithm 2 (SG 8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the cannabidiol dosage							
Cannabidiol dosage	Patients receiving 10 mg/kg/day of cannabidiol: 100%	Patients receive 10 mg/kg/day if they experience <75% response, and 20 mg/kg/day if they experience ≥75% response. Average dose [redacted] mg/kg/day (Table 40)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the resource use in the management of the disease							
Number of visits	Table 29	No variation across seizure categories (number of visits for >8 - ≤ 25 seizures in each age group was applied to all other seizure groups in the corresponding age group. Seizure-free remains the same as in base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of hospital admissions	Table 29	No variation across seizure categories (number of hospital admissions for >8 - ≤ 25 seizures in each age group was applied to all other seizure groups in the corresponding age group. Seizure-free remains the same as in base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

			CCM + CBD		CCM		
Parameter	**Base case**	**Scenario analyses**	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Varying the long-term discontinuation							
Long term discontinuation	Table 19	The same CBD discontinuation percentages were applied across all groups in the long-term. Seizure-free remains the same as in base case. -11 years: [redacted] 12-55 years: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the approach to modelling mortality risk							
Epilepsy-related mortality	According to clinical opinion	All seizure groups have the same risk of death (0.23% for SUDEP and 0.16% for non-SUDEP; i.e. risk ratios = 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the proportion for ICU admissions within the hospitalisations							
Ratio ICU/General ward	5% in ICU and 95% in general ward	10% in ICU and 90% in general ward	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CBD, cannabidiol; CCM, current clinical management; ICER, incremental cost effectiveness ratio; ICU, Intensive Care Unit; N/A, not applicable; SUDEP, Sudden unexpected death in epilepsy

Summary of sensitivity analyses results

An extensive range of sensitivity and scenario analyses were conducted to test the robustness of the model inputs and structural assumptions of the economic analyses. Overall, the base case results were robust to most parameters and structural assumptions, with the ICERs across the majority of the analyses performed below [redacted] per QALY gained.

B.3.9 Subgroup analysis

No subgroup analyses were explored as no subgroups were identified from the Phase 3 trials and the OLE study where the effectiveness of cannabidiol was significantly different.

B.3.10 Validation

Validation of cost-effectiveness analysis

The model was quality-checked by the economists who developed the economic model. A senior economist not involved in the model development reviewed the model for coding errors and inconsistencies. A further validation and quality assessment of the model was conducted by an external consultancy. This review included a check of the model structure (e.g. formulae, VBA coding, cell references and functionality), of cost inputs against the Drug Tariff and NHS Tariff, and of the validity of distributions used in the sensitivity analyses. Pressure tests were conducted, in some cases using extreme values, in order to test the accuracy and validity of the model's results.

The model structure and key assumptions regarding health care resource use and long-term efficacy were validated by UK clinical experts, with extensive experience in treating patients with DS.

Clinical outcomes of the economic model have also been compared to and validated against all available evidence to assess the accuracy of the model estimates (see Appendix J).

B.3.11 Interpretation and conclusions of economic evidence

The comprehensive SLR (described in Appendix G) did not identify any studies assessing the cost-effectiveness of cannabidiol in DS patients. As such, it was not possible to compare the results of the economic model developed in this submission with any other studies.

The base case results of the *de novo* cost-utility model show that cannabidiol plus CCM is associated with higher costs but also higher QALYs than CCM, with an incremental cost per QALY gained of [redacted].

DS is a very rare, severely debilitating, lifelong and treatment-resistant form of epilepsy. There is a substantial unmet need in DS for an intervention that can effectively reduce seizures in the long term, without markedly increasing adverse events.

The core strength of this economic analysis is that it is based on clinical evidence from the Phase 3 RCTs and the open-label extension study of CBD. The model concept, structure and inputs were reviewed and validated by several clinical experts in order to ensure that all assumptions and parameters were clinically relevant to the UK setting. Furthermore, we have explored uncertainty in the model inputs and assumptions in sensitivity analyses to test the robustness of the base case results.

Limitations of this analysis include limited long-term clinical data for cannabidiol. The base case assumption that patients receiving cannabidiol continue to stay (after cycle 9) in the same health state for the remaining duration of the analysis was considered conservative given that no decline in treatment efficacy was observed among patients enrolled in the ongoing CBD open-label extension study.

Secondly, the risk of epilepsy-related deaths in the analyses was linked to the frequency of seizures (refer Section B.3.3), which was validated by UK experts and also tested in the scenario and sensitivity analyses. The results show that mortality rates do not have a significant impact on the ICERs.

Thirdly, there is a paucity of published data on the relationship between resource use (number of visits/hospital admissions) and disease severity in DS, which was

established from clinical expert opinion. The majority of patients receiving CBD experience improvement in their seizure severity and, consequently, lower disease management resource use and costs. This assumption was tested in scenario analyses, with ICERs of [redacted]/QALY gained (visits) and [redacted]/QALY gained (hospitalisations) even when identical disease management costs were assumed across the seizure categories.

Finally, since no relevant utility values were identified from the SLR, an online survey was conducted whereby patients with DS (or other forms of epilepsy) and/or carers of patients with DS evaluated vignettes describing health states included in the cost-utility analysis (refer to Section B.3.4 for details on the strengths and limitations of this study). As the VAS was used to elicit QoL data, the impact of the transformed SG utilities on the ICER was also tested in scenario analyses, resulting in ICERs of [redacted]/QALY gained (SG8) and [redacted]/QALY gained (SG3).

Cannabidiol will have a predictable and limited budget impact due to the orphan nature of DS as well as cost offsets associated with disease management. Patients with DS currently have extremely limited treatment options. Cannabidiol offers them the opportunity of a long-term treatment with durable efficacy that reduces seizure severity (seizure frequency and duration) and seizure-related injuries, and, for some patients who had previously been inadequately controlled, the potential for seizure-freedom.

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B.5 Appendices

Appendices relevant to this submission are as follows:

- Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix F: Adverse reactions
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality-of-life studies
- Appendix I: Cost and healthcare resource identification, measurement and valuation
- Appendix J: Clinical outcomes and disaggregated results from the model
- Appendix K: Checklist of confidential information

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

C1.1 SmPC

Provided as a separate document.

The final SmPC is not yet available. This is the SmPC from Day 180 of the EMA regulatory process.

C1.2 EPAR

EPAR is not yet available.

Appendix D: Identification, selection and synthesis of clinical evidence

D1.1 Identification and selection of relevant studies

We conducted a systematic literature review to identify relevant papers on the efficacy and safety of drug interventions in LGS and DS. The literature review also identified relevant papers on model parameters relating to the quality of life and utility values of children with LGS or DS and their caregivers, costs and resource use associated with the conditions, and existing economic models in LGS and DS.
We searched the following databases and sources for relevant publications:

- Medline via PubMed (for studies on efficacy and safety, quality of life, economic evaluations, costs and resource use)
- EMBASE via ProQuest (for studies on efficacy and safety, quality of life, economic evaluations, costs and resource use)
- Heoro.com (for studies on costs, resource use, quality of life, economic evaluations and mortality), www.heoro.com
- Cochrane library (for reviews, technology assessments, studies on efficacy and safety and economic evaluations) https://www.cochranelibrary.com/
- LGS Foundation Conference http://www.lgsfoundation.org/conference
- American Epilepsy Society https://www.aesnet.org/annual_meeting/abstract_search
- International Epilepsy Congress http://www.epilepsycongress.org/32nd-international-epilepsy-congress/
- European Congress on Epileptology http://www.epilepsyprague2016.org/abstracts.153.html; http://epilepsyvienna2018.org/
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) conference abstracts 2015-2018 https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp
- clinicaltrials.gov www.clinicaltrials.gov

- NHS Economic Evaluation Database 1968 to April 2015 and HTA search via University of York Centre for Reviews and Dissemination site https://www.crd.york.ac.uk/CRDWeb/Homepage.asp
- The University of Sheffield Health Utilities Database (ScHARRHUD) http://www.scharrhud.org/
- EuroQol Database (for quality of life studies) https://euroqol.org/search-for-eq-5d-publications/
- The All Wales Medicines Strategy Group (AWMSG) http://www.awmsg.org/
- The Scottish Medicines Consortium (SMC) https://www.scottishmedicines.org.uk/
- The National Institute for Health and Care Excellence (NICE) https://www.nice.org.uk/

The database searches used a systematic search strategy to identify relevant papers on the efficacy and safety, economic evaluation, quality of life, costs and resource use associated with LGS, DS and childhood myoclonic epilepsies.

The database searches were run on 19th November 2018 and the grey literature sites were searched on 19th November and 3rd December using the search strategies in Table 42. We also requested access to any additional publications of relevance from the manufacturer as a call for evidence, which identified an additional 2 publications.

Table 42. Search strategies

Database	Search	Number of abstracts
PubMed	"Lennox Gastaut Syndrome"[Mesh] OR ("Epilepsies, Myoclonic"[Mesh] AND (child* or infan*)) OR "Dravet* syndrome" OR "Lennox Gastaut" OR "childhood epilep* encephalopath*" OR "severe myoclonic epilepsy" OR SMEI	3157
Embase	(exact("Lennox Gastaut syndrome" OR "Lennox Gastaut syndrome")) OR (exact("Dravet like epileptic encephalopathy" OR "Dravet syndrome" OR "Dravet syndrome spectrum" OR "Dravets syndrome")) OR 'Lennox Gastaut' OR Dravet OR 'severe myoclonic epilepsy' OR SMEI	5439
Cochrane library	Lennox-Gastaut OR "Lennox Gastaut" OR Dravet OR "severe myoclonic epilepsy" OR SMEI	207
Heoro.com	Disease: (Lennox Gastaut syndrome OR Epilepsies, myoclonic OR Epilepsy) AND Study types: (PRO studies OR Costs and resource use studies OR Economic model studies)	870
AES 2015 to 2018	“Lennox Gastaut Dravet” (ALL)	310
LGSF 2016, 2017	Hand searching of presentation slides	19
IEC 2015, 2017	Hand searching of conference abstracts	9

ECE 2016, 2018	Hand searching of conference abstracts	692
ISPOR 2015 - 2018	Lennox Gastaut OR Dravet	15
ScHARRHUD	Lennox Gastaut OR Dravet in any field	0
CRD	Lennox Gastaut OR Dravet (Title) in DARE (all), NHS EED (all) and HTA (all)	9
EuroQol	Lennox Gastaut OR Dravet	0
Clinicaltrials.gov	Lennox Gastaut syndrome OR Dravet syndrome, terminated OR completed OR suspended OR withdrawn	30
All Wales Medicines Strategy Group	Browse central nervous system guidance	5
Scottish Medicines Consortium	Lennox Gastaut OR Dravet	4
National Institute for Health and Care Excellence	Browse epilepsy guidance	0
Call for evidence		2
	Combined, after deduplication	**8823**

The de-duplicated list of abstracts was screened independently according to agreed inclusion criteria by two researchers and any discrepancies agreed by discussion.

Study selection

The inclusion and exclusion criteria used to screen studies for the reviews are reported below. Inclusion and exclusion criteria were the same for abstract and full text screening. Any study of unclear relevance from the abstract was retrieved and screened as the full text.

Inclusion criteria

Population:

- Children and/ or adults with LGS or DS
- Include mixed populations with other types of childhood epilepsy

Study type:

- Efficacy/safety: randomised controlled trials (RCTs); systematic literature reviews (SLRs) of RCTs for citation chasing
- Quality of life (QoL), costs reviews: RCTs, observational studies; SLRs
- Economic model reviews: economic evaluations: cost-benefit, cost-effectiveness, cost-utility, cost-minimisation, cost-consequence, budget impact and other economic evaluations; SLRs of economic evaluations

Intervention:

- Cannabidiol
- No intervention (QoL, costs reviews)

Note: treatments are always given in combination, however we included RCTs that compare one drug with placebo, where all treatment arms also receive standard therapy. Details of concomitant medication were extracted.

Comparators:

- Rufinamide, stiripentol: alone or in combination
- Other antiepileptic drugs (valproate, topiramate, lamotrigine, clobazam, levetiracetam, felbamate, others); alone or in combination
- Placebo/ usual care
- No comparator (QoL, costs reviews)

Outcomes:

- Seizure rate
- Seizure severity
- % seizure-free
- % of participants achieving 50% reduction in seizure rate
- % of participants achieving 75% reduction in seizure rate
- Number of hospital or ICU admissions
- Length of stay
- Status epilepticus episodes
- Mortality
- Adverse events
- Adherence to treatment/ study withdrawals
- Quality of life or utilities
- Direct/indirect costs, resource use
- Measures of cost-effectiveness or cost savings

Publication date:

- Full text publications: any
- Conference abstracts: last 2 years (2016-18)
- Most recent update of systematic reviews

Publication language:

- Efficacy reviews: any
- QoL, costs, economic model reviews: full text in English

Abstract screening algorithm

Abstracts were screened using the algorithm shown in Table 43.

Table 43. Screening algorithm

Population	1. Does the study include patients with LGS and/or DS (or other severe myoclonic epilepsy for QOL and costs)?	Yes: go to 2	No: **1.EX-POPULATION**
Study methodology	2. Is the study a primary report of a clinical study	Yes: go to 3	**No**: Is the study a systematic review of primary clinical studies? No: **2.EX_METHOD** **Yes**: Is it the most up-to-date version of the SR? No: **2. EX_METHOD** Yes: **3. IN_SR**
Date	3. Is the publication a conference abstract published before 2016 or a previous version of a systematic review?	Yes: **4.EX_DATE**	No: Go to 4
Duplicates	4. Is the abstract a duplicate entry?	Yes: **5.EX_DUPLICATE**	No: Go to 5
Language	5. Is the full text of the study available in English?	Yes: go to 6	No: **6. EX_LANGUAGE**
Quality of life study	6. Does the study report utility values or other quality of life measures in LGS, DS or other severe or intractable epilepsies or status epilepticus?	Yes: **7. IN_PRO** Go to 7	No: go to 7
Economic analyses	7. Does the study report a cost-benefit, cost-effectiveness, cost-utility or other economic models for a relevant intervention and comparator for LGS or DS?	Yes: **8. IN_MODEL** Go to 8	No: go to 8
Economic burden	8. Does the study report costs or resource use in LGS, DS or other severe or intractable epilepsies or status epilepticus?	Yes: **9. IN_COSTS** Go to 9	No: Go to 9
Efficacy/ safety study	9. Is the study an RCT assessing the efficacy and/or safety of an included intervention in LGS or DS?	Yes: go to 10	No**: 10. EX_INTERVENTION**
	10. Does the study include a relevant comparator?	Yes: go to 11	No: **11. EX_COMPARATOR**
	11. Does the study report data on seizure rates, response or severity, adverse events, mortality or another relevant outcome?	Yes: **12.IN_EFFICACY**	No: **13. EX_TOPIC**

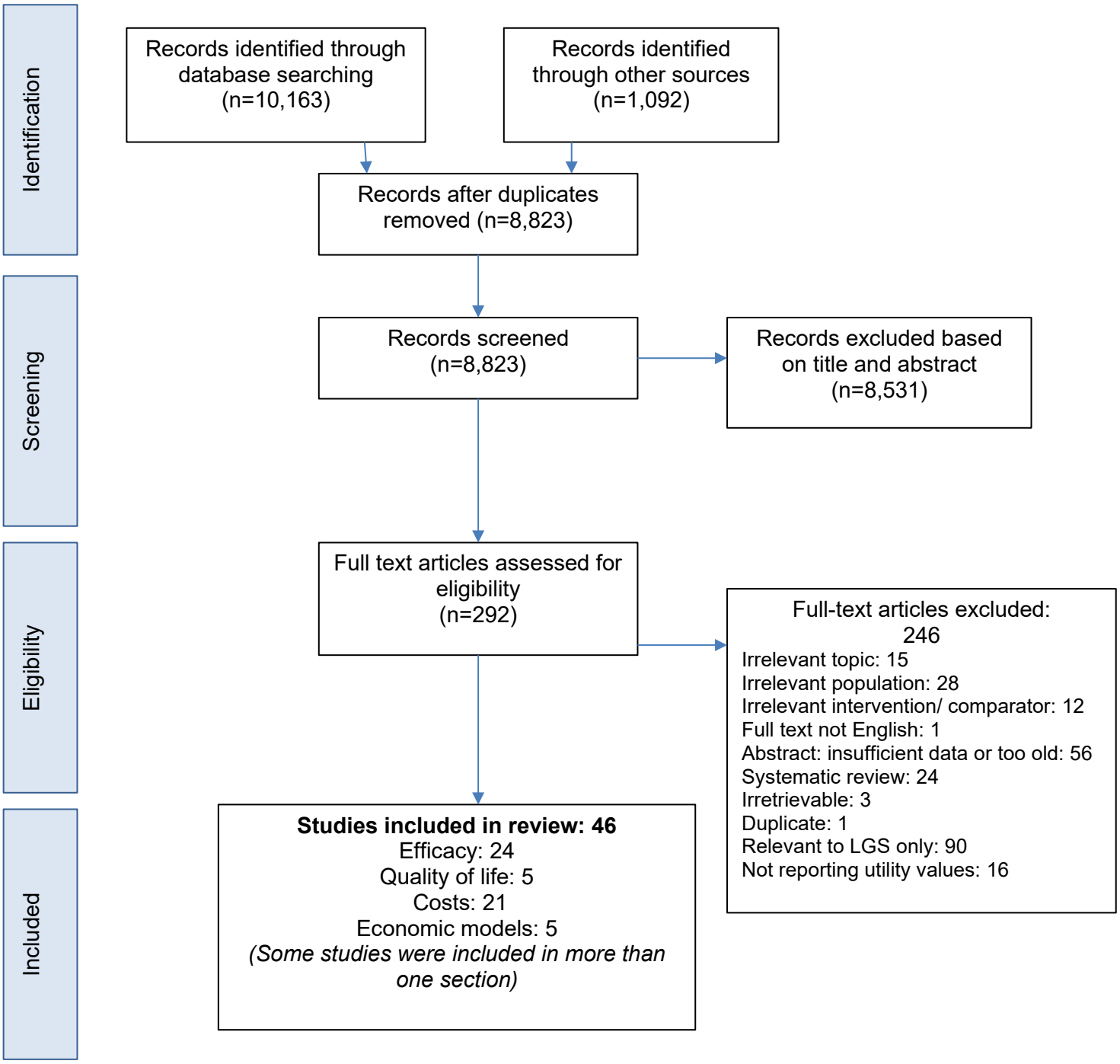


Figure 8. PRISMA diagram

Complete reference lists for included studies and excluded studies

The studies identified for the efficacy review are reported below in Table 44, showing the primary publication for each trial and all secondary publications identified.

Table 44. Primary and secondary references for efficacy studies identified in DS

Trial name	Primary publication	Secondary publications
GWPCARE1	Devinsky O., et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. New England Journal of Medicine. 2017;376(21):2011-20 (27)	• Cross, J.H., et al. (2017). Cannabidiol(CBD) reduces convulsive seizure frequency in Dravet syndrome: results of a multi-center, randomized, controlled trial (GWPCARE1. Neurology 88(16). (81) • Cross, J.H., et al. (2017). "Cannabidiol (CBD) reduces convulsive seizure frequency in Dravet syndrome: Results of a multi-centre, randomised, double-blind, placebo-controlled trial (GWPCARE1)." Epilepsia 58: S12. (82) • Wright, S., et al. (2017). "Cannabidiol (CBD) in Dravet syndrome: A randomised, dose-ranging pharmacokinetics and safety trial (GWPCARE1)." Epilepsia 58: S56. (83) • Devinsky, O., et al. (2018, August). Maintenance of long-term safety and efficacy of cannabidiol treatment in Dravet syndrome: results of the open-label extension trial (GWPCARE5). Poster session presented at the meeting of the European Congress on Epileptology, Vienna. (84) • Wilfong, A., et al. (2018). Cannabidiol (CBD) Reduces Seizure Frequency in Patients with Dravet Syndrome Who Had No Response to Prior Medications: Subgroup Analysis of Phase 3 Study GWPCARE1. American Epilepsy Society. New Orleans.(85) • Privitera, M., et al. (2018). Time to Onset of Efficacy of Cannabidiol (CBD) During Titration in Patients with Lennox–Gastaut Syndrome (LGS) and Dravet Syndrome (DS) Enrolled in 3 Randomized Controlled Trials. American Epilepsy Society. New Orleans. (86) • Zuberi, S.M., et al. (2018). Effect of SCN1A Mutation Type on Cannabidiol (CBD) Response in Patients with Dravet Syndrome: Subgroup Analysis of Phase 3 Trial GWPCARE1. American Epilepsy Society. New Orleans. (87)
Chiron 2000	Chiron C., et al. (2000). Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. Lancet; 356(9242):1638-42. (88)	No secondary publications identified.
Devinsky 2018	Devinsky, O., et al. (2018). Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology 90(14): e1204-e1211. (89)	Patel A, Devinsky O, Thiele E, Wong M, Appleton R, Harden C, et al. A dose ranging safety and pharmacokinetic study of cannabidiol (CBD) in children with Dravet syndrome (GWPCARE1). Neurology. 2017;88(16).(90)
Guerrini 2002	Guerrini R., et al. (2002). Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled Italian trial. Epilepsia 43 Suppl 8:155 (91)	No secondary publications identified.

McCoy 2018	McCoy, B., et al. (2018). "A prospective open-label trial of a CBD/THC cannabis oil in Dravet syndrome." Annals of Clinical and Translational Neurology **5**(9): 1077-1088. (93)	McCoy, B., et al. (2018). Dravet Syndrome: An Open Label Trial of a CBD/THC Cannabis Oil for Drug-Resistant Epilepsy. American Epilepsy Society. New Orleans. (92)
Sullivan 2018	Sullivan, J., et al. (2018). "Effect of ZX008 (fenfluramine HCl oral solution) on total seizures in Dravet syndrome." Neurology. Conference: 70th annual meeting of the American Academy of Neurology, AAN 2018. United states 90(24): e2187-e2188. (94)	• Wirrell, E., et al. (2018). "ZX008 (fenfluramine HCL oral solution) in Dravet syndrome: effect on convulsive seizure frequency in subjects who failed treatment with stiripentol prior to study 1." Neurology. Conference: 70th annual meeting of the American Academy of Neurology, AAN 2018. United states 90(24): e2188-e2189. (95) • Lagae, L., et al (2018). Fenfluramine HCl (Fintepla®) Provides Long-Term Clinically Meaningful Reduction in Seizure Frequency: Results of an Open-Label Extension Study. American Epilepsy Society. New Orleans. (96) • Nabbout, R., et al. (2018). What Defines "Clinical Meaningful Changes in Seizure Frequency?" Analysis of Data from a Phase 3 Clinical Trial of ZX008 in Dravet Syndrome. American Epilepsy Society. New Orleans.(97) • Lai, WW., et al. (2018). Long-Term Cardiovascular Safety of Fenfluramine HCl (Fintepla®) in the Treatment of Dravet Syndrome: Interim Analysis of an Open-Label Safety Extension Study. American Epilepsy Society. New Orleans. (98)
Nabbout 2018	Nabbout, R., et al. (2018). Fenfluramine (Fintepla®) Reduces Convulsive Seizure Frequency in Dravet Syndrome Patients Receiving an Antiepileptic Drug Treatment Regimen Containing Stiripentol: A Phase 3, Randomized, Placebo-Controlled Clinical Trial. American Epilepsy Society. New Orleans. (99)	
GWPCARE5	Devinsky, O., et al. (2017) Maintenance of long-term safety and efficacy of cannabidiol (CBD) treatment in Dravet syndrome (DS): results of the open-label extension (OLE) trial (GWPCARE 5). Developmental medicine and child neurology. Conference: 44th annual conference of the British Paediatric Neurology Association, BPNA 2018. United Kingdom 59, 126 (100)	• Halford, J., et al. (2018). Long-term Safety and Efficacy of Cannabidiol (CBD) in Patients with Lennox-Gastaut Syndrome (LGS): Results from Open-label Extension Trial (GWPCARE5). Neurology 90(15). (30) • Miller, I., et al. (2018). Maintenance of long-term safety and efficacy of cannabidiol (CBD) treatment in Dravet syndrome (DS): Results of the open-label extension (OLE) trial (GWPCARE5). Neurology 90(15). (101) • Laux, L., et al. (2018). Maintenance of long-term safety and efficacy of cannabidiol (CBD) treatment in Dravet syndrome (DS): Results of the open-label extension (OLE) trial (GWPCARE5). Annals of Neurology 84: S344. (31) • Scheffer,IE., J. H., Rima Nabbout, Rocio Sanchez-Carpintero, Yael Shiloh-Malawsky, Matthew Wong, Daniel Checketts, Kevan Van Landingham (2018). Long-Term Safety and Efficacy of Add-on Cannabidiol (CBD) Treatment in Patients with Dravet Syndrome (DS) in an Open-Label Extension (OLE) Trial (GWPCARE5). American Epilepsy Society. New Orleans. (29)

The list of all publications excluded after full text screening for the full systematic review in LGS and DS is shown below in Table 45.

Table 45. Studies excluded on full-text screening

Citation	Reason for exclusion
Aguirre-Velázquez, C.G. (2017). Report from a Survey of Parents Regarding the Use of Cannabidiol (Medicinal cannabis) in Mexican Children with Refractory Epilepsy. Neurology Research International 2017.	No data reported for LGS or DS
All Wales Medicines Strategy Group. (2012). Rufinamide (Inovelon) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS).	No relevant data for DS
All Wales Medicines Strategy Group. (2012). Rufinamide (Inovelon) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS).	No relevant data for DS
Al Otaibi, F., et al. (2011). Vagus nerve stimulation for epilepsy: Quality of life and patients' satisfaction. Epilepsia 52: 205.	Conference abstract before 2015
Alexandre, V., Jr., et al. (2011). Addressing overtreatment in patients with refractory epilepsy at a tertiary referral centre in Brazil. Epileptic Disord 13(1): 56-60.	No data reported for LGS or DS
Amir, M., et al. (1999). Self-efficacy and social support as mediators in the relation between disease severity and quality of life in patients with epilepsy. Epilepsia 40(2): 216-224.	No data reported for LGS or DS
Arzimanoglou, A., et al. (2017). Safety and cognitive development effects of rufinamide in paediatric patients with Lennox-Gastaut syndrome (LGS): Study 303 final results. Developmental Medicine and Child Neurology 59: 135-136.	No relevant data for DS
Arzimanoglou A., et al. (2016). Safety and pharmacokinetic profile of rufinamide in pediatric patients aged less than 4 years with Lennox-Gastaut syndrome: an interim analysis from a multicenter, randomized, active-controlled, open-label study. European Journal of Paediatric Neurology; 20(3):393-402.	No relevant data for DS
Arzimanoglou, A., et al. (2018). Efficacy and safety of adjunctive rufinamide in Lennox-Gastaut Syndrome (LGS): Results from studies 022, 022e, 303, 304, and 305. Neurology 90(15).	No relevant data for DS
Arzimanoglou, A., et al. (2016). Safety and Cognitive Development Effects of Adjunctive Rufinamide in Pediatric Subjects with Inadequately Controlled Lennox-Gastaut Syndrome (LGS): Final Results From Study 303. Conference: American Epilepsy Society (AES).	No relevant data for DS
Arzimanoglou, A., et al. (2018). Evaluation of long-term safety, tolerability, and behavioral outcomes with adjunctive rufinamide in pediatric patients (>1 to <4 years old) with Lennox-Gastaut syndrome: Final results from randomized study 303." European Journal of Paediatric Neurology	No relevant data for DS
Auvin S., et al. (2016). European non-interventional registry study of antiepileptic drug use in patients with Lennox-Gastaut syndrome. Epilepsia;57:180.	No relevant data for DS
Auvin, S., et al. (2018). Post Hoc analysis of rufinamide study 303: Seizure-free days in patients with Lennox-Gastaut Syndrome (LGS). Neurology 90(15).	No relevant data for DS
Baca, C. B., et al. (2011). Psychiatric and medical comorbidity and quality of life outcomes in childhood-onset epilepsy. Pediatrics 128(6): e1532-1543.	No data reported for LGS or DS
Bailey L.D., et al. (2018). Impact of severe childhood epilepsy on siblings under 18 years of age. European Congress on Epileptology, Vienna.	No relevant data for DS
Baker, G.A., et al. (2002). The effects of adjunctive topiramate therapy on seizure severity and health-related quality of life in patients with refractory epilepsy - a Canadian study. Seizure 11(1): 6-15.	No data reported for LGS or DS
Battaglia, A., et al. (1991) Double-blind placebo-controlled trial of flunarizine as add-on therapy in refractory childhood epilepsy. Brain & development 13, 217-222.	No data reported for LGS or DS
Begley, C. E., et al. (2000). The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. Epilepsia 41(3): 342-351.	No data reported for LGS or DS

Citation	Reason for exclusion
Benbadis, S., et al. (2013). Response to clobazam in VNS vs. Non-VNS patients: Post-hoc subgroup analyses of contain. Neurology 80(1).	Conference abstract before 2015
Benedict A, et al. (2010). The cost effectiveness of rufinamide in the treatment of Lennox-Gastaut syndrome in the UK. PharmacoEconomics; 28(3):185-99.	No relevant data for DS
Bien, C. G., et al. (2006). Assessment of the long-term effects of epilepsy surgery with three different reference groups. Epilepsia 47(11): 1865-1869.	No data reported for LGS or DS
Boon, P., et al. (2002). Direct medical costs of refractory epilepsy incurred by three different treatment modalities: a prospective assessment. Epilepsia 43(1): 96-102.	No data reported for LGS or DS
Borlot, F., et al. (2014). Epilepsy transition: Challenges of caring for adults with childhood-onset seizures. Epilepsia 55(10): 1659-1666.	No data reported for LGS or DS
Brigo F., et al. (2017). Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy. Cochrane Database of Systematic Reviews (5).	Systematic review
Brunklaus, A., et al. (2011). Assessment and predictors of health-related quality of life in Dravet syndrome. Developmental Medicine and Child Neurology 53: 15.	Conference abstract before 2015
Brunklaus A., et al. (2011). Comorbidities and predictors of health-related quality of life in Dravet syndrome. Epilepsia;52(8):1476-82.	No relevant data for DS
Buchanan, N. (1996). Lamotrigine: Clinical experience in 200 patients with epilepsy with follow-up to four years. Seizure 5(3): 209-214.	No relevant outcomes reported
Buchhalter, J., et al. (2014). Long-term efficacy of clobazam for drop attacks in patients with Lennox-Gastaut syndrome is consistent across the age spectrum. Epilepsy Currents 14: 207-208.	Conference abstract before 2015
Camfield, C. and Camfield, P. (2008). Twenty years after childhood-onset symptomatic generalized epilepsy the social outcome is usually dependency or death: A population-based study. Developmental Medicine and Child Neurology 50(11): 859-863.	No data reported for LGS or DS
Camfield, C., et al. (2003). Assessing the impact of pediatric epilepsy and concomitant behavioral, cognitive, and physical/neurologic disability: Impact of Childhood Neurologic Disability Scale. Dev Med Child Neurol 45(3): 152-159.	No data reported for LGS or DS
Camfield, P. (2011). Helping families cope with the devastation of Dravet syndrome. Epilepsia 52: 268.	Conference abstract before 2015
Camfield, P.R., et al. (2011). Strategies for transitioning to adult care for youth with Lennox-Gastaut syndrome and related disorders. Epilepsia 52(SUPPL. 5): 21-27.	Conference abstract before 2015
Camfield, P., et al. (2016). Helping Families Cope with the Severe Stress of Dravet Syndrome. Canadian Journal of Neurological Sciences 43(S3): S9-S12.	No relevant outcomes reported
Cárdenas, J. M., et al. (2014). Clinical response in patients with vagus nerve stimulator for drug-resistant epilepsy. Epileptic Disorders 16: 31.	Conference abstract before 2015
Carpay, H. A., et al. (1998). Epilepsy in childhood: an audit of clinical practice. Arch Neurol 55(5): 668-673.	No relevant outcomes reported
Choi, E. J., et al. (2011). Factors contributing to concerns of persons living with epilepsy. Seizure 20(1): 14-17.	No data reported for LGS or DS
Chung, S. S., et al. (2018). Combination AED treatment with clobazam in patients with Lennox-Gastaut syndrome: Post hoc analyses of the contain study. Neurology 90(15).	No relevant data for DS
Clements, K. M., et al. (2012). Cost-effectiveness analysis of antiepileptic drugs in the treatment of Lennox-Gastaut syndrome. Value in Health 15(4): A144.	Conference abstract before 2015
Clements K.M., et al. (2013). Cost-effectiveness analysis of antiepileptic drugs in the treatment of Lennox-Gastaut syndrome. Epilepsy and Behavior;29(1):184-9.	No relevant data for DS
Conry J., et al. (2009). Clobazam in the treatment of Lennox-Gastaut syndrome. Epilepsia; 50(5):1158-66.	No relevant data for DS
Conry, J. A., et al. (2014). Stable dosages of clobazam for Lennox-Gastaut syndrome are associated with sustained drop-seizure and total-seizure improvements over 3 years. Epilepsia 55(4): 558-567.	No relevant data for DS

Citation	Reason for exclusion
Conry, J., et al. (2014). Efficacy and safety of clobazam in Lennox-Gastaut syndrome: Completers analysis of the 15-week, phase III contain trial. Neurology 82(10).	Conference abstract before 2015
Coqué, N., et al. (2012). On the use of intra rectal Valium in patients with Dravet syndrome: Families opinion. Epilepsia 53: 113.	Conference abstract before 2015
Coqué, N., et al. (2013). Comparative assessment of families' experience of patients with Dravet syndrome on the use of rectal Valium and oral midazolam. Epilepsia 54: 336.	Conference abstract before 2015
Coqué, N., et al. (2014). Antiepileptic treatment in Dravet syndrome: An additional complexity for the families. Epilepsia 55: 213.	Conference abstract before 2015
Cramer, J., et al. (2009). Domains of concern for families whose child has Lennox-Gastaut syndrome. Epilepsia 50: 177.	Conference abstract before 2015
Crumrine P., et al. (1989). Double-blind, placebo-controlled evaluation of cinromide in patients with the Lennox-Gastaut Syndrome. Epilepsia;30(4):422-9.	No relevant data for DS
Dainese, F., et al. (2012). Efficacy of vagus nerve stimulation in 28 consecutive patients with treatment resistant epilepsy not eligible for epilepsy surgery. Epilepsia 53: 106.	Conference abstract before 2015
Davidson, D. L. and Macdonald, S. (2002). The costs of trauma caused by seizures: can they be reduced? Seizure 11(5): 344-347.	No data reported for LGS or DS
de Kinderen, R. J., et al. (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): 41-50.	No data reported for LGS or DS
De Liso, P., et al. (2014). AEDs efficacy in the Dravet syndrome: A cross-sectional study. Epilepsia 55: 28.	Conference abstract before 2015
Deck, G. and Montouris, G. (2014). Clobazam as an adjunctive treatment in refractory seizures: One year follow up in the clinical setting. Epilepsy Currents 14: 226.	Conference abstract before 2015
Desnous, B., et al. (2011). Parental perceptions of fever and fever management practices in children with Dravet Syndrome. European Journal of Paediatric Neurology 15: S34-S35.	Conference abstract before 2015
Devinsky, O., et al. (2018). Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. New England Journal of Medicine 378(20): 1888-1897.	No relevant data for DS
Dodson, W. E. (1993). Felbamate in the treatment of Lennox-Gastaut syndrome: Results of a 12- month open-label study following a randomized clinical trial. Epilepsia 34(SUPPL. 7): S18-S24.	No relevant data for DS
Dolenc, M. and Rener Primec, Z. (2009). Efficacy of VNS treatment on seizure frequency and daily activities in children and adolescents. European Journal of Paediatric Neurology 13: S80.	Conference abstract before 2015
Donaldson, J. A., et al. (1997). Lamotrigine adjunctive therapy in childhood epileptic encephalopathy (the Lennox Gastaut syndrome). Epilepsia 38(1): 68-73.	No relevant outcomes reported
Dumitrascu, V., et al. (2009). Safety and efficacy of Topiramate, in pediatric epileptic Patients. Basic and Clinical Pharmacology and Toxicology 105: 129.	Conference abstract before 2015
Eisai LTD., (2013) A Placebo-Controlled, Double-Blind Comparative Study of E2080 in Lennox-Gastaut Syndrome Patients (Study E2080-J081-304). NCT online	No relevant data for DS
Eom, S., et al. (2013). Psychological characteristics of pediatric epilepsy with autistic regression. Epilepsia 54: 99.	Conference abstract before 2015
Eriksson, A.S., et al. (2001). The effect of lamotrigine on epileptiform discharges in young patients with drug-resistant epilepsy. Epilepsia 42(2): 230-236.	No relevant outcomes reported
Eriksson A., et al. (1998). The efficacy of lamotrigine in children and adolescents with refractory generalized epilepsy: a randomized, double-blind, crossover study. Epilepsia; 39(5):495-501.	No relevant data for DS
Fasano, A., et al. (2015). Antecollis and levodopa-responsive parkinsonism are late features of Dravet syndrome. Epilepsy Currents 15: 50.	No relevant outcomes reported

Citation	Reason for exclusion
Ferreira J., et al. (2015). Effect of adjunctive rufinamide in pediatric patients with inadequately controlled Lennox-Gastaut syndrome (LGS): Interim pharmacokinetic and safety results from study 303. Neurology;84.	No relevant data for DS
Feucht, M., et al. (2010). Long-term outcome of vagus nerve stimulation (VNS) in children with Dravet syndrome (DS). Epilepsia 51: 92-93.	Conference abstract before 2015
Forbes, R. B., et al. (2003). Cost-utility analysis of vagus nerve stimulators for adults with medically refractory epilepsy. Seizure 12(5): 249-256.	No data reported for LGS or DS
Francois C., et al. (2016). Healthcare resource utilization among commercially insured clobazam-treated patients with Lennox-Gastaut syndrome. Neurology;86(16).	No relevant data for DS
French J., et al. (2017). Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a multi-center, randomized, double-blind, placebo controlled trial (GWPCARE4). Neurology;88(16).	No relevant data for DS
Frost, M., et al. (2001). Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. Epilepsia 42(9): 1148-1152.	No relevant outcomes reported
Gallop K., et al. (2010). Lennox-Gastaut Syndrome (LGS): Development of conceptual models of health-related quality of life (HRQL) for caregivers and children. Seizure;19(1): 23-30.	No relevant data for DS
Gibson P.A. (2014). Lennox-Gastaut syndrome: Impact on the caregivers and families of patients. Journal of Multidisciplinary Healthcare;7:441-8.	No relevant data for DS
Glauser, T., et al. (2005) Efficacy and safety of rufinamide adjunctive therapy in patients with Lennox-Gastaut syndrome (LGS): a multicenter, randomized, double-blind, placebo-controlled, parallel trial. Neurology 64, 1826	Conference abstract before 2015
Glauser, T., et al. (2009) Early and sustained response to rufinamide as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome. Epilepsia 50 Suppl 11, 261	Conference abstract before 2015
Glauser T., et al. (2008). Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology;70(21):1950-8.	No relevant data for DS
Glauser, T., et al. (2009) Early and sustained response to rufinamide as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome. Epilepsia 50 Suppl 11, 261	No relevant data for DS
Glauser, T. A., et al. (2000). Topiramate in Lennox-Gastaut syndrome: Open-label treatment of patients completing a randomized controlled trial. Epilepsia 41(4 Suppl.): S86-S90.	No relevant data for DS
Gomez, G.S. and Pizarro Castellanos, M. (2013). Direct costs of Lennox-Gastaut syndrome in a highly specialized hospital. Epilepsy Currents 13: 156.	Conference abstract before 2015
Goodacre, S. W., et al. (2012). Health utility after emergency medical admission: a cross-sectional survey. Health Qual Life Outcomes 10: 20.	Conference abstract before 2015
Goodkin, H., et al. (2014). Critical care of pediatric refractory convulsive status epilepticus. Results from the pediatric status epilepticus research group (pSERG). Epilepsy Currents 14: 445-446.	No data reported for LGS or DS
Gottas A., et al. (2016). Surveillance of the orphan drug rufinamide in Norway: Patient and population aspects. Epilepsia;57:187.	No relevant data for DS
Guerreiro, M.M., et al. (1999). A pilot study of topiramate in children with Lennox-Gastaut syndrome. Arq Neuropsiquiatr 57(2a): 167-175.	No relevant outcomes reported
Guerrini, R., et al. (2001). The costs of childhood epilepsy in Italy: comparative findings from three health care settings. Epilepsia 42(5): 641-646.	No data reported for LGS or DS
Hamer, H.M., et al. (2006). Direct and indirect costs of refractory epilepsy in a tertiary epilepsy center in Germany. Epilepsia 47(12): 2165-2172.	No data reported for LGS or DS
Hancock, E.C, Cross, J.H. (2013) Treatment of Lennox-Gastaut syndrome. Cochrane Database of Systematic Reviews; (2).	No relevant data for DS

Citation	Reason for exclusion
Hewage, N.N., et al. (2015). Efficacy of add on corticosteroids in the management of pharmaco resistant epilepsy in Lennox-Gastaut syndrome (LGS), multi center pilot study. Epilepsia 56: 96.	No relevant outcomes reported
Ilyas, M., et al. (2014). Palliative surgical resections in children with intractable epilepsy and bilateral epileptic foci: Surgical results in the Detroit series. Epilepsy Currents 14: 62.	Conference abstract before 2015
Inanaga K., et al.(1989). Clinical study of oral administration of DN-1417, a TRH analog, in patients with intractable epilepsy. Epilepsia;30(4):438-45.	No relevant data for DS
Isojarvi, J. and Lee, D. (2013). Response to clobazam in relationship to baseline seizure frequency. Annals of Neurology 74: S70.	Conference abstract before 2015
Isojarvi, J., et al. (2014). Long-term efficacy of clobazam for drop attacks in Lennox-Gastaut syndrome is consistent across patient age ranges. Neurology 82(10).	Conference abstract before 2015
Isojarvi, J., et al. (2014). Patients treated with clobazam experienced fewer seizure-related injuries than placebo patients during the phase III contain trial in Lennox-Gastaut syndrome. Neurology 82(10).	Conference abstract before 2015
Isojarvi, J., et al. (2018) Optimizing clobazam treatment in patients with Lennox-Gastaut syndrome. Epilepsy & Behavior **78**, 149-154 DOI: 10.1016/j.yebeh.2017.10.003	No relevant data for DS
Isojarvi, J., et al. (2016) Clobazam-treated patients with Lennox-Gastaut syndrome experienced fewer seizure-related injuries than placebo patients during trial OV-1012. Epilepsia 57, e113-e116 DOI: 10.1111/epi.13388	No relevant data for DS
Isojarvi J. and Lee, D (2013). Response to clobazam in relationship to baseline seizure frequency. Neurology 80(1 Meeting Abstracts).	Conference abstract before 2015
Jensen, P.K. (1994). Felbamate in the treatment of Lennox-Gastaut syndrome. Epilepsia 35(Suppl. 5): S54-S57.	No relevant data for DS
Joo, E., et al. (2014). Sleep wake disturbances and seizures in children with Dravet syndrome. Sleep 37: A319.	Conference abstract before 2015
Joshi, C., et al. (2017). Treatment with cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a Multicenter, Randomized, Double-blind, Placebo Controlled Trial (GWPCARE4)." Annals of Neurology 82: S293.	No relevant data for DS
Kellett, M.W., et al. (1997). Quality of life after epilepsy surgery. J Neurol Neurosurg Psychiatry 63(1): 52-58.	No data reported for LGS or DS
Kim, J.A., et al. (2013). Treatment outcome of Lennox-Gastaut syndrome. Epilepsia 54: 233.	Conference abstract before 2015
Kjelgaard, D.B., et al. (2016). Experiences of receiving a genetic diagnosis and the impact on everyday life. Epilepsia 57: 117-118.	No relevant outcomes reported
Klimach, V.J. (2009). The community use of rescue medication for prolonged epileptic seizures in children. Seizure 18(5): 343-346.	No data reported for LGS or DS
Kluger, G., et al. (2010). Adjunctive rufinamide in Lennox-Gastaut syndrome: A long-term, open-label extension study. Acta Neurologica Scandinavica 122(3): 202-208.	No relevant data for DS
Korsak T., et al. (2018). How to manage the impossible (HMI)? Anthropological research: understanding parents facing diagnosis of Dravet syndrome in their child. European Congress on Epileptology, Vienna.	No relevant data for DS
Kothare, S., et al. (2017). Dosing considerations for rufinamide in patients with Lennox-Gastaut syndrome: Phase III trial results and real-world clinical data. Seizure 47: 25-33.	No relevant data for DS
Kuchenbuch, M., et al. (2012). Transition's gap from paediatric to adult system care of patients with epileptic encephalopathy: A myth or a reality? Epilepsia 53: 71-72.	No data reported for LGS or DS
Lachaine., J. and Lambert-Obry, V. (2014). Cost-effectiveness of stiripentol in the treatment of severe myoclonic epilepsy in infancy in Canada. Value in Health 17(3): A61.	Conference abstract before 2015
Lee, D., et al. (2014). Clobazam response in patients with previous benzodiazepine use: Sub-analysis of the phase III contain trial in Lennox-Gastaut syndrome (LGS). Neurology 82(10).	Conference abstract before 2015

Citation	Reason for exclusion
Lee, D., et al. (2014). Clobazam-treated patients with LGS experienced fewer seizure-related injuries than placebo patients during the contain trial. Epilepsy Currents 14: 396-397.	Conference abstract before 2015
Lee, D., et al. (2014). Long-term response to clobazam by baseline seizure frequency in patients with Lennox-Gastaut syndrome (LGS). Neurology 82(10).	Conference abstract before 2015
Li, X. and Knoth, R. (2015). Examining healthcare utilization and costs in patients with Lennox-Gastaut syndrome: A real-world observational study in a U.S. health plan. Journal of Managed Care and Specialty Pharmacy 21: S48.	No relevant data for DS
Liang, S., et al. (2015). Resective operation combined corpus callosotomy in patients with Lennox-Gastaut syndrome. Epilepsia 56: 144-145.	No relevant outcomes reported
Lundgren, J., et al. (1998). Vagus nerve stimulation in 16 children with refractory epilepsy. Epilepsia 39(8): 809-813.	No relevant outcomes reported
Majoie, H.J.M., et al. (2005). Vagus nerve stimulation in patients with catastrophic childhood epilepsy, a 2-year follow-up study. Seizure 14(1): 10-18.	No data reported for LGS or DS
Mak, W., et al. (1999). Cost of epilepsy in Hong Kong: experience from a regional hospital. Seizure 8(8): 456-464.	No data reported for LGS or DS
Marras, C. E., et al. (2013). Health Technology Assessment report on the presurgical evaluation and surgical treatment of drug-resistant epilepsy. Epilepsia 54 Suppl 7: 49-58.	No data reported for LGS or DS
Marsh E, et al. (2018). Maintained safety and efficacy of cannabidiol in a long-term open-label trial in patients with Lennox-Gastaut syndrome (GWPCARE5). European Congress on Epileptology, Vienna.	No relevant data for DS
Mazurkiewicz-Beldzinska, M., et al. (2017). Treatment with cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a multi-center, randomised, double-blind, placebo controlled trial (GWPCARE4). Epilepsia 58: S55.	No relevant data for DS
McMurray, R. and Striano, P. (2016). Treatment of Adults with Lennox-Gastaut Syndrome: Further Analysis of Efficacy and Safety/Tolerability of Rufinamide. Neurology and Therapy 5(1): 35-43.	No relevant data for DS
Mikati, M.A., et al. (2009). Quality of life after vagal nerve stimulator insertion. Epileptic Disorders 11(1): 67-74.	No data reported for LGS or DS
Mitchell, W., et al. (2012). Clobazam is efficacious for drop attacks in patients with Lennox-Gastaut syndrome across the age spectrum: Subgroup analysis of the contain trial. Neurology 78(1).	Conference abstract before 2015
Mohan, M., et al. (2014). Neuropsychiatric comorbidities in patients with VNS for intractable epilepsy in a tertiary neuropsychiatry service. Epilepsia 55: 108.	Conference abstract before 2015
Montouris G., et al. (2016). A life-course assessment of medication use and medical costs of Lennox-Gastaut syndrome (LGS). Value in Health;19(3):A67.	No relevant data for DS
Montouris G., et al. (2016). A life-course assessment of treatment patterns and healthcare costs of Lennox-Gastaut syndrome (LGS). Neurology;86(16).	No relevant data for DS
Morrison, G., et al. (2018). Exposure-Response Analysis of Cannabidiol (CBD) oral solution for the treatment of Lennox-Gastaut syndrome. Neurology 90(15).	No relevant data for DS
Morrison G., (2018). Exposure-response analysis of cannabidiol for the treatment of Lennox-Gastaut syndrome. European Congress on Epileptology, Vienna.	No relevant data for DS
Motte J., et al. (1997) Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. Lamictal Lennox-Gastaut Study Group. New England Journal of Medicine; 337(25):1807-12.	No relevant data for DS
Mount, C.E., et al. (2016). The role of stiripentol in intractable epilepsy. Developmental Medicine and Child Neurology 58: 46.	No relevant outcomes reported
Mount, C., et al. (2016). The role of stiripentol in intractable epilepsy. Archives of Disease in Childhood 101: A58-A59.	No relevant outcomes reported
Nabbout, R., et al. (2012). On the use of intra rectal Valium in patients with Dravet syndrome: Families' experience. Epilepsia 53: 121.	Conference abstract before 2015

Citation	Reason for exclusion
Nabbout, R., et al. (2018). Development and content validation of a preliminary core set of patient- and caregiver-relevant outcomes for inclusion in a potential composite endpoint for Dravet Syndrome. Epilepsy and Behavior 78: 232-242.	No relevant data for DS
Nabbout, R., et al. (2016). Towards a composite clinical endpoint: Identifying a core set of patient and caregiver relevant outcome measures through qualitative research on the global impact of Dravet syndrome. Epilepsia 57: 95.	No relevant outcomes reported
Nanda, R.N., et al. (1977). Treatment of epilepsy with clonazepam and its effect on other anticonvulsants. J Neurol Neurosurg Psychiatry 40(6): 538-543.	No data reported for LGS or DS
Ng, Y.T., et al. (2012). Early and sustained response to clobazam by patients with Lennox-Gastaut syndrome during the contain trial. Neurology 78(1).	Conference abstract before 2015
Ng Y, et al. (2016). Response durability analyses from a rufinamide pivotal trial in Lennox-Gastaut syndrome (LGS). Neurology;86(16).	No relevant data for DS
Ng, Y.T., et al. (2015). Clobazam is equally safe and efficacious for seizures associated with Lennox-Gastaut syndrome across different age groups: Post hoc analyses of short- and long-term clinical trial results. Epilepsy Behav 46: 221-226.	No relevant data for DS
Ng, Y.T., et al. (2012). Long-term safety and efficacy of clobazam for Lennox-Gastaut syndrome: interim results of an open-label extension study. Epilepsy Behav 25(4): 687-694.	No relevant data for DS
Ng, Y.T., et al. (2011). Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology;77(15):1473-81.	No relevant data for DS
Nielsen C., et al. (2018). Dravet syndrome – parents coping with adversity. European Congress on Epileptology, Vienna.	No relevant data for DS
NIHR HSRIC. (2016) Fenfluramine for Dravet syndrome - first line.	No relevant outcomes reported
Nikanorova, M., et al. (2011). A European registry of antiepileptic drug use in patients with Lennox-Gastaut syndrome: Update of current status. Epilepsia 52: 132.	Conference abstract before 2015
Ohtahara, S., et al. (2007). Single-blind and controlled comparative study of lamotrigine with zonisamide for refractory pediatric epilepsy. Journal of the Japan Epilepsy Society 25(4): 425-440.	Irretrievable
Ohtsuka Y., et al.(2014). Rufinamide as an adjunctive therapy for Lennox-Gastaut syndrome: A randomized double-blind placebo-controlled trial in Japan. Epilepsy Research;108(9):1627-36.	No relevant data for DS
Ohtsuka, Y., et al. (2016). Long-term safety and seizure outcome in Japanese patients with Lennox-Gastaut syndrome receiving adjunctive rufinamide therapy: An open-label study following a randomized clinical trial. Epilepsy Research 121: 1-7.	No relevant data for DS
Orosz, I., et al. (2014). Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. Epilepsia 55(10): 1576-1584.	No data reported for LGS or DS
Paolicchi, J., et al. (2013). Aggression in Lennox-Gastaut syndrome (LGS) patients treated with clobazam during the contain trial. Neurology 80(1).	Conference abstract before 2015
Paolicchi, J.M., et al. (2015). Clobazam and Aggression-Related Adverse Events in Pediatric Patients with Lennox-Gastaut Syndrome. Pediatric Neurology **53**(4): 338-342.	No relevant data for DS
Patel, A., et al. (2017). Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): results of a dose-ranging, multi-center, randomized, double-blind, placebo-controlled trial (GWPCARE3). Neurology 89(8): e100.	No relevant data for DS
Patel, A.D., et al.(2018). Long-Term Safety and Efficacy of Add-on Cannabidiol (CBD) Treatment in Patients with Lennox-Gastaut Syndrome (LGS) in an Open-Label Extension (OLE) Trial (GWPCARE5). American Epilepsy Society. New Orleans.	No relevant data for DS
Penberthy, L.T., et al. (2005). Estimating the economic burden of status epilepticus to the health care system. Seizure 14(1): 46-51.	No data reported for LGS or DS
Perez, J., et al. (1999). Stiripentol: Efficacy and tolerability in children with epilepsy. Epilepsia 40(11): 1618-1626.	No data reported for LGS or DS

Citation	Reason for exclusion
Pina-Garza J.E., et al. (2017). Healthcare resource utilization among patients with Lennox-Gastaut syndrome treated with clobazam. Neurology;88(16).	No relevant data for DS
Pina-Garza J.E., et al. (2015). Development of a claims-based classifier to identify Lennox-Gastaut syndrome. Neurology;84.	No relevant data for DS
Pina-Garza M.G., et al. (2017). Healthcare costs among patients with Lennox-Gastaut syndrome treated with clobazam. ISPOR. Boston.	No relevant data for DS
Ragona, F., et al. (2015). Long-term evolution of Dravet syndrome: Cognitive impairment, behavioral phenotype and adaptive functioning. Epilepsia 56: 159-160.	No relevant outcomes reported
Reaven, N.L., et al. (2018). Burden of illness in patients with possible Lennox-Gastaut syndrome: A retrospective claims-based study. Epilepsy and Behavior 88: 66-73.	No relevant data for DS
Renfroe, J., et al. (2012). Effects of concomitant lamotrigine or valproate therapy on clobazam for Lennox-Gastaut syndrome: Sub-analyses of the contain trial. Neurology 78(1).	Conference abstract before 2015
Renfroe, J., et al. (2013). Somnolence and sedation were transient adverse events for most patients receiving clobazam therapy during the contain study in Lennox-Gastaut syndrome (LGS). Neurology 80(1).	Conference abstract before 2015
Ritter, F. J. and Wical, B (2012). Successful corpus callosotomy in a child with Dravet syndrome and SCN1A abnormality. Epileptic Disorders 14(2): 203-204.	Conference abstract before 2015
Ritter, F.J., et al. (1993). Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). New England Journal of Medicine; 328(1):29-33.	No relevant data for DS
Rosenberg, E.C., et al. (2017). Quality of Life in Childhood Epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. Epilepsia 58(8): e96-e100.	No relevant data for DS
Rosenfeld, W., et al. (2013). Use of rescue medications by Lennox-Gastaut (LGS) patients treated with clobazam during the contain trial. Neurology 80(1).	Conference abstract before 2015
Rosenfeld, W., et al. (2014). Response to clobazam among benzodiazepine experienced LGS patients during the contain trial. Epilepsy Currents 14: 390-391.	Conference abstract before 2015
Rychlicki, F., et al. (2006). Vagus nerve stimulation: Clinical experience in drug-resistant pediatric epileptic patients. Seizure 15(7): 483-490.	No data reported for LGS or DS
Sabaz, M., et al. (2000). Validation of a new quality of life measure for children with epilepsy. Epilepsia 41(6): 765-774.	No data reported for LGS or DS
Sabaz, M., et al. (2001). The health-related quality of life of children with refractory epilepsy: a comparison of those with and without intellectual disability. Epilepsia 42(5): 621-628.	No data reported for LGS or DS
Sachdeo R., et al. (1999). A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. Neurology; 52(9):1882-7.	No relevant data for DS
Scottish Medicines Consortium (2012). Rufinamide 40mg/mL oral suspension (Inovelon®)	No relevant data for DS
Scottish Medicines Consortium (2007). Rufinamide 100mg, 200mg and 400mg tablets.	No relevant data for DS
Scottish Medicines Consortium (2008). Rufinamide, 100mg, 200mg and 400mg tablets (Inovelon®)	No relevant data for DS
Siegel H., et al. (1999). The efficacy of felbamate as add-on therapy to valproic acid in the Lennox-Gastaut syndrome. Epilepsy Research; 34(2-3):91-97.	No relevant data for DS
Skornicki, M., et al. (2012). Budget impact analysis of antiepileptic drugs in the treatment of Lennox-Gastaut syndrome. Value in Health 15(4): A141-A142.	Conference abstract before 2015
Skornicki M, et al. (2004). Budget impact analysis of antiepileptic drugs for Lennox-Gastaut syndrome. Journal of Managed Care Pharmacy;20(4):400-6.	No relevant data for DS
Stavem, K., et al. (2000). Acupuncture in intractable epilepsy: lack of effect on health-related quality of life. Seizure 9(6): 422-426.	No data reported for LGS or DS

Citation	Reason for exclusion
Steel D., et al. (2017). Caregiver burden in a large cohort of Dravet syndrome patients: Impact on quality of life and association with disease severity. Developmental Medicine and Child Neurology; 59:72-3.	No relevant data for DS
Stern J., et al. (2016). Changes in healthcare resource utilization among Medicaid patients with Lennox-Gastaut syndrome initiating clobazam treatment. Neurology;86(16).	No relevant data for DS
Stern J., et al. (2016). Characteristics of clobazam and non-clobazam treated Lennox-Gastaut syndrome patients: A retrospective cohort study. Neurology;86(16).	No relevant data for DS
Stern, J., et al. (2016). Healthcare resource utilization and projected long-term cost savings following clobazam initiation in patients with Lennox-Gastaut syndrome. Journal of Managed Care and Specialty Pharmacy 22: S56.	No relevant data for DS
Striano P., McMurray R. (2016). Efficacy of rufinamide as adjunctive treatment for adults with Lennox-Gastaut syndrome: Subgroup analysis from a phase III trial. Neurology;86(16).	No relevant data for DS
Striano P., McMurray R. (2015). Rufinamide as adjunctive treatment for adults with Lennox-Gastaut syndrome: Subgroup analysis from a phase III trial. Epilepsia;56:211.	No relevant data for DS
Swindle, J. P., et al. (2012). Economic burden of Lennox-Gastaut syndrome. Value in Health 15(4): A143.	Conference abstract before 2015
Taft, C., et al. (2014). Health-related quality of life, mood, and patient satisfaction after epilepsy surgery in Sweden - a prospective controlled observational study. Epilepsia 55(6): 878-885.	No data reported for LGS or DS
Thiele E., et al. (2016). Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome; results of a multi-center, randomized. double-blind, placebo-controlled trial (GWPCARE4). American Epilepsy Society.	No relevant data for DS
Thiele, E., et al. (2018). Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet; 391:1085-1096.	No relevant data for DS
Thiele, E., et al. (2018). Long-term safety and efficacy of cannabidiol (CBD) in patients with Lennox-Gastaut syndrome (LGS): Results of the open-label extension (OLE) trial (GWPCARE5). Annals of Neurology 84: S336.	No relevant data for DS
Tolbert, D., et al. (2012). Withdrawal-related adverse events from clinical trials of clobazam in Lennox-Gastaut syndrome (LGS). Neurology 78(1).	Conference abstract before 2015
Tolbert, D., et al. (2014) Withdrawal-related adverse events from clinical trials of clobazam in Lennox-Gastaut syndrome. Epilepsy & Behavior 37, 11-15	No relevant data for DS
van Hout, B., et al. (1997). Relationship between seizure frequency and costs and quality of life of outpatients with partial epilepsy in France, Germany, and the United Kingdom. Epilepsia 38(11): 1221-1226.	No data reported for LGS or DS
Vassella, F., et al. (1978) Double-blind crossover trial of the anticonvulsive effect of phenobarbital and valproate in Lennox syndrome. Schweizerische Medizinische Wochenschrift 108, 713-716	Irretrievable
Verdian, L., et al. (2009). The impact of Lennox-Gastaut syndrome (LGS) on health related quality of life - A conceptual model. Value in Health 12(3): A194.	Conference abstract before 2015
Verdian L., Yi Y. (2010). Cost-utility analysis of rufinamide versus topiramate and lamotrigine for the treatment of children with Lennox-Gastaut Syndrome in the United Kingdom. Seizure;19(1):1-11.	No relevant data for DS
Villanueva, V., et al. (2013). Quality of life and economic impact of refractory epilepsy in Spain: the ESPERA study. Neurologia 28(4): 195-204.	Full text not in English
Wang, C.Y. and Yeh, G.C. (2011). First report of Taiwan child neurology society project on vagus nerve stimulation results for intractable epileptic children. Epilepsia 52: 73.	Conference abstract before 2015
Wheless, J., et al. (2014). Long-term response to clobazam in relation to baseline seizure frequency in patients with Lennox-Gastaut syndrome. Epilepsy Currents 14: 207.	Conference abstract before 2015

Citation	Reason for exclusion
Wheless, J.W., et al. (2014). Clobazam is efficacious for patients across the spectrum of disease severity of LGS: post hoc analyses of clinical trial results by baseline seizure-frequency quartiles and VNS experience. Epilepsy & Behavior:B 41: 47-52.	No relevant data for DS
Widjaja, E., et al. (2013). Diagnostic evaluation in patients with intractable epilepsy and normal findings on MRI: a decision analysis and cost-effectiveness study. AJNR Am J Neuroradiol 34(5): 1004-1009, s1001-1002.	No relevant outcomes reported
Wild, D., et al. (2009). The impact of Lennox-Gastaut syndrome (LGS) on health related quality of life: A conceptual model. Epilepsia 50: 165-166.	Conference abstract before 2015
Wirrell, E., et al. (2017). Cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a dose ranging, multicenter, randomized, double blind, placebo-controlled trial (GWPCARE3). Annals of Neurology 82: S279-S280.	No relevant data for DS
Wirrell, E. C., et al. (2018). Cannabidiol (CBD) treatment effect and adverse events (AEs) by time in patients with Lennox-Gastaut syndrome (LGS): Pooled results from 2 trials." Neurology 90(15).	No relevant data for DS
Wirrell, E., et al. (2017). Cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox Gastaut syndrome (LGS): results of a dose ranging, multicenter, randomized, double blind, placebo controlled trial (GWPCARE3). Annals of neurology. Conference: 46th annual meeting of the child neurology society. United States 82(Supplement 21): S279 - S280.	No relevant data for DS
Wirrell, E., et al. (2018). "Cannabidiol (CBD) treatment effect and adverse events (AES) by time in patients with Lennox-Gastaut syndrome (LGS): Pooled results from 2 trials." Annals of Neurology 84: S341.	No relevant data for DS
Yasumoto, S., et al. (2011). Steroid pulse therapy as an effective treatment for refractory epilepsy in children with glutamate receptor (GLuR) antibodies. Epilepsia 52: 208.	Conference abstract before 2015
Zamponi, N., et al. (2011). Effectiveness of vagal nerve stimulation (VNS) in patients with drop-attacks and different epileptic syndromes. Seizure 20(6): 468-474.	No relevant outcomes reported
Zuberi, S., et al. (2017). Cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox-Gastaut syndrome (LGS): Results of a dose-ranging, multi-centre, randomised, double-blind, placebo-controlled trial (GWPCARE3). Epilepsia 58: S13-S14.	No relevant data for DS
Zuberi, S., et al. (2017). Cannabidiol (CBD) significantly reduces drop-seizure frequency in Lennox-Gastaut syndrome (LGS): Pooled efficacy and safety results from two randomized controlled trials. Developmental Medicine and Child Neurology 59: 18-19.	No relevant data for DS
NCT00004776 Phase III Randomized, Double-Blind, Placebo-Controlled Study of Oral Topiramate for Lennox-Gastaut Syndrome	Irretrievable

D1.2 Participant flow in the relevant randomised control trials

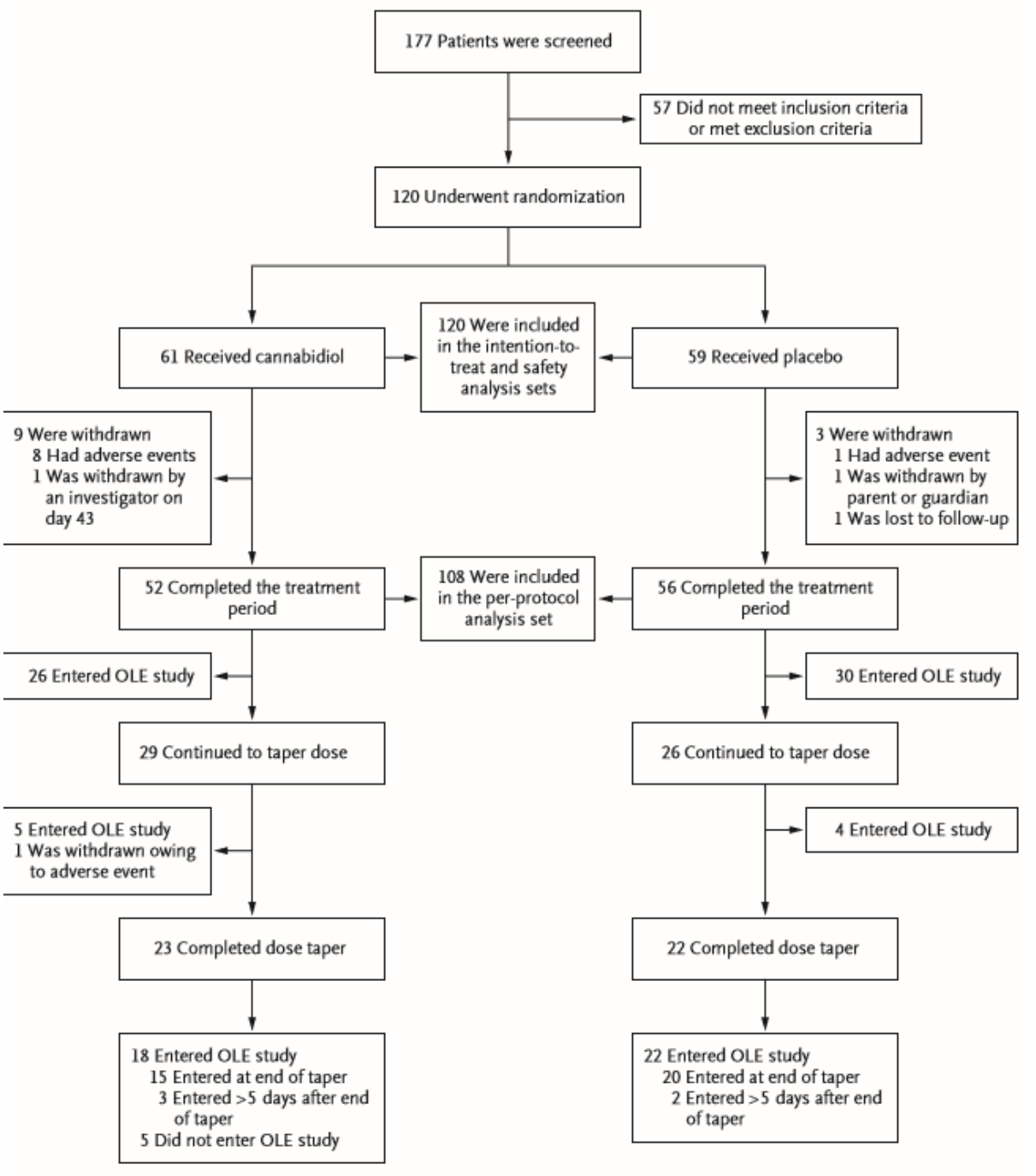


Figure 9. Flow of patients in GWPCARE1 (27)

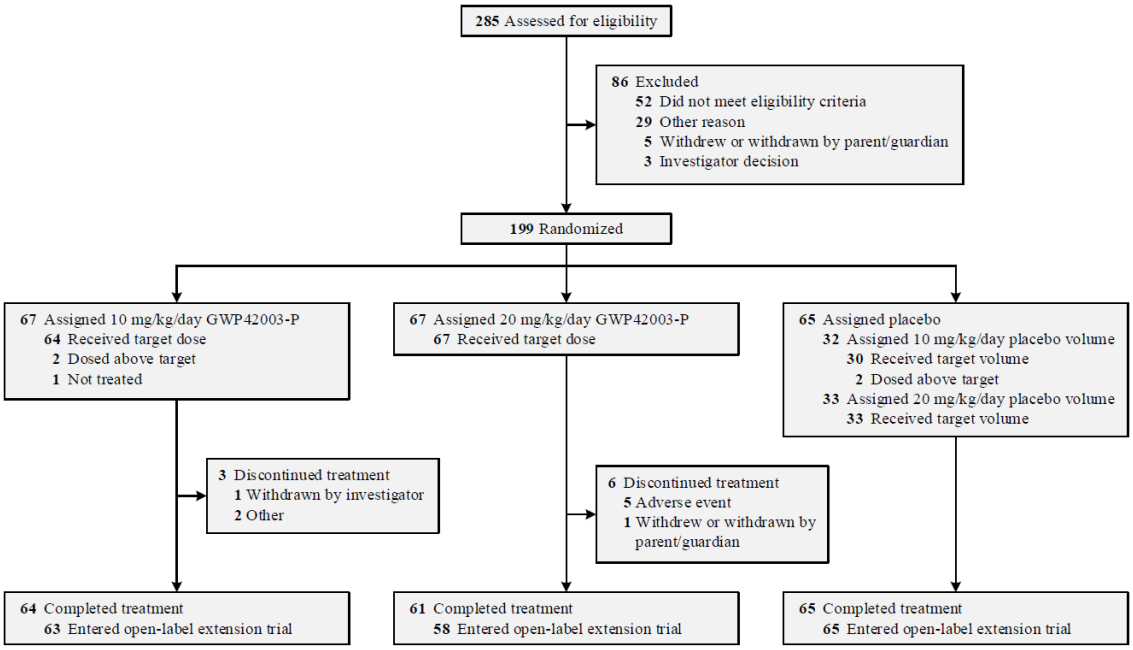


Figure 10: Flow of patients in GWPCARE2 (28)

D1.3 Quality assessment for each trial

The quality assessment of the cannabidiol RCTs are reported below in Table 46.

Table 46. Quality assessment for cannabidiol RCTs

Trial acronym	**GWPCARE1 (27)**	**GWPCARE2 (28)**
Randomisation appropriate?	Yes	Yes
Treatment concealment adequate?	Unclear	Unclear
Baseline comparability adequate?	Unclear	Unclear
Researcher blinding adequate?	Yes	Yes
Dropout imbalances?	No	No
Outcome reporting selective?	No	No
Intention to treat?	Yes	Yes
Overall risk of bias?	**Low**	**Low**

Appendix E: Subgroup analysis

No subgroup analyses were conducted.

Appendix F: Adverse reactions

Detailed data on adverse events from the GWPCARE2 trial are reported below in Table 47 (28).

Table 47*:* Adverse events reported in ≥3% of patients in any treatment group (safety analysis set)

	10 mg/kg/day (N=[redacted])		20 mg/kg/day (N=[redacted])		Placebo (N=[redacted])	
	[redacted]	Treatment-related n (%)	All-causality n (%)	Treatment-related n (%)	All-causality n (%)	Treatment-related n (%)
Patients experiencing any TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gait disturbance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngitis streptococcal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Toxicity to various agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wound	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	10 mg/kg/day (N=[redacted])		20 mg/kg/day (N=[redacted])		Placebo (N=[redacted])	
	[redacted]	Treatment-related n (%)	All-causality n (%)	Treatment-related n (%)	All-causality n (%)	Treatment-related n (%)
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood triglycerides increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver function test abnormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Status epilepticus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Convulsion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lethargy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Poor quality sleep	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Seizure cluster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drooling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Speech disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aggression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Irritability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal behaviour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sleep disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervousness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash generalised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pallor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preliminary results of the open-label extension GWPCARE5 trial have been published as conference abstracts (29-31) for those participants who were recruited from the core DS trials GWPCARE1 and GWPCARE2. Mean age of participants was 16 years and 33% were aged 18 years and older. At the time of analysis, 67 (18%) of the 366 participants enrolled in the trial had withdrawn.

At the latest update in 2018 after a median 50 weeks of treatment, 14% of 278 participants had completed treatment, treatment was ongoing in 52% and 34% had withdrawn. Adverse events have been recorded in 96% of patients, were severe in 32% and led to withdrawals in 7% of patients (29). Of all adverse events, 58% were considered treatment-related, as were 6% of serious adverse events. Four participants died during the trial, but no deaths were considered to be treatment-related (30). An interim analysis of 257 participants followed up after a median of 39 weeks found that 67 had decreased appetite, 40 reported seizures and 29 status epilepticus, 91 had diarrhoea, 27 had fatigue, 72 had pyrexia, 36 had upper respiratory tract infections, 65 had somnolence and 37 had vomiting (31).

Appendix G: Search strategy for cost-effectiveness studies

Identification of studies

The search to identify studies reporting cost-effectiveness was conducted as part of the single search for these reviews, as reported in Appendix D. The inclusion and exclusion criteria used to select relevant cost-effectiveness studies are reported below in Table 48.

Table 48: Eligibility criteria used in the search strategy

	Inclusion criteria	Exclusion criteria
Population	Any age Any gender Any race Has DS/SMEI	No data reported on relevant population
Intervention	Any intervention included in the efficacy review	No data reported on relevant intervention
Comparators	Any of the included interventions Placebo Best supportive care	No data reported on relevant comparator
Outcomes	Cost per life-year saved Cost per QALY gained Costs saved	No data reported on a relevant outcome
Study design	Cost-benefit analyses Cost-effectiveness analyses Cost-utility analyses Budget Impact models Cost minimisation models Other economic models Systematic reviews will be used for citation chasing only Studies only available as conference abstracts will be included if they report sufficient relevant data to inform model development or parameterisation	Other study design
Language restrictions	English only	Full text publication in other language
Publication dates	Any (journal articles) Last 2 years of conference abstracts	Published outside relevant dates
Abbreviations: DS: Dravet syndrome; QALY: Quality-adjusted life year; SMEI: severe myoclonic epilepsy in infancy.		

Quality of included economic evaluations

The lack of a full publication or manufacturer's submission means that the quality assessment of the HTA models is difficult, with many features unclear due to lack of reported details. More information is available for the Elliott cost-utility model which is generally of high quality.

The quality scores of the included cost-effectiveness and cost-utility analyses are shown below in Table 49 based on the Drummond criteria (102).

Table 49. Quality assessment of relevant cost-effectiveness studies

Item\ Study	AWMSG 2008 (32)	AWMSG 2017 CUA (34)	AWMSG 2017 BIM (34)	SMC 2017 (35)	CADTH 2014 (36)	Elliott 2018 (37)
Study design						
1. The research question is stated.	Yes	Yes	Yes	Yes	Yes	Yes
2. The economic importance of the research question is stated.	Yes	Yes	Yes	Yes	Yes	Yes
3. The viewpoint(s) of the analysis are clearly stated and justified.	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
4. The rationale for choosing alternative programmes or interventions compared is stated.	Unclear	Yes	NR	Yes	Yes	Yes
5. The alternatives being compared are clearly described.	Yes	Yes	NR	Yes	Yes	Yes
6. The form of economic evaluation used is stated.	Unclear	Unclear	Unclear	Unclear	Yes	Yes
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
Data collection						
8. The source(s) of effectiveness estimates used are stated.	Yes	Yes	Yes	Yes	Yes	Yes
9. Details of the design and results of effectiveness study are given (if based on a single study).	Yes	Yes	Yes	Yes	Yes	Yes
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	NA	NA	NA	NA	NA	NA

Item\ Study	AWMSG 2008 (32)	AWMSG 2017 CUA (34)	AWMSG 2017 BIM (34)	SMC 2017 (35)	CADTH 2014 (36)	Elliott 2018 (37)
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Yes	Yes	Yes	Yes	Yes
12. Methods to value benefits are stated.	Unclear	Yes	NA	Yes	Unclear	Unclear
13. Details of the subjects from whom valuations were obtained were given.	Yes	Unclear	Unclear	Yes	Yes	Yes
14. Productivity changes (if included) are reported separately.	NA	NA	NA	NA	NA	NA
15. The relevance of productivity changes to the study question is discussed.	NA	NA	NA	NA	NA	NA
16. Quantities of resource use are reported separately from their unit costs.	Unclear	Unclear	NA	Unclear	Unclear	No
17. Methods for the estimation of quantities and unit costs are described.	Unclear	Yes	Yes	Yes	Unclear	Yes
18. Currency and price data are recorded.	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
19. Details of currency of price adjustments for inflation or currency conversion are given.	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
20. Details of any model used are given.	Unclear	Yes	Yes	Yes	Yes	Yes
21. The choice of model used and the key parameters on which it is based are justified.	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
Analysis and interpretation of results						
22. Time horizon of costs and benefits is stated.	Yes	Yes	Yes	Yes	Yes	Yes
23. The discount rate(s) is stated.	NA	Yes	NA	Unclear	Unclear	Yes

Item\ Study	AWMSG 2008 (32)	AWMSG 2017 CUA (34)	AWMSG 2017 BIM (34)	SMC 2017 (35)	CADTH 2014 (36)	Elliott 2018 (37)
24. The choice of discount rate(s) is justified.	NA	Unclear	NA	Unclear	Unclear	Yes
25. An explanation is given if costs and benefits are not discounted.	Unclear	NA	NA	Unclear	Unclear	NA
26. Details of statistical tests and confidence intervals are given for stochastic data.	Unclear	Unclear	NA	Unclear	Unclear	Unclear
27. The approach to sensitivity analysis is given.	NA	Yes	NA	Unclear	Unclear	Yes
28. The choice of variables for sensitivity analysis is justified.	NA	Unclear	Unclear	Unclear	Unclear	Yes
29. The ranges over which the variables are varied are justified.	NA	Unclear	Unclear	Unclear	Unclear	Yes
30. Relevant alternatives are compared.	Yes	Yes	NA	Yes	Yes	Yes
31. Incremental analysis is reported.	Unclear	Yes	NA	Yes	Yes	Yes
32. Major outcomes are presented in a disaggregated as well as aggregated form.	Unclear	Unclear	NA	Unclear	Unclear	Yes
33. The answer to the study question is given.	Yes	Yes	Yes	Yes	Yes	Yes
34. Conclusions follow from the data reported.	Unclear	Yes	Yes	Yes	Yes	Yes
35. Conclusions are accompanied by the appropriate caveats.	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Adapted from Drummond and Jefferson (1996) (102)
Abbreviations: AWMSG, All Wales Medicines Strategy Group; BIM, Budget Impact Model; CUA, cost-utility analysis; SMC, Scottish Medicine Consortium; CADTH, Canadian Agency for Drug and Technologies in Health

Description of the identified studies

The description of the identified studies mentioned in Section B.3.1.are presented in Table 50 for the UK studies and Table 51 for the rest of the world studies.

Table 50: Summary list of published cost-effectiveness studies in the UK

Parameters	Study details			
Study	**AWMSG 2008 (32)**	**AWMSG 2017 (34)**		**SMC 2017 (35)**
Study objective	To demonstrate the budget impact of adopting stiripentol in an HTA submission	To demonstrate the cost-effectiveness of stiripentol in an HTA submission	To demonstrate the budget impact of adopting stiripentol in an HTA submission	To demonstrate the cost-effectiveness of stiripentol in an HTA submission
Study characteristics	- **Analyses type:** BI analyses - **Model Structure:** BIM based on simplistic cost listing - **Patient population:** Children aged 3-18 years with DS - **Tx in the analyses:** stiripentol as adjunct to clobazam plus valproate - **Country:** UK - **Perspective:** NHS - **Outcome measure:** financial consequences of adopting stiripentol - **Time horizon:** 1 yr - **Cycle length:** NA - **Cost yr and currency:** Assume 2008. GBP - **Discount rate:** NA	- **Analyses type:** Cost-utility analyses - **Model Structure:** Markov model. 3-month cycle - **Patient population:** Children aged 3-18 years with DS - **Tx in the analyses:** stiripentol as adjunct to clobazam plus valproate - **Country:** UK - **Perspective:** NHS - **Outcome measure:** Cost/QALY - **Time horizon:** 15 yr - **Cycle length:** 3 months - **Cost yr and currency:** GBP. assume 2017 - **Discount rate:** 3.5%	- **Analyses type:** BI analyses - **Model Structure:** BIM based on simplistic cost listing - **Patient population:** Children aged 3-18 years with DS - **Tx in the analyses:** stiripentol as adjunct to clobazam plus valproate - **Country:** UK - **Perspective:** NHS - **Outcome measure:** financial consequences of adopting stiripentol - **Time horizon:** 5 yr - **Cycle length:** NA - **Cost yr and currency:** GBP. assume 2017 - **Discount rate:** NA	- **Analyses type:** Cost-utility analyses - **Model Structure:** Markov model. 3-month cycle - **Patient population:** Children aged 3-18 years with DS - **Tx in the analyses:** stiripentol as adjunct to clobazam plus valproate - **Country:** UK - **Perspective:** NHS - **Outcome measure:** cost/QALY - **Time horizon:** 15 yr - **Cycle length:** 3 months - **Cost yr and currency:** GBP. assume 2017 - **Discount rate:** NA
Health states	NA	- Seizure -free - Not seizure-free - Not adequately controlled - Maintenance therapy - Death	NR	- Seizure -free (100% reduction in seizures) - Not seizure-free (50% to 100% reduction in seizure frequency) - Not adequately controlled (<50% reduction in seizure frequency) - Maintenance therapy (discontinue due to adverse events and continue on maintenance therapy)
Model assumptions	- Preventing seizures early in the disease course would reduce physical and cognitive retardation later - Patients not adequately controlled on stiripentol will switch treatment - Control group were all inadequately controlled on clobazam and valproate and could only progress to death - No assumption on adherence	- Patients automatically transition from not-adequately-controlled to maintenance states after 1 cycle - Mortality rates vary by health state and are lower in seizure-free than other health states	- Models costs of first year of treatment with stiripentol for patient aged 9 years - All patients with DS are currently treated and 30% refractory to duel therapy so suitable for stiripentol - Stiripentol market share will increase from 60% year 1 to 100% in year 5	- Both treatment arms have the same transition probabilities from cycle 2 onwards
Efficacy data	From 2 RCTs for stiripentol: Chiron et al. 2000 (88) and Guerrini et al. 2002 (91)	STICLO-France (Chiron et al. 2000) (88). STICLO-Italy (Guerrini et al. 2002) (91). DIAVEY long-term study	Same as cost-utility model	Pooled pivotal studies
Resource inputs	- **Resource use:** NR; no data reported on market share - **Cost data:** Scottish cross-boundary costs for seizure management [Scottish Health Service Costs 2006-07]; no data on how far reduction in seizures will reduce direct cost Indirect costs of caregiver burden and productivity losses not included	- Resource use from STICLO study(88, 91). Canadian stiripentol model. NICE model and expert opinion - Unit costs from published sources	Same as cost-utility model	- **Drug doses** based on WHO child growth standards for children and BMI mean values for adults - **Resource use**: from NICE model on focal epilepsy in children and expert opinion - **Costs** include hospitalisation. monitoring. inpatient costs. outpatient visits. emergency room visits. epilepsy nurse phone calls

QALYs	NA	Adjuvant stiripentol = 5.670 Clobazam + valproate = 5.444	NR	Incremental QALY gain = 0.214
Costs	Drug costs for stiripentol = £6.862/patient/year Indirect costs: £5504 annual costs for younger physically disabled services	**Drug costs:** Adjuvant Stiripentol: £37.882 Clobazam +Valproate: £24.558 **Management costs:** Adjuvant Stiripentol: £188.508 Clobazam +Valproate: £199.221 **Ongoing therapy costs:** Adjuvant Stiripentol: £858 Clobazam +Valproate: £959 **Status epilepticus costs:** Adjuvant Stiripentol: £5.999 Clobazam +Valproate: £6.206 **Adverse event costs:** Adjuvant Stiripentol: £311 Clobazam +Valproate: £122 **Total cost:** Adjuvant Stiripentol: £233.558 Clobazam +Valproate: £231.067	**Medication cost per patient per 30 days** Stiripentol 500 mg capsules. 50 mg/kg/day = £739.50 Stiripentol 500 mg powder. 50 mg/kg/day = £739.50 Clobazam 10 mg tablets. 1 mg/kg/day = £8.97 Clobazam 2 mg/mL oral suspension. 1 mg/kg/day = £285.00 Sodium valproate 200 mg/5mL liquid. 30 mg/kg/day = £17.50 Topiramate 200 mg tablets. 400 mg/day = £110.23 Topiramate 50 mg sprinkle capsules. 400 mg/day = £145.80 Levetiracetam 100 mg/mL oral solution. 60 mg/kg/day = £9.59	Incremental cost = £3.055
Results	- **Base case:** Annual cost of treating 19 to 38 patients = £130.000 to £260.000 - **Scenario analyses:** NR AWMSG did not recommend stiripentol in DS in 2008	**Base case**: - ICER = £11.009/QALY gained **Scenario analyses** - Waning of effect and discontinuation = STP dominant - Number of in-patient visits in not-adequately-controlled state = £9.529/QALY - Utility values from observational study of adjunctive AEDs = £25.173/QALY - Utility values based on individual sampling model for focal epilepsy in children = £24.918/QALY - Time horizon 20 years = £11.883/QALY - Time horizon 45 years = £13.156/QALY - 10% patients remain on treatment at 18yr. 40-year horizon = £36.555/QALY - 30% patients remain on treatment at 18yr. 40-year horizon = £60.565/QALY **Deterministic and probabilistic sensitivity analyses:** ICERs ranged from stiripentol dominant to £66.690/QALY Probability of stiripentol being cost-effective vs valproate + clobazam = 53.7% at WTP threshold of £20.000/QALY; 57.5% at WTP threshold of £30.000/QALY	**Net medicine acquisition costs**: Year 1 = £32.344 (60% uptake of stiripentol) Year 2 = £40.431 (70% uptake) Year 3 = £48.517 (80% uptake) Year 4 = £56.603 (90% uptake) Year 5 = £64.689 (100% uptake) Overall net financial cost is the same as net medicine acquisition cost as there are no additional supportive medicine costs.	**Base case:** - ICER = £14.261/QALY gained vs clobazam + valproate **One-way sensitivity and scenario analyses:** - Cost of maintenance therapy /kg/cycle decreased in comparator arm to £0.153 from £0.191 = £37.493/QALY - Cost of maintenance therapy /kg/cycle increased in stiripentol arm to £0.229 from £0.191 = £34.284/QALY - 100% probability of staying in not seizure-free state in comparator arm. from 91.5% = £35.646/QALY - 20% increase in hospital stay costs in not seizure-free state = £31.194/QALY - Weight factor increased to 1.2 from 1 = £21.260/QALY - Alternative utility source = £30.585/QALY - 10% patients remain on stiripentol at 18 yrs old = £41.976/QALY - 30% patients remain on stiripentol at 18 years old = £62.733/QALY
Abbreviations: AWMSG, All Wales Medicines Strategy Group; ICER. incremental cost-effectiveness ratio; NA, Not Applicable; NR, Not Reported; QALYs, quality-adjusted life years; RCT, Randomised Controlled Trial; SMC, Scottish Medicines Consortium; SUDEP, sudden unexpected death in epilepsy				

Table 51: Summary list of published cost-effectiveness studies in the rest of the world

Parameters	Study details	
Study	**CADTH 2014 (36)**	**Elliott 2018 (37)**
Study objective	To demonstrate the cost-effectiveness of stiripentol in an HTA submission	To evaluate the cost-effectiveness of stiripentol as an adjunctive treatment to clobazam and valproate for the treatment of DS from the Canadian public healthcare payer perspective
Study characteristics	- **Analyses type:** Cost-utility - **Model Structure:** Markov model - **Patient population:** Pts with DS uncontrolled with clobazam + valproate - **Tx comparisons:** stiripentol as adjunct to clobazam plus valproate; clobazam + valproate alone - **Country:** Canada - **Perspective:** NR. assume healthcare payer - **Outcome measure:** Incremental cost per QALY - **Time horizon:** 5 yrs - **Cycle length:** NR - **Cost yr and currency:** Assume 2014. CAD - **Discount rate:** NR	- **Analyses type:** Cost-utility - **Model Structure:** Markov model - **Patient population:** Pts with DS uncontrolled with clobazam + valproate - **Tx comparisons:** stiripentol as adjunct to clobazam plus valproate; clobazam + valproate alone - **Country:** Canada - **Perspective:** healthcare payer - **Outcome measure:** Incremental cost per QALY - **Time horizon:** 10 yrs - **Cycle length:** 1 month - **Cost yr and currency:** 2017 CAD - **Discount rate:** 1.5%
Health states	**Five health states:** 1) Initial treatment 2) <50% reduction in seizure rate (not adequately controlled) 3) 50 to <100% reduction in seizures (not seizure-free) 4) 100% reduction in seizures (seizure-free) 1) Dead	**Four health states:** 1) Seizure-free (SF: 100% reduction in seizures from baseline) 2) Not seizure-free (NSF: 50-99% reduction) 3) Not adequately controlled (NAC: 0-49% reduction) 4) Dead
Model assumptions	- Efficacy of stiripentol at the end of the 2-month trials would continue unchanged throughout the 5-year time horizon - Preventing seizures early in the disease course would reduce physical and cognitive retardation later - Patients not adequately controlled on stiripentol will switch treatment - Control group were all inadequately controlled on clobazam and valproate and could only progress to death - No assumption on adherence	- Patients enter the model in NAC state - Patients who are unresponsive after 6 cycles will discontinue stiripentol. responders (SF or NSF) will continue with stiripentol - Patients who continue to have seizures are at risk of SUDEP and non-SUDEP mortality. those who are seizure-free are at risk of non-SUDEP deaths - Medication changes will occur during routine clinic visits and not incur additional charges - Patients will take maximum approved dose of each medication
Efficacy data	From 2 RCTs for stiripentol: Chiron et al. 2000 (88) and Guerrini et al. 2002 (91)	STICLO study (Chiron 2000) (88) Japanese open-label study (Inoue 2015) (103)
Resource inputs	- **Resource use:** NR - **Cost data:** NR - **Utility data:** based on the study used to determine utilities in LGS [Reference not cited]; Drug Review Committee considered other utility values, also NR Indirect costs of caregiver burden and productivity losses not included	- **Resource use:** NICE cost-effectiveness analyses for paediatric epilepsy - **Costs:** Ontario reference costs. British Columbia drug formulary **Utility data:** LGS utility values used (Verdian 2008) (63)
QALYs	NR	Adjuvant stiripentol = 4.37 Clobazam + valproate = 3.77
Costs	NR	**Drug costs**: Adjuvant Stiripentol: $CAN 105.293 Clobazam +Valproate: $CAN 6.231 **Other healthcare costs**: Adjuvant Stiripentol: $CAN 41.183 Clobazam +Valproate: $CAN 49.165 **Total cost:**

		Adjuvant Stiripentol: $CAN 146.477 Clobazam +Valproate: $CAN 55.397
Results	**Base case**: ICUR $51.160 to $120.419. most likely estimate $104.491/QALY gained vs clobazam+ valproate alone (CDR revised estimate) - **Sensitivity analyses:** NR - **Scenario analyses:** NR CADTH recommended stiripentol in combination with clobazam and valproate as adjunctive therapy of refractory DS provided that the patient is under the care of a neurologist and the price of stiripentol was reduced to make it cost-effective.	**Base case:** ICER = $CAN 151.310/QALY gained **Sensitivity analyses** (details NR): At willingness to pay threshold of $CAN 50.000. adjunctive stiripentol is optimal treatment in 5.2% of replications. At willingness to pay threshold of $CAN 100.000, adjunctive stiripentol is optimal treatment in 20.7% of replications. - **Scenario analyses:** Adjusted for reduced price of stiripentol. patient mean age. if no correlation between utility values. different dose of concomitant valproate. discount rate 5 and 3%. time horizon 1 yr. 20yr: ICER ranged from $19.022 (when price reduced by 80%) to $155.491. Cost of stiripentol needs to be reduced by 61.4% to be cost effective.
Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; ICER. incremental cost-effectiveness ratio; LGS, Lennox-Gastaut Syndrome; NA, Not Applicable; NR, Not Reported; QALYs, quality-adjusted life years; RCT, Randomised Controlled Trial; SUDEP, sudden unexpected death in epilepsy		

Appendix H: Health-related quality-of-life studies

Identification of studies

The search to identify studies reporting quality of life and utilities was conducted as part of the single search for these reviews, as reported in Appendix D. The inclusion and exclusion criteria used to select relevant quality of life studies are reported below in Table 52.

Table 52. Eligibility criteria used in the search strategy

	Inclusion criteria	Exclusion criteria
Population	Any age Any gender Any race Has DS/SMEI or is a caregiver of a patient with DS	No data reported on relevant population
Intervention	Any intervention included in the efficacy review Placebo Best supportive care No intervention	No data reported on relevant intervention
Comparators	Any of the included interventions No comparator	No data reported on relevant comparator
Outcomes	Utility values Other quality of life measures using an established questionnaire	No data reported on a relevant outcome; qualitative study reporting views
Study design	Randomised controlled trials Observational studies Systematic reviews will be used for citation chasing only Studies only available as conference abstracts will be included if they report sufficient relevant data to allow analysis	Other study design
Language restrictions	English only	Full text publication in other language
Publication dates	Any (journal articles) Last 2 years of conference abstracts	Published outside relevant dates

Description of the identified studies

The search identified six publications that were relevant to the reference case of patients with DS who were either receiving a relevant drug therapy or were reporting on quality of life regardless of treatments, and which reported utility values. Of these*:*

- Four assessed quality of life or the impact of disease in patients with DS and their families (10, 25, 103, 104).
- Three reported EQ-5D utility values for patients with DS (10, 25, 103).

- One model reported utility values for LGS (37) and one reported EQ-5D values in caregivers (104).
- One model reported utility values taken from a time trade-off study in the UK general population (35).

Table 53. Utility values reported in relevant studies

	Campbell 2018 (104)	**Elliott 2018** (37)	**Lagae 2018** (10) **and Irwin 2017** (25)	**Strzelczyk 2018** (105)	**SMC 2017** (35)
Population	34 caregivers of patients with DS aged 2 to 22 years in the USA	Canadian patients with Dravet syndrome not previously responding to concomitant treatment. Typical patient based on the STICLO France trial (Chiron) (88): mean age: 9.3 years	Caregivers of 584 patients with DS aged 0 to 48 years via an online survey (EQ-5D values by proxy responses) in 10 European countries (UK included)	91 patients with DS aged and their caregivers in Germany (patients' range 1.3 to 33.7 years)	Children aged 3-18 years with DS in Scotland
Recruitment	Email invitation to anyone who cares for a friend or family member with DS	NA	Email invites sent to approx 1000 members of patient advocacy groups and through social media sources	Clinic and patient advocacy group	NA
Interventions	NR	Stiripentol, clobazam, valproate	Valproate, stiripentol, topiramate, clobazam, bromide, cannabidiol, other cannabis derivatives, carbamazepine, oxcarbazepine, phenytoin, lamotrigine, vigabatrin, phenobarbital, rufinamide, ketogenic diet, vagus nerve stimulation	NR	Stiripentol, clobazam, valproate
Response rates	88%	NA	NR	NR	NA
Health states and appropriateness	NR	- NAC: 0 to 49% reduction in seizures - NSF: 50 to 99% reduction in seizures - SF: 100% reduction in seizures	NR	NR	- Seizure-free - Not seizure-free - Not adequately controlled Maintenance
Adverse events	NR	NR	NR	NR	NR
Elicitation. validation. mapping	NR	Cholesky decomposition	Index values of EQ-5D-5L were based on UK value set.	NR	Based on study assessing TTO utilities from the UK general population

	Campbell 2018 (104)	**Elliott 2018** (37)	**Lagae 2018** (10) **and Irwin 2017** (25)	**Strzelczyk 2018** (105)	**SMC 2017** (35)
Results uncertainty	- Mean EQ-5D Index score = 0.78 (SD = 0.17) Range = 0.31 to 1.0 - Mean EQ-VAS = 67 (SD = 21) Range =11 to 94	- NAC: 0.427 - NSF: 0.605 - SF: 0.699	- Mean EQ-5D Values (SD): Overall: 0.42 (0.29) 2 years and older: 0.42 (0.29) Infants: 0.33 (0.37) 2-5 years: 0.46 (0.31) 6-11 years: 0.43 (0.28) 12-17 years: 0.43 (0.28) Adults: 0.34 (0.26) - Range: -0.35 to 1.0 - Lowest EQ-5D stratum: <3% of patients were seizure-free in past 3 months. - Highest EQ-5D stratum: 15% were seizure-free in the previous 3 months (p=0.002)	- EQ-5D scores: comparable to the general adult German population (Figures not specified) - BDI-II scores: 14% BDI-II scores 20-28 (moderate depression) 9% scored 29-63 (severe depression)	TTO values: Seizure-free = 0.699 Not seizure-free = 0.605 Not adequately controlled = 0.427 Maintenance = 0.516
Appropriateness for cost-utility model	Moderate – does not report utility values by health state	Moderate	High	Low – does not report utility values for patients	High
Abbreviations: BDI-II, Beck Depression Inventory-II; EQ-5D, European Quality of Life-5 Dimensions; EQ-5D-5L, European Quality of Life-5 Dimensions 5 levels; EQ-VAS, European Quality of Life-visual analogue scale; NR, not reported; NAC, not adequately controlled; NSF, not seizure-free; SD, standard deviation; SF: seizure-free.					

Utilities survey developed

Patient's vignettes

Table 54: Narrative vignette on patient's current condition

David is 11 years old and has had Dravet syndrome (rare form of epilepsy) from early infancy. Due to the multiple seizures. he is intellectually and developmentally delayed. He is prone to convulsive seizures lasting between 15 and 30 minutes. He has previously been treated with more than 6 antiepileptic drugs and is currently being treated with 3 antiepileptic drugs. but continues to have multiple convulsive seizures.

Table 55: Definitions of health states

David has approximately 32 convulsive seizures in a month and 4 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_4
David has approximately 32 convulsive seizures in a month and 8 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_8
David has approximately 32 convulsive seizures in a month and 12 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_12
David has approximately 32 convulsive seizures in a month and 18 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_18
David has approximately 32 convulsive seizures in a month and 21 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_21
David has approximately 32 convulsive seizures in a month and 24 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_24
David has approximately 32 convulsive seizures in a month and 28 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_28
David has approximately 25 convulsive seizures in a month and 8 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_25_8

David has approximately 25 convulsive seizures in a month and 12 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_25_12
David has approximately 25 convulsive seizures in a month and 18 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_25_18
David has approximately 25 convulsive seizures in a month and 21 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_25_21
David has approximately 25 convulsive seizures in a month and 24 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_25_24
David has approximately 25 convulsive seizures in a month and 28 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_25_28
David has approximately 16 convulsive seizures in a month and 18 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_16_18
David has approximately 16 convulsive seizures in a month and 21 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_16_21
David has approximately 16 convulsive seizures in a month and 24 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_16_24
David has approximately 16 convulsive seizures in a month and 28 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_16_28
David has approximately 8 convulsive seizures in a month and 24 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_8_24
David has approximately 8 convulsive seizures in a month and 28 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_8_28
David has approximately 6 convulsive seizures in a month and 24 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_6_24

David has approximately 6 convulsive seizures in a month and 28 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_6_28
David has approximately 4 convulsive seizures in a month and 28 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_4_28
David does not have any convulsive seizures. He still has Dravet syndrome and needs to take his medication. His intellectual abilities and delayed development remain unchanged. Reminder: You are David and the scenario above describes your current health status. Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_no seizures
Abbreviations: DS. Dravet syndrome	

Caregiver's vignettes

Table 56: Narrative vignette on patient's current condition

Ally is the caregiver of an 11 year old child. David who has had Dravet syndrome (rare form of epilepsy) from early infancy. Due to the multiple seizures. he is intellectually and developmentally delayed. He is prone to convulsive seizures lasting between 15 and 30 minutes. David has previously been treated with more than 6 antiepileptic drugs and is currently being treated with 3 antiepileptic drugs. but continues to have multiple convulsive seizures. David needs constant supervision. limiting the time Ally can dedicate to herself and other members of the family.

Table 57: Definitions of health states

David has approximatively 32 convulsive seizures in a month. and 18 seizure-free days in a month. Therefore. he needs supervision on a daily basis. Reminder: You are Ally and the scenario above describes your current situation. Please select the number that indicates how you rate this situation. (Use the slider or write the number in the box)	DS_CG_32_18
David's treatment is helpful in reducing the number of convulsive seizures. He has approximately 16 convulsive seizures in a month. and 21 seizure-free days in a month. Therefore. he needs less supervision on a daily basis. Reminder: You are Ally and the scenario above describes your current situation. Please select the number that indicates how you rate this situation. (Use the slider or write the number in the box)	DS_CG_16_21
David does not have any convulsive seizures. He still has Dravet syndrome and needs to take his medication. Although his intellectual abilities and delayed development remain unchanged. he needs less supervision on a daily basis. Reminder: You are Ally and the scenario above describes your current situation. Please select the number that indicates how you rate this situation. (Use the slider or write the number in the box)	DS_CG_no seizures
Abbreviations: CG: caregiver; DS. Dravet syndrome	

Questions included in the survey

Table 58: Survey questions

Section	Question	Answers / Health state
Consent form	The survey is conducted by [redacted] a firm that specialises in pharmaceutical and biotech industry research. We are conducting the survey on behalf of our client. a pharmaceutical company. There is limited evidence on the quality of life and well-being of individuals with Dravet syndrome (DS) and this research will help us understand how the quality of an individual's daily life may be affected due to this condition. The survey should take no more than 15-20 minutes. and your responses are completely anonymous. If you have any questions about the survey. please email us: [redacted] As part of this survey. we will ask you questions on general information such as your age, gender, marital status and current health status. The security of your personal information is very important to [redacted] We use commercially reasonable physical. electronic and administrative safeguards that are designed to protect your personal information from loss. misuse and unauthorised access. disclosure. alteration. and destruction. This survey is for our client's research purposes only and all personal information collected for this project will be presented only in an aggregated form to our client and no attributions made to individuals. For further information, please refer to our Privacy notice. We really appreciate your input! Do you agree for us to gather and process personal information you provide as part of this survey?	Do not accept Accept
Screening	Which of the following best describes your status?	Carer of a person with epilepsy Person with epilepsy None of the above
Caregiver Background Questions	Please record your gender	Female Male Do not want to specify
	Please record your age	< 17 years 17 - 20 years 21 - 30 years 31 - 40 years 41 - 50 years 51 - 60 years > 61 years
	Which of the following best describes your marital status?	Single Married / Partnership Widow / Widower Divorced / Separated
	Which of the following best describes your employment status?	Employed Unemployed / Homemaker

		Student
		Carer
		Part / Full-time Volunteer
		Retired
	What is the highest level of education you completed?	Degree or equivalent
		Higher education
		A level or equivalent
		GCSEs grade A* - C or equivalent
		Other qualifications
		No qualifications
		Don't know
	What is the diagnosed condition of the person you are caring for?	Dravet syndrome
		Lennox Gastaut syndrome
		Other severe forms of epilepsy
		Other forms of epilepsy
	What is the age of this person?	< 17 years
		17 - 20 years
		21 - 30 years
		31 - 40 years
		41 - 50 years
		51 - 60 years
		> 60 years
	What is your relationship with this person?	Mother
		Father
		Professional caregiver
		Relative
		Other
	How long have you been the caregiver of this person?	Less than a year
		Between 1 and 5 years
		Between 6 and 10 years
		More than 10 years
	For how long has this person had the condition?	Less than a year
		Between 1 and 5 years
		Between 6 and 10 years
		More than 10 years
	How many medicines is this person currently taking? Please select the number on the slider below	Restricted to maximum 20
	Has this person's condition improved since they started taking their current set of medicines?	Yes
		No
		Partially
	How many convulsive seizures did this person have in the last 30 days? Please select the number on the slider below	Restricted to maximum 50
	How many convulsive seizure-free days did this person have in the last 30 days? Please select the number on the slider below	Restricted to maximum 30

Patient Background Questions	Please record your gender	Female
		Male
		Do not want to specify
	Please record your age	< 17 years
		17 - 20 years
		21 - 30 years
		31 - 40 years
		41 - 50 years
		51 - 60 years
		> 60 years
	Which of the following best describes your marital status?	Single
		Married / Partnership
		Widow / Widower
		Divorced / Separated
	Which of the following best describes your employment status?	Employed
		Unemployed / Homemaker
		Student
		Carer
		Part / Full-time Volunteer
		Retired
	What is the highest level of education you completed?	Degree or equivalent
		Higher education
		A level or equivalent
		GCSEs grade A* - C or equivalent
		Other qualifications
		No qualifications
		Don't know
	What is your medical condition?	Dravet syndrome
		Lennox Gastaut syndrome
		Other severe forms of epilepsy
		Other forms of epilepsy
	How long have you had the condition for?	Less than a year
		Between 1 and 5 years
		Between 6 and 10 years
		More than 10 years
	How many treatments are you currently taking for this condition? Please select the number on the slider below	Restricted to maximum 20
	Has your condition improved since you started taking the current set of medicines?	Yes
		No
		Partially
	How many convulsive seizures did you have in the last 30 days? Please select the number on the slider below	Restricted to maximum 50
	How many convulsive seizure-free days did you have in the last 30 days? Please select the number on the slider below	Restricted to maximum 30

Own QoL assessment	We would like to know how your health is TODAY. Below there is a scale numbered from 0 to 100. 0 means the worst health you can imagine 100 means the best health you can imagine Please select the number that indicates how your health is TODAY. (Use the slider or write the number in the box)	
Survey instructions	In this survey. we will ask you to score several scenarios for an example of a person with Dravet syndrome. These scenarios are defined based on the number of convulsive seizures and the number of seizure-free days that a person with Dravet syndrome experiences in a month. You will be asked to select a number from 0 (worst health you can imagine) to 100 (best health you can imagine) on a slider. For each scenario you will be shown a vertical bar on the left side with the number of convulsive seizures in a month. The bar will show you the maximum and minimum number of convulsive seizures you can evaluate. and the current number of convulsive seizures for each scenario. There are 32 maximum convulsive seizures in a month. and the minimum is 0 convulsive seizures in a month. In the example shown below. the example of a person with Dravet syndrome experiences 25 convulsive seizures in a month. (Figure DS_Instructions_No_Seizures) On the centre. you will see a horizontal bar illustrating the number of seizure-free days in an average month. Green lines represent seizure-free days and red lines represent days when the person is experiencing convulsive seizures. The minimum number of seizure-free days is 4. and the maximum is 30 days. In the example shown below. the person is experiencing 8 seizure-free days in an average month of 30 days. (Figure DS_Instructions_No_Seizure-Free_Days) The scenarios explore different combinations of number of convulsive seizures and seizure-free days. You can go back and change your answer should you wish to do so. The focus of this evaluation is to capture the impact of different number of convulsive seizures and seizure-free days in a month.	
Separating page	Now you will start evaluating the different scenarios for the example person with Dravet syndrome.	
Hypothetical patient QoL Assessment	Health states included in Table 55 above	
Caregiver screener	Are you a caregiver for a person with epilepsy?	Yes
		No
Hypothetical caregiver QoL assessment	Health states include in Table 57 above	

Results

Table 59: Pilot test results

Respondent ID	Tester 1	Tester 2	Absolute difference	Absolute difference >30%
Hypothetical patient's age assessed	11 years old	15 years old	$\frac{Value1 - Value2}{\frac{Value1 + Value2}{2}} * 100$	
DS_32_4				
DS_32_8				
DS_32_12				
DS_32_18				
DS_32_21				
DS_32_24				
DS_32_28				
DS_25_8				
DS_25_12				
DS_25_18				
DS_25_21				
DS_25_24				
DS_25_28				
DS_16_18				
DS_16_21				
DS_16_24				
DS_16_28				
DS_8_24				
DS_8_28				
DS_6_24				
DS_6_28				
DS_4_28				
DS_no seizures				
Are you a caregiver for a patient with epilepsy?				
DSCG_1				
DSCG_2				
DSCG_3				
Number of assessed health states				
Number of health states with >30% variation in QoL valuations				
Abbreviations: CG: caregiver; DS: Dravet syndrome; QoL: quality of life				

Table 60: Survey results

Summary data			% / Mean	No / SD
Consent form	The survey is conducted by [redacted] a firm that specialises in pharmaceutical and biotech industry research. We are conducting the survey on behalf of our client. a pharmaceutical company. There is limited evidence on the quality of life and well-being of individuals with Dravet syndrome (DS) and this research will help us understand how the quality of an individual's daily life may be affected due to this condition. The survey should take no more than 15-20 minutes. and your responses are completely anonymous. If you have any questions about the survey. please email us: [redacted] As part of this survey. we will ask you questions on general information such as your age, gender, marital status and current health status. The security of your personal information is very important to [redacted] We use commercially reasonable physical. electronic and administrative safeguards that are designed to protect your personal information from loss. misuse and unauthorised access, Disclosure, alteration and destruction. This survey is for our client's research purposes only and all personal information collected for this project will be presented only in an aggregated form to our client and no attributions made to individuals. For further information, please refer to our Privacy notice. We really appreciate your input! Do you agree for us to gather and process personal information you provide as part of this survey?	Do not accept		
		Accept		
Screening	Which of the following best describes your status?	Carer of a person with epilepsy		
		Person with epilepsy		
		None of the above		

Summary data			% / Mean	No / SD
		Other (please specify)		
Caregiver Background Questions	Please record your gender	Female		
		Male		
		Do not want to specify		
	Please record your age	< 17 years		
		17 - 20 years		
		21 - 30 years		
		31 - 40 years		
		41 - 50 years		
		51 - 60 years		
		> 61 years		
	Which of the following best describes your marital status?	Single		
		Married / Partnership		
		Widow / Widower		
		Divorced / Separated		
	Which of the following best describes your employment status?	Employed		
		Unemployed / Homemaker		
		Student		
		Carer		
		Part / Full-time Volunteer		
		Retired		
	What is the highest level of education you completed	Degree or equivalent		
		Higher education		
		A level or equivalent		
		GCSEs grade A* - C or equivalent		
		Other qualifications		
		No qualifications		
		Don't know		
	What is the diagnosed condition of the person you are caring for?	Dravet syndrome		
		Lennox Gastaut syndrome		
		Other severe forms of epilepsy		
		Other forms of epilepsy		
	What is the age of this person?	< 17 years		
		17 - 20 years		
		21 - 30 years		
		31 - 40 years		
		41 - 50 years		
		51 - 60 years		
		> 60 years		
	What is your relationship with this person?	Mother		
		Father		
		Professional caregiver		
		Relative		
		Other		
	How long have you been the caregiver of this person?	Less than a year		
		Between 1 and 5 years		
		Between 6 and 10 years		
		More than 10 years		
	For how long has this person had the condition?	Less than a year		
		Between 1 and 5 years		
		Between 6 and 10 years		
		More than 10 years		
	How many medicines is this person currently taking? Please select the number on the slider below			
	Has this person's condition improved since they started taking their current set of medicines?	Yes		
		No		

Summary data			% / Mean	No / SD
		Partially		
	How many convulsive seizures did this person have in the last 30 days? Please select the number on the slider below	Open-Ended Response		
	How many convulsive seizure-free days did this person have in the last 30 days? Please select the number on the slider below	Open-Ended Response		
Patient Background Questions	Please record your gender	Female		
		Male		
		Do not want to specify		
	Please record your age	< 17 years		
		17 - 20 years		
		21 - 30 years		
		31 - 40 years		
		41 - 50 years		
		51 - 60 years		
		> 60 years		
	Which of the following best describes your marital status?	Single		
		Married / Partnership		
		Widow / Widower		
		Divorced / Separated		
	Which of the following best describes your employment status?	Employed		
		Unemployed / Homemaker		
		Student		
		Carer		
		Part / Full-time Volunteer		
		Retired		
	What is the highest level of education you completed	Degree or equivalent		
		Higher education		
		A level or equivalent		
		GCSEs grade A* - C or equivalent		
		Other qualifications		
		No qualifications		
		Don't know		
	What is your medical condition?	Dravet syndrome		
		Lennox Gastaut syndrome		
		Other severe forms of epilepsy		
		Other forms of epilepsy		
	How long have you had the condition for?	Less than a year		
		Between 1 and 5 years		
		Between 6 and 10 years		
		More than 10 years		
	How many treatments are you currently taking for this condition? Please select the number on the slider below			
	Has your condition improved since you started taking the current set of medicines?	Yes		
		No		
		Partially		
	How many convulsive seizures did you have in the last 30 days? Please select the number on the slider below			
	How many convulsive seizure-free days did you have in the last 30 days? Please select the number on the slider below			
Own QoL assessment	We would like to know how your health is TODAY. Below there is a scale numbered from 0 to 100. 0 means the worst health you can imagine 100 means the best health you can imagine Please select the number that indicates how your health is TODAY. (Use the slider or write the number in the box)			

	Summary data		% / Mean	No / SD
Survey instructions	In this survey. we will ask you to score several scenarios for an example of a person with Dravet syndrome. These scenarios are defined based on the number of convulsive seizures and the number of seizure-free days that a person with Dravet syndrome experiences in a month. You will be asked to select a number from 0 (worst health you can imagine) to 100 (best health you can imagine) on a slider. For each scenario you will be shown a vertical bar on the left side with the number of convulsive seizures in a month. The bar will show you the maximum and minimum number of convulsive seizures you can evaluate. and the current number of convulsive seizures for each scenario. There are 32 maximum convulsive seizures in a month. and the minimum is 0 convulsive seizures in a month. In the example shown below, the example of a person with Dravet syndrome experiences 25 convulsive seizures in a month. (Figure DS_Instructions_No_Seizures) On the centre. you will see a horizontal bar illustrating the number of seizure-free days in an average month. Green lines represent seizure-free days and red lines represent days when the person is experiencing convulsive seizures. The minimum number of seizure-free days is 4. and the maximum is 30 days. In the example shown below. the person is experiencing 8 seizure-free days in an average month of 30 days. (Figure DS_Instructions_No_Seizure-Free_Days) The scenarios explore different combinations of number of convulsive seizures and seizure-free days. You can go back and change your answer should you wish to do so. The focus of this evaluation is to capture the impact of different number of convulsive seizures and seizure-free days in a month.			
Separating page	Now you will start evaluating the different scenarios for the example person with Dravet syndrome			
Hypothetical Patient QoL Assessment	David is 11 years old and has had Dravet syndrome (rare form of epilepsy) from early infancy. Due to the multiple seizures. he is intellectually and developmentally delayed. He is prone to convulsive seizures lasting between 15 and 30 minutes. He has previously been treated with more than 6 antiepileptic drugs and is currently being treated with 3 antiepileptic drugs. but continues to have multiple convulsive seizures.			
	David has approximately 32 convulsive seizures in a month and 4 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_4	[redacted]	[redacted]
	David has approximately 32 convulsive seizures in a month and 8 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_8	[redacted]	[redacted]
	David has approximately 32 convulsive seizures in a month and 12 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_12	[redacted]	[redacted]
	David has approximately 32 convulsive seizures in a month and 18 seizure-free days in a month. Reminder: You are David and the scenario above describes your	DS_32_18	[redacted]	[redacted]

Summary data		% / Mean	No / SD
current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)			
David has approximately 32 convulsive seizures in a month and 21 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_21	[redacted]	[redacted]
David has approximately 32 convulsive seizures in a month and 24 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_24	[redacted]	[redacted]
David has approximately 32 convulsive seizures in a month and 28 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_32_28	[redacted]	[redacted]
David has approximately 25 convulsive seizures in a month and 8 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_25_8	[redacted]	[redacted]
David has approximately 25 convulsive seizures in a month and 12 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_25_12	[redacted]	[redacted]
David has approximately 25 convulsive seizures in a month and 18 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_25_18	[redacted]	[redacted]
David has approximately 25 convulsive seizures in a month and 21 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_25_21	[redacted]	[redacted]
David has approximately 25 convulsive seizures in a month and 24 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_25_24	[redacted]	[redacted]
David has approximately 25 convulsive seizures in a month and 28 seizure-free days in a month.	DS_25_28	[redacted]	[redacted]

Summary data		% / Mean	No / SD
Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)			
David has approximately 16 convulsive seizures in a month and 18 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_16_18	[redacted]	[redacted]
David has approximately 16 convulsive seizures in a month and 21 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_16_21	[redacted]	[redacted]
David has approximately 16 convulsive seizures in a month and 24 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_16_24	[redacted]	[redacted]
David has approximately 16 convulsive seizures in a month and 28 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_16_28	[redacted]	[redacted]
David has approximately 8 convulsive seizures in a month and 24 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_8_24	[redacted]	[redacted]
David has approximately 8 convulsive seizures in a month and 28 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_8_28	[redacted]	[redacted]
David has approximately 6 convulsive seizures in a month and 24 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_6_24	[redacted]	[redacted]
David has approximately 6 convulsive seizures in a month and 28 seizure-free days in a month. Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_6_28	[redacted]	[redacted]
David has approximately 4 convulsive seizures in a month and 28 seizure-free days in a month.	DS_4_28	[redacted]	[redacted]

Summary data			% / Mean	No / SD
	Reminder: You are David and the scenario above describes your current health status Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)			
	David does not have any convulsive seizures. He still has Dravet syndrome and needs to take his medication. His intellectual abilities and delayed development remain unchanged. Reminder: You are David and the scenario above describes your current health status. Please select the number that indicates how you rate this health status. (Use the slider or write the number in the box)	DS_no_seizures	[redacted]	[redacted]
Caregiver screener	Are you a caregiver for a patient with epilepsy?	Yes		
		No		
Hypothetical caregiver QoL assessment	Ally is the caregiver of an 11 year old child. David who has had Dravet syndrome (rare form of epilepsy) from early infancy. Due to the multiple seizures. he is intellectually and developmentally delayed. He is prone to convulsive seizures lasting between 15 and 30 minutes. David has previously been treated with more than 6 antiepileptic drugs and is currently being treated with 3 antiepileptic drugs. but continues to have multiple convulsive seizures. David needs constant supervision. limiting the time Ally can dedicate to herself and other members of the family.			
	David has approximatively 32 convulsive seizures in a month. and 18 seizure-free days in a month. Therefore. he needs supervision on a daily basis. Reminder: You are Ally and the scenario above describes your current situation. Please select the number that indicates how you rate this situation. (Use the slider or write the number in the box)	DS_CG_32_18	[redacted]	[redacted]
	David's treatment is helpful in reducing the number of convulsive seizures. He has approximately 16 convulsive seizures in a month. and 21 seizure-free days in a month. Therefore. he needs less supervision on a daily basis. Reminder: You are Ally and the scenario above describes your current situation. Please select the number that indicates how you rate this situation. (Use the slider or write the number in the box)	DS_CG_16_21	[redacted]	[redacted]
	David does not have any convulsive seizures. He still has Dravet syndrome and needs to take his medication. Although his intellectual abilities and delayed development remain unchanged. he needs less supervision on a daily basis. Reminder: You are Ally and the scenario above describes your current situation. Please select the number that indicates how you rate this situation. (Use the slider or write the number in the box)	DS_CG_no_seizures	[redacted]	[redacted]
Abbreviations: CG: caregiver; DS: Dravet syndrome; QoL: quality of life				

Table 61: Utility values converted

Health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_32_4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_32_8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_32_12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_32_18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_32_21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_32_24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_32_28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_25_8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_25_12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_25_18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_25_21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_25_24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_25_28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_16_18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_16_21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_16_24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_16_28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_8_24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_8_28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_6_24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_6_28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_4_28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_no_seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_CG_32_18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_CG_16_21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DS_CG_no_seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: CG: caregiver; DS. Dravet syndrome; SG; standard gamble									

Appendix I: Cost and healthcare resource identification, measurement and valuation

Identification of studies

The search to identify studies reporting cost and healthcare resource was conducted as part of the single search for these reviews, as reported in Appendix D. The inclusion and exclusion criteria used to select relevant costs studies are reported below in Table 62.

Table 62. Eligibility criteria used in the search strategy

	Inclusion criteria	**Exclusion criteria**
Population	Any age Any gender Any race Has DS/ SMEI or is a caregiver of a patient with DS	No data reported on relevant population
Intervention	Any intervention included in the efficacy review Best supportive care No intervention	No data reported on relevant intervention
Comparators	Any of the included interventions No comparator	No data reported on relevant comparator
Outcomes	Direct costs Indirect and informal costs Resource use	No data reported on a relevant outcome
Study design	Randomised controlled trials Observational studies Database studies Systematic reviews will be used for citation chasing only Studies only available as conference abstracts will be included if they report sufficient relevant data to inform model development or parameterisation	Other study design
Language restrictions	English only	Full text publication in other language
Publication dates	Any (journal articles) Last 2 years of conference abstracts	Published outside relevant dates

Description of the identified studies

The review identified twenty-one publications that reported cost or resource use data for patients with DS of which nine were relevant to England. Of these:

- Two were HTA submissions of stiripentol for Wales (32, 34).
- One was on cannabidiol, GWPCARE1, recruiting patients from the UK, USA, France and Poland (27).

- Three were surveys of families and caregivers internationally (10, 23, 105)
- Two were secondary publications that are only available as conference abstracts (25, 106)
- One surveyed parents in Austria, USA, Italy and the UK on indirect costs and resource use (24).

These papers related to the UK are summarised in Table 63 to Table 64 below. A summary of publications that reported cost and resource use data from non-UK countries is shown below in Table 65 to Table 67.

Table 63. Summary of relevant studies reporting costs or resource use relevant to the UK

	AWMSG, 2008 (32)	AWMSG 2017 (34)	GWPCARE1 (27)	Irwin 2018 (107)	Lagae et al., 2018 (10)
Country	UK	UK	UK, USA, France, Poland	France, Germany, Italy, Spain, UK (EU5)	Italy, UK, Germany, France, Netherlands, Spain, Poland, Croatia, Romania, Portugal
Date (cost-year)	Assume 2008	Assume 2017	NR	2016	2016
Population	Children aged 3-18 years with DS	Patients aged 3 years and older with inadequate control of seizures on valproate and clobazam	Children and adolescents aged 2-18 years with uncontrolled DS	Caregivers of patients with DS (Subgroup of Lagae 2018 study) (10)	Caregivers of patients with DS
Applicability to England	High	High	High	High	Moderate
Cost valuations	Costs of seizures taken from Scottish cross boundary costs for epilepsy which are costs associated with care in a different health board from that in which patient is resident, which may not reflect usual costs of care for DS seizures in Wales	Resource use from STICLO study, Canadian stiripentol model, NICE model and expert opinion. Unit costs from published sources.	Data collected during RCT	Caregiver-reported	Caregiver-reported
Direct costs	Cost per seizure: £4,555 Cost per day patient attendance at younger physically disabled service: £5,504	Drug costs: Adjuvant Stiripentol: £37,882 Clobazam +Valproate: £24,558 Management costs: Adjuvant Stiripentol: £188,508 Clobazam +Valproate: £199,221 Ongoing therapy costs: Adjuvant Stiripentol: £858 Clobazam +Valproate: £959 Status epilepticus costs: Adjuvant Stiripentol: £5,999 Clobazam +Valproate: £6,206 Adverse event costs: Adjuvant Stiripentol: £311 Clobazam +Valproate: £122 Total cost: Adjuvant Stiripentol: £233,558 Clobazam +Valproate: £231,067	NR	Mean annual costs in the UK, in 2016 US$ Seizure-related symptoms Emergency visits: $783 Ambulance calls: $1343 Epilepsy specialist visits: $1410 Valproic acid: $232 Clobazam: $57 Stiripentol: $8284 Topiramate: $4 Total with drugs: $12,112 Total without drugs: $3,535 Non-seizure-related symptoms Physiotherapy: $1,678 Speech therapy: $1765 Therapy for learning difficulties: $466 Therapy for Autism: $480 Therapy for ADHD: $102	NR
Indirect costs	NR	NR	NR	Career impact of caregiving (parents from EU5) Career choices affected = 83% Missed 2+ days of work in past 4 weeks = 31% Unemployed = 27%	Proportion attending mainstream school: 26.2% overall Infant: 8.8% Preschool (2-5 yr): 33.3%

	AWMSG, 2008 (32)	AWMSG 2017 (34)	GWPCARE1 (27)	Irwin 2018 (107)	Lagae et al., 2018 (10)
				Use of private childcare for DS patients: Median out-of-pocket costs per patient per year in UK = $1920 (15% uptake)	Middle school (5-11 yr): 34.2% Adolescent (12-17 yr): 26.2% Adult: 6.0% Proportion attending special school: 36.6% overall Infant: 2.9% Preschool (2-5 yr): 11.3% Middle school (5-11 yr): 55.4% Adolescent (12-17 yr): 59.8% Adult: 21.0% Proportion home schooled: 2.6% overall Infant: 2.9% Preschool (2-5 yr): 2.1% Middle school (5-11 yr): 1.5% Adolescent (12-17 yr): 2.8% Adult: 5.0% Proportion with no schooling: 19.5% overall Infant: 70.6% Preschool (2-5 yr): 37.6% Middle school (5-11 yr): 3.5% Adolescent (12-17 yr): 4.7% Adult: 25.0%
Technology costs	NR	NR	NR	NR	NR
Resource use	NR	NR	Mean difference in hospitalisation rate between groups: 0.0 (95%CI 0.0 to 0.1) Rescue medication use: 36/61 (59%) patients taking cannabidiol 41/59 (69%) patients taking placebo	Epilepsy-related resource use in past 12 months (all EU5): 50% needed at least 1 emergency admission 46% required at least 1 emergency ambulance call Patients took an average of 3 AEDs and visited an epilepsy specialist on average of 4 times. Non-epilepsy-related resource use: 99.6% of patients >5 years experienced at least 1 motor, speech, learning or behavioural impairment. Data reported for the UK 50% had treatment for motor impairments 18% had treatment for autism 9% had treatment for behavioural difficulties Data reported for EU5 47% (Italy) to 81% (Spain) had treatment for speech impairments 17% (Germany) to 50% (Spain) had treatment for learning impairments 4% (Italy) to 30% (Germany) had treatment for ADHD	Emergency events in past 12 months: Infants: None: 5.9% 1 to 5 events: 47.1% 6 to 10 events: 17.6% 11 to 20 events: 11.8% >20 events: 17.6% Preschool (2-5 yr): None: 24.1% 1 to 5 events: 54.6% 6 to 10 events: 10.6% 11 to 20 events: 6.4% >20 events: 4.3% Middle school (6-11 yr): None: 53.0% 1 to 5 events: 37.1% 6 to 10 events: 6.4% 11 to 20 events: 1.0% >20 events: 2.5% Adolescents (12-17 yr): None: 70.1% 1 to 5 events: 28% 6 to 10 events: 0.9%

	AWMSG, 2008 (32)	AWMSG 2017 (34)	GWPCARE1 (27)	Irwin 2018 (107)	Lagae et al., 2018 (10)
					11 to 20 events: 0.9% >20 events: 0% Adult: None: 72.0% 1 to 5 events: 24% 6 to 10 events: 4% 11 to 20 events: 0% >20 events: 0% Overall: None: 49.7% 1 to 5 events: 38.0% 6 to 10 events: 6.7% 11 to 20 events: 2.7% >20 events: 2.9% Ambulance calls in past 12 months: Infants: None:17.6% 1 to 5 calls: 50.0% 6 to 10 calls: 14.7% 11 to 20 calls: 5.9% >20 calls: 11.8% Preschool (2-5 yr): None: 41.8% 1 to 5 calls: 41.1% 6 to 10 calls: 10.6% 11 to 20 calls: 3.5% >20 calls: 2.8% Middle school (6-11 yr): None: 51.5% 1 to 5 calls: 35.6% 6 to 10 calls: 8.4% 11 to 20 calls: 2.5% >20 calls: 2.0% Adolescents (12-17 yr): None: 73.8% 1 to 5 calls: 24.3% 6 to 10 calls: 1.9% 11 to 20 calls: 0% >20 calls: 0% Adult: None: 67.0% 1 to 5 calls: 32.0% 6 to 10 calls: 1.0% 11 to 20 calls: 0% >20 calls: 0% Overall: None: 53.9% 1 to 5 calls: 35.1% 6 to 10 calls: 6.8% 11 to 20 calls: 2.1% >20 calls: 2.1%

Table 64. Summary of relevant studies reporting costs or resource use relevant to the UK

	Irwin et al. 2017 (25)	Lagae et al. 2017 (23)	Nabbout et al. 2017 (24)	Aras et al. 2015 (106)
Country	Europe	Europe	Austria, USA, Italy, UK	15 European countries
Date	2016	2017	NR	2014
Population	Caregivers of children and adults with DS	Patients and caregivers of patients with DS	Caregivers of children with DS	Caregivers of patients with DS
Applicability to England	Moderate	Moderate	Moderate	Moderate
Cost valuations	Family/ caregiver self-report	Family/ caregiver self-report	Caregiver-reported	Family self-report
Direct costs	Annual healthcare utilisation costs (not including drugs) were on average $1467 per patient	80% of families have costs partially or fully covered, but costs are high for those paying out of pocket	Caregivers in the US reported greater impacts than other countries regarding medical equipment and bills	NR
Indirect costs	30%of caregivers were unemployed. 65% employed Of those employed: 28% missed >3 working days over past 4 weeks	23% take support from social services 30% of caregivers were unemployed. 81% of these gave up work to care 77% of caregivers had <1 hour a day to themselves	Caregivers in the US reported greater impacts than other countries with regard to specialist schools support	NR
Technology costs	NR	NR	NR	NR
Resource use	Proportion with at least 1 emergency admission: Half overall 28% of adults 46% had at least 1 ambulance call over the past 12 months	Proportion with at least 1 emergency admission: Half overall 94% of infants 76% of pre-school children 30% of adolescents 28% of adults 46% had at least 1 ambulance call over the past 12 months. decreasing with increasing age Treatment pattern: Valproate: 76% Clobazam: 53% Stiripentol: 47% Topiramate: 34% Ketogenic diet: 6.5%	NR	Admissions to ER for status epilepticus in past year

Table 65: Summary of non-UK cost and resource use studies: Europe

Study	Strzelczyk 2018 (105)	Strzelczyk 2014 (108)	De Liso 2016 (109)	Coqué 2015 (110)	Berkvens 2015 (111)
Country	Germany	Germany	France	France	Netherlands
Date	2018	2011	2013	2013	Unclear
Population	Patients with DS and their caregivers	Children and adolescents with DS who were switched to stiripentol	Patients with DS with SCN1A mutations who had received stiripentol	Families of patients with DS	Adults with DS in a tertiary care residence for people with epilepsy and intellectual disability
Applicability to England	Moderate	Moderate	Moderate	Moderate	Moderate
Cost valuations	NR	Seizure diaries, chart review specified as resource use for epilepsy; Official German drug price list (Rote list). German Diagnosis Related Group inpatient costs; official German doctors' fee scale	NR	Family self-report	Chart review
Direct costs	Patient seizure burden was the major contributor to direct costs. and other costs (specialist care. therapy for additional symptoms) were substantial	1-year baseline period. whole population. mean [SD]: Total direct costs (€): 6506 [3974]. range 1174 to 12.980. median 5088 Medication (AEDs. €): 1559 [1356]. 24% of total direct costs. range 47 to 4623. median 1332 Valproate: 140 [101] Topiramate: 813 [681] Clobazam: 10 [31] Other AEDs: 597 [925] Non-AED costs (€): 4946 [4136]. 76% of total direct costs. range 136 to 12437. median 3701 Hospitalisation: 4483 [3684]. 69% of total direct costs Emergency transport: 391 [903] Outpatient care:46 [56] Diagnostic tests: 26 [42] Patients with few baseline seizures who attained in seizure remission on conventional AEDs (n=4). mean [SD] Total direct costs. (€): baseline 2378 [1214]. after 1yr follow-up 1744 [734] Medication (AEDs. €): baseline 1156 [597]. after 1yr follow-up 1351 [395] Valproate: baseline 171 [81]. after 1yr follow-up 159 [96] Topiramate: baseline 869 [614]. after 1yr follow-up 1096 [614] Clobazam: baseline 0. after 1yr follow-up 0 Other AEDs: baseline 116 [184]. after 1yr follow-up 97 [194] Non-AED costs (€): baseline 1222 [1656]. after 1yr follow-up 392 [645] Hospitalisation: baseline 1129 [1709]. after 1yr follow-up 338 [677] Emergency transport: baseline 0. after 1yr follow-up 0 Outpatient care: baseline 30 [30]. after 1yr follow-up 39 [34] Diagnostic tests: baseline 64 [65]. after 1yr follow-up 15 [11] Patients with refractory seizures on adjunctive therapy with stiripentol and clobazam. n=9	NR	NR	NR

		Total direct costs (€): baseline 8340 [3291]. after 1yr follow-up 11901 [5472] Medication (AEDs. €): baseline 1738 [1584]. after 1yr follow-up 1276 [852] Valproate: baseline 126 [110]. after 1yr follow-up 115 [79] Topiramate: baseline 788 [742]. after 1yr follow-up 643 [601] Clobazam: baseline 14 [36]. after 1yr follow-up 91 [31] Other AEDs: baseline 810 [1050]. after 1yr follow-up 429 [786] Stiripentol: baseline 0. after 1 yr follow-up 6610 [3553] Non-AED costs (€): baseline 6601 [3823]. after 1yr follow-up 4014 [5694] Hospitalisation: baseline 5974 [3336]. after 1yr follow-up 3423 [5117] Emergency transport: baseline 565 [1054]. after 1yr follow-up 490 [899] Outpatient care: baseline 53 [65]. after 1yr follow-up 64 [38] Diagnostic tests: baseline 9 [6]. after 1yr follow-up 38 [48]			
Indirect costs	NR	NR	NR	NR	NR
Technology costs	NR	NR	NR	NR	NR
Resource use	Most patients (89%) have a severely disabled pass. and 76% require significant (level 1) to extreme (level 3) categories of nursing care: Level 1: 23% Level 2: 27% Level 3: 26%	NR	Prior AED use: Levetiracetam: 13 patients Topiramate: 12 Carbamazepine: 8 (inappropriate use) Clonazepam: 7 Phenobarbital: 5 (inappropriate use) Clobazam: 5 Vigabatrin: 4 Valproate: 4 Zonisamide: 3 Ethosuximide: 3 Stiripentol: 2 Acetazolamide: 2 Stiripentol (started in 92% of patients) was used as triple therapy with valproate and clobazam in 42/49 patients and maintained to a mean 20 months in 96%; 31 also received a 4th AED (topiramate in 20, levetiracetam in 6, clonazepam in 5, zonisamide in 4, bromide in 1, Mean daily doses: Stiripentol: 42 mg/kg/day. range 35 to 50 mg/kg/day Clobazam: 0.31 mg/kg/day. range 0.22 to 0.40 mg/kg/day Valproate: 21 mg/kg/day. range 16 to 24 mg/kg/day	Most used AEDs: Clobazam: 92%. 28% of use is outside licensed age group. 52% inappropriate posology. 57% incorrect dose for age; Valproate: 90%. 66% inappropriate posology. 11% incorrect dose for age; Stiripentol: 81%. 21% inappropriate posology. 26% incorrect dose for age; Topiramate: 46%. all off-label. 93% inappropriate posology. 10% incorrect dose for age	Prior AED use: Mean 7.8 AEDs Carbamazepine: 8 patients Clobazam: 9 Clonazepam: 8 Ethosuximide: 3 Felbamate: 2 Gabapentin: 5 Levetiracetam: 8 Lamotrigine: 11 Oxcarbazepine: 3 Phenobarbital: 5 Phenytoin: 2 Stiripentol: 3 Topiramate: 9 Vigabatrin: 8 Valproate: 13 Zonisamide: 2 Diamox: 2 3/13 currently used psychoactive medication: pipamperone (n=1). citalopram (n=2). promethazine (n=1)

Table 66. Summary of non-UK cost and resource use studies: Europe (continued)

Study	Irwin 2018 (26)	Irwin 2018 (112)	Irwin 2018 (107)
Country	Denmark	Germany	France, Germany, Italy, Spain, UK
Date	2017	NR	2016
Population	Children and adults with DS	Caregivers of patients with DS	
Applicability to England	Moderate	Moderate	Moderate
Cost valuations	Treatment patterns: Danish epilepsy centre, Filadelfia	Costs: Literature, participant reports	Costs: Literature, participant reports
Direct costs	NR	Annual per patient direct costs Total = €25,000 €1702 inpatient costs, €1130 care grade benefits, €892 total AED costs, €559 ancillary treatments (€ 81 out of pocket), €520 other patient co-payments (100% out of pocket), €464 medical aids (€41 out of pocket), €274 outpatient costs, €239 healthcare professionals (€46 out of pocket), €121 emergency transportation (€3 out of pocket), €53 emergency medicines, €47 diagnostic studies, €41 rehabilitation.	Annual direct costs for a patient with DS in the EU5 (US$) Total = $15,886: $6185 = AED costs (38% of total), $9,783 =other costs Seizure-related = $7957 ($1854 excluding AEDs) Non-seizure-related = $7929: 79% of this is physiotherapy and speech therapy Mean annual costs across the EU5 (US$): Seizure-related symptoms Emergency visits: UK = $783, France = $176, Germany = $1060, Italy = $262, Spain = $714, Average = $587 Ambulance calls: UK= $1343, France = $736, Germany = $1036, Italy = $284, Spain = $492, Average = $774 Epilepsy specialist visits: UK= $1410, France =$182, Germany = $215, Italy = $155, Spain = $504, Average = $493 Valproic acid: UK=$232, France= $185, Germany = $187, Italy = $198, Spain = $45, Average = $175 Clobazam: UK= $57, France= $30, Germany = $95, Italy= $56, Spain = $64, Average = $60 Stiripentol: UK= $8284, France=$4726, Germany= $6613, Italy= $4340, Spain= $5203, Average = $5831 Topiramate: UK= $4, France= $24, Germany = $52, Italy = $53, Spain = $49, Average = $36 Total drug costs: UK = $8577, France= $4965, Germany = $6947, Italy = $4647, Spain = $5360, Average = $6103 Total with drugs: UK = $12,112, France = $6060, Germany = $9258, Italy = $5348, Spain = $7071, Average = $7957 Total without drugs: UK = $3535, France = $1094, Germany = $2311, Italy = $701, Spain = $1711, Average = $1854 Non-seizure-related symptoms Physiotherapy: UK= $1678, France= $3995, Germany = $4921, Italy = $3048, Spain = $3337, Average = $3358 Speech Therapy: UK= $1765, France = $3279, Germany = $2767, Italy= $2091, Spain = $5420, Average = $2932

			Therapy for learning difficulties: UK = $466, France = $836, Germany = $366, Italy = $841, Spain = $1231, Average = $732 Therapy for autism: UK= $480, France = $650, Germany = $228, Italy= $121, Spain = $408, Average = $365 Therapy for ADHD: UK= $102, France = $53, Germany = $38, Italy = $158, Spain = $454, Average = $152 Behavioural therapy: UK= $192, France= $272, Germany= $209, Italy= $851, Spain = $325, Average = $390 All therapies: UK= $4681, France= $9084, Germany= $8529, Italy = $7110, Spain= $11175, Average= $7929
Indirect costs	NR	Total out of pocket costs over 3 months per patient = €1151 Equipment expenditure = €270 Childcare costs = €230 Employment 62% maternal absenteeism and 30% paternal absenteeism in last 3 months. School attendance in children aged 5 to 17 years: 26% mainstream school 66% special school or sheltered workplace	Career impact of caregiving Career choices affected = 83% Missed 2+ days of work in past 4 weeks = 31% Unemployed = 27% Use of private childcare for DS patients: median out-of-pocket costs per patient per year UK = $1920 (15% uptake) France = $5393 Germany = $1618 Italy = $4045 Spain = $2697 Difficulties reported by caregivers due to caring for a child with DS Daily activities = 91% Family relationships =70% Social life =80%
Technology costs	NR	NR	NR
Resource use	Trends are for addition of more drugs over time. Most paediatric patients (64%) started on monotherapy, but few (7%) remain on it over time. Number of AEDs used by age - at first diagnosis <1 year: monotherapy = 12/28, dual = 7/28; triple = 1/28; quadruple = 0/28 1 to 3 years: monotherapy = 6/28, dual = 0/28; triple = 2/28; quadruple = 0/28 4 to 6 years: monotherapy = 0/28, dual = 0/28; triple = 0/28; quadruple = 0/28 7 to 12 years: monotherapy = 0/28, dual = 0/28; triple = 0/28; quadruple = 0/28 Adults: NR Number of AEDs used by age - current treatment <1 year: monotherapy = 0/28, dual = 0/28; triple = 0/28; quadruple = 0/28 1 to 3 years: monotherapy = 0/28, dual = 4/28; triple = 2/28; quadruple = 0/28 4 to 6 years: monotherapy = 0/28, dual = 1/28; triple = 3/28; quadruple = 0/28 7 to 12 years: monotherapy = 2/28, dual = 2/28; triple = 8/28; quadruple = 6/28	Care needs (Pflegebedürftigkeit scale) No need of care = 12% No care level but in need of care = 11% Care level I = 24% Care level II = 27% Care level III = 27% Treatment patterns Valproate = 66% Bromide = 44% Clobazam = 41% Stiripentol = 35% Topiramate = 24% Resource use Half of patients had called emergency services in the past 12 months	Epilepsy-related resource use in past 12 months: 50% needed at least 1 emergency admission 46% required at least 1 emergency ambulance call Patients took an average of 3 AEDs and visited an epilepsy specialist on average of 4 times. Non-epilepsy-related resource use: 99.6% of patients >5 years experienced at least 1 motor, speech, learning or behavioural impairment. Uptake of therapies for these impairments varied across the EU5: 50% (UK, Spain) to 78% (France) for motor impairments 47% (Italy) to 81% (Spain) for speech impairments 17% (Germany) to 50% (Spain) for learning impairments 18% (UK) to 50% (France) for autism 4% (Italy) to 30% (Germany) for ADHD 9% (UK) to 46% (Spain) for behavioural difficulties

	Adults: monotherapy = NR, dual = NR; triple = 13/27; quadruple = 7/27; 5 drugs = 2/27 Mean cumulative number of AEDs tried increased with age, plateauing at 8 drugs at 9 years old. An average of 2 AEDs were tried by age 1. Stiripentol: actively prescribed to 35%-54% of pediatric patients; suggests this is a core treatment. Valproate: Prescribed for 75-90% patients <1-year old; suggests this is common monotherapy. Topiramate: use increases with age, to approx 90% of 12-year-olds; suggests this is a core 2nd-4th-line therapy. Clobazam: use increased with age to approx 70% of 12-year-olds, suggests this is a core 2nd-4th-line therapy. Cannabidiol or derivatives: Not prescribed for patients younger than 7 yr; peak use is 20% at age 9 yr. Lamotrigine: use increases with age, reaches approx 70% of 12-year-olds despite being contraindicated. Levetiracetam: use decreases with age, peak is approx 70% at 2 years old. Time on monotherapy was less than 1.5 years, triple therapies lasted 1 year for ages 1 to 3 yr, and 1.9 to 2.5 years for ages 7 to12 yr. Switches from monotherapy were usually escalation to dual therapy. <20% of patients de-escalated from dual therapy to monotherapy. Treatment switches for those starting on triple therapy were usually for a change in drug type rather than increasing or decreasing the number prescribed. Escalation from dual to triple was common (>50%) in older patients.		

Table 67. Summary of non-UK cost and resource use studies: Rest of World and unknown

Study	Campbell 2018 (104)	CADTH 2014 (36)	Whittington 2018 (113)	Misra 2015 (114)	Ito 2018 (115)
Country	USA	Canada	USA	NR	Japan
Date	2016	Assume 2014	2017	Assume 2015	NR
Population	Caregivers of patients with DS	Patients with DS uncontrolled with clobazam + valproate	Caregivers of patients with DS	Children with DS and SCN1A mutations	Caregivers of patients with DS
Applicability to England	Moderate	Moderate	Moderate	Unclear	Moderate
Cost valuations	Work productivity and activity impairment questionnaire	Unclear	Caregiver reported resource use. Costs calculated using Medical Expenditure Panel Survey adjusted to 2016 USD$	Unclear. assume chart review	NR
Direct costs	NR	Drug costs: Stiripentol $6.37/250 mg capsule or sachet Stiripentol $12.73/ 500 mg capsule/sachet Clobazam 0.5 to 1.0 mg/kg/d $0.01 to $0.44 daily Valproate 15 to 60 mg/kg/day $0.27 to $1.43 daily	Mean unit cost: In-home visits: $214 Doctor visits: $245 Emergency department visits: $788 Hospitalisations: $10,204 Ground ambulance: $1,111 Air ambulance: $7,160 Chiropractic services: $36 Multivitamin use: $10 Essential oil use: $10 Marijuana prescription: $150 Annual cost mean (SD): In-home visits: $9,894 ($29,456) Doctor visits: $2,728 ($2,221) Emergency department visits: $1,497 ($1,789) Hospitalisations: $11,565 ($22,001) Ground ambulance: $741 ($1,753) Air ambulance: $477 ($1,786) Chiropractic services: $235 ($605) Multivitamin use: $63 ($91) Essential oil use: $26 ($59) Marijuana prescription: $50 ($125) Total annual direct cost Mean = $27,276 (95%CI $15,757 to £41,904)	NR	NR
Indirect costs	Caregivers reporting higher quality of life (EQ-VAS score ≥65: Weekly time missed from work (hrs): Mean = 7.4 (SD 15.2) Median = 0.5 (IQR 0 to 2.8) Weekly time missed from leisure (hrs): Mean = 31.0 (SD 53.9) Median = 7.0 (IQR 1.8 to 23.0) Effect of caregiving on work productivity (0 = no impact, 100= completely prevented productivity): Mean = 39.1 (SD 25.6)	NR	Employed: 72.7% yes; 27.3% no 18.2% switched jobs due to caregiving 27.3% quit job or retired early 18.2% lost job 58.4% of those employed were employed as caregiver Annual salary of employed: 25%: <$20,000 33.3%: $20,000- 39,999 25%: $40,000- 59,999 16.7%: >$60,000 Caregiver reported time, mean (SD)	NR	Employment rates 20.8% of mothers of children with DS vs 47.3% for all Japanese mothers 98% of fathers School attendance 25% of patients under 6 yr enrolled in nursery vs 46% for all Japanese children

Study	Campbell 2018 (104)	CADTH 2014 (36)	Whittington 2018 (113)	Misra 2015 (114)	Ito 2018 (115)
	Median = 52.0 (IQR 13.8 to 58.0) Effect of caregiving on leisure (0 = no impact, 100= completely prevented leisure time) mean = 55.1 (SD 24.0), median = 55.5 (IQR 39.5 to 69.3) Caregivers reporting worse quality of life (EQ-VAS <65) Weekly time missed from work (hrs): Mean = 6.9 (SD 12.3) Median = 0.0 (IQR 0 to 8.0) Weekly time missed from leisure (hrs): Mean = 57.8 (SD 59.2) Median = 40.0 (IQR 7.3 to 84.0) Effect of caregiving on work productivity (0 = no impact, 100= completely prevented productivity): Mean = 76.9 (SD 19.8) Median = 75.0 (IQR 68.0 to 90.0) Effect of caregiving on leisure (0 = no impact, 100= completely prevented leisure time) Mean = 82.6 (SD 12.4) Median = 81.0 (IQR 77.3 to 91.8)		Absenteeism: 381 (704) hours Presenteeism: 616 (719) hours Lost leisure time: 2047 (2929) hours Annual cost, mean (SD): Absenteeism: $7,587 ($16,941) Presenteeism: $12,338 ($19,196) Lost leisure time: $52,415 ($74,934) Income loss due to caregiving: $9,242 ($19,410) Total annual indirect cost: $81,582 ($57,253 to $110,151)		
Technology costs	NR	NR	NR	NR	NR
Resource use	Number of hospital/ ER visits per year: None: 33% 1 to 2 visits: 40% 3+ visits: 27% Number of outpatient visits per year: None: 3% 1 to 4 visits: 13% 5 to 9 visits: 33% 10 to 14 visits: 20% 15 to 19 visits: 7% 20+ visits: 23%	NR	Caregiver-reported annualised rate mean (SD) In-home visits: 46.23(137.64) Doctor visits: 11.13(9.07) Emergency department visits: 1.90(2.27) Hospitalisations: 1.13 (2.16) Ground ambulance: 0.67 (1.58) Air ambulance: 0.07 (0.25) Chiropractic services: 6.53(16.80) Multivitamin use: 6.33(9.07) Essential oil use: 2.57(5.90) Marijuana prescription: 0.33 (0.83)	Resource use during status epilepticus in DS: Intubation for respiratory failure: 30/102 episodes Diazepam monotherapy: 28% of events Diazepam + other medication: 53% of events Fosphenytoin: 27% of episodes	Nurseries refused to give antiepileptic medication routinely for 10.5% of children Nurseries refused to give emergency medication for 36.8% of children

Appendix J: Clinical outcomes and disaggregated results from the model

J1.1 Clinical outcomes from the model

As the model outcomes are based on the absolute convulsive seizure frequency categories and the clinical trial outcomes measure percentage reduction in seizure frequency, we were only able to test and compare the seizure-free and mortality estimates from the model to evidence published in the literature and the results from the Phase 3 trials and the OLE study.

Proportion of seizure-free patients in the cannabidiol arm

The proportion of seizure-free patients in the cannabidiol arm estimated by the model at 1 year is similar to the estimates from the OLE study.

Table 68: Proportion of seizure-free patients in the cannabidiol arm at baseline and at 1 year

	Baseline	1 year
Seizure-free estimates		
Seizure-Free (model)	[redacted]	[redacted]
Seizure-Free (OLE study)	[redacted]	[redacted]
References: Scheffer 2018 (29) Abbreviations: OLE, Open-Label Extension		

Mortality

The disease-specific mortality rate/1000-person-years was estimated to be 15.84 (8) and the estimated number of deaths in the CCM alone arm in the model are similar to the evidence in the published literature.

Table 69: Total number of disease-specific deaths at 10-year in the cannabidiol + CCM and CCM arms

	CBD+CCM	CCM
SUDEP (model)	[redacted]	[redacted]
Non-SUDEP(model)	[redacted]	[redacted]
Total deaths (model)	[redacted]	[redacted]
Total deaths (Cooper for 10,000 patients)		1,584
Abbreviation: SUDEP, Sudden unexpected death in epilepsy		

J1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 70: Summary of QALY gain by health state

Health state	QALY intervention (CCM + CBD)	QALY comparator (CCM)	Increment	Absolute increment	% absolute increment
Seizure-Free, > 24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤ 8 seizures, ≤ 18 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤ 8 seizures, > 18 - ≤ 24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤ 8 seizures, > 24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>8 - ≤ 25 seizures, ≤ 18 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>8 - ≤ 25 seizures, > 18 - ≤ 24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>8 - ≤ 25 seizures, > 24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 25 seizures, ≤ 18 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 25 seizures, > 18 - ≤ 24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 25 seizures, > 24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CBD, cannabidiol; CCM, current clinical management; QALY, quality-adjusted life year

Table 71: Summary of costs by health state

Health state	Cost intervention (CCM + CBD)	Cost comparator (CCM)	Increment	Absolute increment	% absolute increment
Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤ 8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 8 - ≤ 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CBD, cannabidiol; CCM, current clinical management

Table 72: Disaggregated costs for treatment and adverse events per year

	Treatment		Adverse events	
Year	CCM + CBD	CCM	CCM + CBD	CCM
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Table 73: Disaggregated costs for mortality per year

	Mortality			
	CCM + CBD		CCM	
Year	Non-SUDEP	SUDEP	Non-SUDEP	SUDEP
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Table 74: Disaggregated costs for management per year

	Visits to HCP		Hospitalisation		Rescue medicine		Institutionalisation		Total management	
Year	CCM + CBD	CCM	CCM + CBD	CCM	CCM + CBD	CCM	CCM + CBD	CCM	CCM + CBD	CCM
1	£5,480.40	£6,240.52	£7,814.76	£8,915.41	£643.50	£737.66	£114.25	£119.35	£14,052.90	£16,012.94
2	£4,877.02	£6,056.90	£6,880.69	£8,677.06	£565.22	£714.88	£103.87	£113.49	£12,426.79	£15,562.33
3	£4,689.87	£5,746.57	£6,604.54	£8,231.00	£540.89	£678.10	£95.65	£107.91	£11,930.95	£14,763.58
4	£2,978.47	£3,622.40	£3,368.77	£4,182.00	£397.53	£497.15	£1,206.37	£1,366.92	£7,951.14	£9,668.47
5	£2,842.81	£3,436.61	£3,218.44	£3,967.12	£378.87	£471.58	£1,509.40	£1,708.41	£7,949.51	£9,583.72
6	£2,712.35	£3,260.39	£3,073.56	£3,763.33	£360.95	£447.33	£1,437.15	£1,624.61	£7,584.00	£9,095.65
7	£2,587.32	£3,093.25	£2,934.30	£3,570.06	£343.82	£424.33	£1,368.37	£1,544.95	£7,233.81	£8,632.59
8	£1,993.13	£2,377.82	£1,876.63	£2,284.77	£290.37	£358.12	£1,302.90	£1,469.22	£5,463.03	£6,489.93
9	£1,433.64	£1,713.40	£885.27	£1,094.25	£239.85	£296.47	£1,240.58	£1,397.22	£3,799.35	£4,501.33
10	£1,361.85	£1,625.28	£840.47	£1,037.95	£227.71	£281.22	£2,517.75	£2,865.34	£4,947.78	£5,809.78
11	£1,293.66	£1,541.68	£797.94	£984.54	£216.19	£266.75	£2,397.13	£2,725.36	£4,704.91	£5,518.33
12	£1,228.89	£1,462.39	£757.56	£933.88	£205.25	£253.02	£2,282.31	£2,592.25	£4,474.01	£5,241.54
13	£1,167.38	£1,387.18	£719.22	£885.83	£194.86	£240.00	£2,173.01	£2,465.66	£4,254.47	£4,978.67
14	£1,108.96	£1,315.85	£682.83	£840.25	£185.00	£227.65	£2,480.39	£2,818.27	£4,457.18	£5,202.03
15	£1,053.46	£1,248.16	£648.27	£797.01	£175.64	£215.94	£2,762.74	£3,142.04	£4,640.10	£5,403.15
Total	£36,809.21	£44,128.40	£41,103.23	£50,164.46	£4,965.64	£6,110.19	£22,991.86	£26,061.00	£105,869.94	£126,464.05

Table 75 and Figure 11 below present the impact of cannabidiol on the frequency of seizures when added to CCM. After 15 years, [redacted] of patients who receive cannabidiol in addition to CCM are seizure-free compared to [redacted] when cannabidiol is not added to the treatment.

Table 75: Patients' distribution per health state at baseline versus after 15 years

	Baseline		At 15 years	
Health states	**CCM + CBD**	**CCM**	**CCM + CBD**	**CCM**
Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]
≤ 8 convulsive seizures	[redacted]	[redacted]	[redacted]	[redacted]
> 8 - ≤ 25 convulsive seizures	[redacted]	[redacted]	[redacted]	[redacted]
> 25 convulsive seizures	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: CBD, cannabidiol; CCM, current clinical management				

Figure 11: Patients' distribution per health state at baseline versus after 15 years

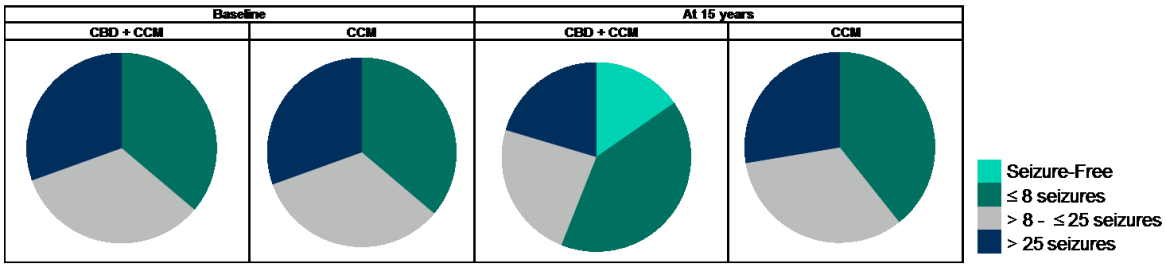


Table 76: Number of deaths per death category after 15 years

	CCM + CBD	**CCM**	Difference
SUDEP	[redacted]	[redacted]	[redacted]
Non-SUDEP	[redacted]	[redacted]	[redacted]
Background	[redacted]	[redacted]	[redacted]
Total of lives saved	[redacted]	-	-

J1.3 DSA results

	CBD + CCM vs. CCM							
Parameter	**Lower limit**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Upper limit**	**Incremental costs**	**Incremental QALYs**	**ICER**
Discount rates - Costs								
Discount rates - Outcomes								
Utilities based on standard errors								
Weight								
Emergency Department Visit								
SUDEP mortality (Probabilities)								
Daily Cost General Ward								
Daily Cost ICU								
Hospitalisation Costs								
Visits Costs								
Non-SUDEP mortality (Probabilities)								
% of institutionalisation								
Institutionalisation Costs								
Phone Call Follow-up								
Discontinuation								
SUDEP mortality (RR)								
Non-SUDEP mortality (RR)								
Rescue Med Costs								
Non-SUDEP costs, n days in ICU								

Abbreviations: CBD, cannabidiol; CCM, current clinical management; CI, confidence interval; ICU, intensive care unit; RR, relative risk; SUDEP, sudden unexpected death in epilepsy

Appendix K: Checklist of confidential information

Provided as a separate document.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

Revised economic assessment

May 2019

File name	Version	Contains confidential information	Date
ID1211 Revised economic assessment CBD in DS 15May19	Final	Yes	15 May 2019

1 Document overview

As per our communication with NICE on 13th February 2019, an updated economic evaluation has been conducted for Epidyolex® (cannabidiol) in Dravet syndrome (DS).

This document is intended to be read in conjunction with Document B "Company evidence submission: Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]". It provides an overview of the revised inputs and outputs for the updated cost-utility analysis.

The overall structure of the cost-utility model remains the same (see Section B3 of Document B for a detailed description). Inputs and assumptions remain the same as the original submission, except where indicated in this document.

The following content is covered:

- Section 2: Updated model parameters (inputs and assumptions)
- Section 3: Updated base case results
- Section 4: Updated sensitivity analyses
- Section 5: Updated scenario analyses
- Section 6: Updated disaggregated results of the base case and DSA
- Section 7: Appendix

Throughout the document, the relevant tables and figures in Document B, as well as relevant ERG questions, are listed.

In order for the reader to easily identify the parameters that have been updated, they are highlighted in red text throughout this document.

As per convention, yellow indicates academic in confidence and blue indicates commercial in confidence. Red text within yellow or blue text should also be considered to be academic in confidence or commercial in confidence respectively.

2 Updated model parameters (inputs and assumptions)

Patient weight

Document B	Excel Tab	ERG Questions	Source	Appendices
B.3.3 Clinical parameters and variables (p56) Table 15 (p58)	COHORT DEFINITION	B5	Data on file: Patient level data GWPCARE1 and GWPARE2	SAS Tables

Due to outliers, patient weights at baseline in the GWPCARE1 and GWPCARE2 trials were asymmetrically distributed. To account for this, the median instead of the mean weight is now used from the trials to set the average weight of patients in each age group within the model. The updated assumptions are show in Table 1.

Table 1: Baseline characteristics per age group used in the model

	<12 years		≥12 years	
Demographic characteristics at baseline	**2-5 years**	**6-11 years**	**12-17 years**	**18-55 years**
% of patients	[redacted]	[redacted]	[redacted]	[redacted]
Mean age	[redacted]	[redacted]	[redacted]	[redacted]
Median weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]
Health state allocation at baseline: Number of convulsive seizures per 28 days				
≤8 convulsive seizures per 28 days	[redacted]		[redacted]	
>8 - ≤25 convulsive seizures per 28 days	[redacted]		[redacted]	
>25 convulsive seizures per 28 days	[redacted]		[redacted]	
Health state allocation at baseline: Number of days without convulsive seizures per 28 days				
≤8 convulsive seizures				
≤18 days	[redacted]		[redacted]	
>18 - ≤24 days	[redacted]		[redacted]	
>24 days	[redacted]		[redacted]	
>8 - ≤25 convulsive seizures				
≤18 days	[redacted]		[redacted]	
>18 - ≤24 days	[redacted]		[redacted]	
>24 days	[redacted]		[redacted]	
>25 convulsive seizures				
≤18 days	[redacted]		[redacted]	
>18 - ≤24 days	[redacted]		[redacted]	
>24 days	[redacted]		[redacted]	

Treatment discontinuation

Document B	Excel Tab	ERG Questions	Source
B.3.3 Clinical parameters and variables (p64-65)	DISCONTINUATION	A26, B12c/d, B14e/f, B29a	Data on file: Patient level data GWPCARE1 and GWPCARE2 Data on file: Patient level data US Early Access Program

Updated discontinuation rates have been implemented in the model that consider discontinuations for all-causes as observed during the GWPCARE1 and GWPCARE2 trials, GWPCARE5 Open Label Extension Study, and US Early Access Program. These are shown in Table 2.

Discontinuation rates: Cycle 1

Treatment discontinuation in the first few months of a new treatment is mostly related to tolerability. This was the case in the GWPCARE1 and GWPCARE2 studies: adverse events were the most common reason for withdrawal in the treatment period.

In the original model, treatment discontinuations as observed for all patients in each health state during the treatment period of the clinical trials were used to set assumptions for cycle 1. As treatment discontinuations in the first 3 months are likely to be driven by adverse events, rates are unlikely to vary between health states based on seizure frequency. As such, we have assigned a flat discontinuation rate for all health states in the first cycle, using the overall treatment withdrawal rates as observed for each age group at baseline (<12 and ≥12 years old) in the Phase 3 trials.

In GWPCARE2, no discontinuations were observed in the ≥12 year old age group in the 10 mg/kg/day arm. To avoid a zero-assumption, we have assumed that the discontinuation rates across health states for this age group were the same as those for patients aged <12 years old.

Discontinuation rates: Subsequent cycles

For the subsequent cycles (cycles 2-9), we have continued to use the discontinuation rates as observed in patients in each health state over the follow-up period of the GWPCARE5 Open-Label Extension study.

During this period of time it is expected that discontinuations would be largely driven by a lack of perceived treatment effect rather than adverse events. This was the case in the GWPCARE5 study: although withdrawals were rare, the majority of patients withdrew in this study for reasons other than an adverse event. The discontinuation rates from GWPCARE5 show the expected gradient of worsening with increasing seizure frequency across health states. As such, these data are considered to provide the best available evidence for medium-term persistence on cannabidiol across health states, and have therefore been retained in the model. All discontinuation rates as observed have been adjusted to account for the 3-month cycle period.

In the GWPCARE5 study, there were low numbers of patients with DS who were seizure-free. Having no discontinuations in patients who are seizure-free is unlikely to be fully representative of a real-world clinical setting. Therefore, we have assumed a [redacted] discontinuation rate per cycle as a conservative estimate.

Discontinuation rates: Long-term

Discontinuation rate assumptions have been revised over the long term (cycle 10 onwards) to account for real-world persistence on treatment.

For the health state ">25 convulsive seizures":

- A "stopping rule" is assumed for these patients. If seizure burden remains high after 2 years, it is assumed that patients would be recommended to stop treatment. A discontinuation rate of [redacted] is assumed. To be conservative, the rate is not 100%: this accounts for a proportion of patients who would continue treatment due to perceived benefits beyond seizure control.

No “stopping rule” guidance has yet been recommended for cannabidiol. It is anticipated that these could be based on a certain percentage reduction in convulsive seizure frequency over time.

To apply a stopping rule only to the highest seizure-frequency health state would not be realistic; it is not the case that every patient experiencing 25 convulsive seizures per month after 2 years would continue, whilst all those experiencing 26 would stop. For this reason, “stopping” has been applied at a rate of [redacted] to the most severe health state, and on a decreasing gradient to the next most severe health state (see next bullet point below).

For the health state “>8 - ≤25 convulsive seizures”:

- We have assumed a [redacted] discontinuation rate per cycle for both age groups. This reflects a level of drop-out that would be expected in patients who do not achieve seizure-freedom or a low rate of seizures. It also accounts for a “stopping rule” being applied to patients at the upper end of the seizure-frequency band.

- The rate chosen reflects the following:

    - The highly refractory nature of the disease and high seizure burden at baseline means that some patients will still be benefiting from treatment versus baseline

    - Treatment continuation is partly a matter of subjective choice: some patients (and/or their caregivers) will want to continue due to perceived benefits beyond seizure control.

For the health state “≤8 convulsive seizures”:

- A discontinuation rate of [redacted] per cycle has been implemented, as measured from patient level data for patients with DS from the April 2017 readout of the US Early Access Program for cannabidiol. This dataset reports treatment withdrawals over up to 36 months of follow-up. It is considered to be the best dataset available to inform on long-term persistence in a real-world setting.

For the health state "convulsive seizure-free":

- We have assumed a discontinuation rate of [redacted] per cycle, reflecting that long-term persistence on any treatment is unlikely to be 100% in a chronic condition.

Table 2: Treatment discontinuation per timepoint and age group

		<12 years			≥12 years		
		Cycle 1	Subsequent Cycles	Long-term Cycles	Cycle 1	Subsequent Cycles	Long-term Cycles
20 mg	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>8 - ≤25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 mg	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>8 - ≤25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events

Document B	Excel Tab	ERG Questions	Source
B.3.3 Clinical parameters and variables (p66) Table 21 (p67) B.3.5 Cost and healthcare resource use identification, measurement and valuation (p86)	SAFETY	B17a/b.	MAA CTD 2.7.4 Summary Clinical Safety 2.1.5.2-6

In the previous model, adverse events could occur for the entire duration of time that patients were receiving CBD. In the updated economic analysis, they are accounted for until cycle 9 at incidence levels as observed in the 14-week treatment periods of the pooled Phase 3 safety datasets.

Adverse events generally occur in the first few months after treatment initiation. After a long period of time stable on drug, their incidence would be expected to be very low. Therefore, we have assumed that they do not occur from cycle 10 onwards. However, to be conservative, we have assumed that they occur up to cycle 9 (representing more than 2 years) at the same rate as observed in the first 14 weeks in the Phase 3 studies.

Adjustment of model parameters to 3-month cycles

Both treatment costs and quality-adjusted life years have been adjusted to reflect the cycle length of 3 months (i.e. 91 days, or one fourth of a year).

Mortality rates

Document B	Excel Tab	ERG Questions	Sources
B.3.3 Clinical parameters and variables (p65)	MORTALITY	B1b. B16.	Cooper MS, *et al*. 2016 Epil Res 128:43-7 Skluzacek JV, *et al*. Epilepsia. 2011;52 Suppl 2:95-101. Trinka E, *et al*. Epilepsia,54(3):495-501,2013

Based on comments from the ERG, in the updated model it has been assumed that convulsive seizure-free patients may still be at risk of death due to epilepsy. Mortality rate assumptions in the updated model are shown in **Error! Not a valid bookmark self-reference.**.

The mortality rate in the convulsive seizure-free health state is based on the risk ratio (0.42) between patients with persistent seizures and those who are seizure-free, as reported in Trinka *et al* 2013 for all epilepsy syndromes. This was applied to the mortality rate assumed for the “middle” health state (>8 - ≤25 seizures), as derived from Cooper *et al* 2016.

The same risk ratios were applied to the mortality rate for non-SUDEP reasons, as also reported in Cooper *et al* 2016, in order to calculate death rates in this category.

Table 3: Epilepsy-related mortality rates

	<12 years		≥12 years		All ages
	SUDEP	Non-SUDEP	SUDEP	Non-SUDEP	Risk ratios
Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	0.42†
≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>8 - ≤25 seizures	0.23%**	0.16%**	0.23%**	0.16%**	[redacted]
>25 seizures	0.33%*	[redacted]	0.33%*	[redacted]	1.40*

*From Skluzacek *et al.* 2011
**From Cooper *et al* 2016
†From Trinka *et al.* 2013

Institutionalisation rates

Document B	Excel Tab	ERG Questions	Source
B.3.5 Cost and healthcare resource use identification, measurement and valuation (p83). Table 29 (p84)	COSTS	B22b.	Assumption

Based on comments from the ERG, we have assumed that convulsive seizure-free patients can also be institutionalised.

The original assumption was that 10% of adult patients in health states with convulsive seizures would be institutionalised. For convulsive seizure-free patients, this proportion has been set at a lower percentage (2%) to account for the lower risk with better controlled epilepsy, as advised by clinical experts.

Table 4: Institutionalisation rates

	<12 years	≥12 years*
Seizure-Free	0%	2%
≤8 seizures	0%	10%
>8 - ≤25 seizures	0%	10%
>25 seizures	0%	10%

*Only patients over 18 are assumed to be institutionalised

Caregiver utilities

Document B	Excel Tab	ERG Questions	Source
B.3.4 Measurement and valuation of health effects (p68). Appendix H	UTILITIES	B18e	Vignette study (see Document B)

Quality of life decrements for caregivers obtained from the vignette study have been included in the model. Values are shown in Table 5.

The following three additional vignettes were valued by carers in consideration of their own QoL, using the EQ5D VAS within the study:

- A severe health state: 32 convulsive seizures per month and 18 seizure-free days
- A moderately severe health state: 16 convulsive seizures per month and 21 seizure-free days
- A convulsive seizure-free state.

Please refer to Appendix H of Document B for full vignette descriptions and mean VAS scores. Section B.3.4 gives a detailed methodological description of the study.

The difference in valuations between each of the above health states and the seizure-free health state were applied as utility decrements to patients in the most severe (>25 convulsive seizures) and “middle” (>8 - ≤25 convulsive seizures) health states in the model, irrespective of the assigned number of seizure-free days.

The model assumes one caregiver per patient, which is a conservative assumption.

Table 5: Summary of mean caregiver VAS score utility decrements

Health state		Mean decrements (standard error)
No seizures	No seizure	-
≤8 seizures	≤18 seizure-free days	-
	>18 - ≤24 seizure-free days	-
	>24 seizure-free days	-
>8 - ≤25 seizures	≤18 seizure-free days	[redacted]
	>18 - ≤24 seizure-free days	[redacted]
	>24 seizure-free days	[redacted]
>25 seizures	≤18 seizure-free days	[redacted]
	>18 - ≤24 seizure-free days	[redacted]
	>24 seizure-free days	[redacted]

3 Updated base case results

Base case incremental cost-effectiveness analysis results

The base case results of the updated economic model are presented in Table 6.

The base case assumed that all patients are on a dose of 10 mg/kg/day.

Over a time horizon of 15 years, cannabidiol in addition to CCM was associated with total QALYs of 4.01 and a total overall cost of £227,309. In contrast, CCM alone was associated with total QALYs of 3.10 and a total overall cost of £195,786.

Cannabidiol in addition to CCM was therefore associated with an incremental QALY gain of 0.91 and an incremental cost of £31,522.

This is an Incremental Cost-Effectiveness Ratio (ICER) versus CCM alone of £34,789 per QALY gained.

The disaggregated results of the base case incremental cost-effectiveness analysis (QALYs and costs) are presented in Section 6.

Table 6: Base-case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM + CBD	£227,309	4.01	£31,522	0.91	£34,789
CCM	£195,786	3.10	-	-	-

Table 7 details the costs (over a 15-year time horizon) per patient by category. The introduction of cannabidiol as an add-on therapy to CCM resulted in lower management costs and non-SUDEP costs ([redacted] and [redacted], respectively). Cannabidiol was associated with a marginal increase in the cost of management of AEs ([redacted]). The difference in treatment costs between cannabidiol with CCM and CCM alone is [redacted].

Table 7: Total costs by category of cost with 15-year time horizon

Cost categories	CCM + CBD	CCM	Difference
Total costs per patient	£227,309	£195,786	£31,522
Treatment costs per patient	[redacted]	[redacted]	[redacted]
Adverse Events costs per patient	[redacted]	[redacted]	[redacted]
Management costs per patient	[redacted]	[redacted]	[redacted]
SUDEP cost per patient	[redacted]	[redacted]	[redacted]
Non-SUDEP cost per patient	[redacted]	[redacted]	[redacted]

4 Sensitivity analyses

Deterministic sensitivity analysis

Document B	Excel Tab	ERG Questions	Source	Appendices
B.3.8 Sensitivity analyses (p104) Table 32 (p87)	DSA	B29a.	Various	SAS TablesSAS tables

The parameters included in the DSA are presented in Table 8.

The lower and upper values for each parameter included in the DSA were either obtained from the literature, based on clinical opinion, or varied across a specified range (e.g. +/-10%). Details are provided in Document B.

The DSA did not include transition probabilities as the movement of patients between the different health states at the end of each cycle in the model is interdependent, and all the transition probabilities would have to be changed simultaneously in order to ensure clinically meaningful results. Therefore, transition probabilities were tested only in the PSA using a bootstrapping method.

Table 8*:* Parameter values for univariate sensitivity analysis

Parameter	Base Case	Lower Bound	Upper Bound	References
Discount Rates				
Costs	3.5%	0.0%	6.0%	NICE recommendation
Outcomes	3.5%	0.0%	6.0%	
Weight (kg)				
2 - 5 years	[redacted]	[redacted]	[redacted]	Based on the PLD from the GWCARE1 & 2 studies, using 40th and 60th percentiles Section 7 Appendix - SAS tables
6 - 11 years	[redacted]	[redacted]	[redacted]	
12 - 17 years	[redacted]	[redacted]	[redacted]	
18 - 55 years	[redacted]	[redacted]	[redacted]	
Discontinuation (all cycles)				
Discontinuation	As observed in GWPCARE 1,2, and 5	-10%	+10%	Assumption applied to base case rates for all cycles
Management Unit Costs				
Visits Costs	Between £106 and £3,529	-20%	+20%	Assumption
Hospitalisation Costs	Between £0 and £5,817	-20%	+20%	Assumption
Rescue Med Costs	Between £0 and £408	-20%	+20%	Assumption

Parameter	Base Case	Lower Bound	Upper Bound	References
Institutionalisation Costs	Between £0 and £1,604	-20%	+20%	Assumption
Daily Cost ICU				
Adults	£1,299	£643	£4,482	Tables 32 & 38 of Document B
Paediatric	£1,583	£784	£5,867	
Daily Cost General Ward				
Adults	£460	£402	£807	Tables 32 & 38 of Document B
Paediatric	£597	£560	£760	
Phone Call Follow-up				
Neurologist	£107	£57	£153	Tables 32 & 38 of Document B
Paediatric neurologist	£258	£55	£234	
Emergency Department Visit				
Per episode	£237	£56	£838	Tables 32 & 38 of Document B
Non-SUDEP costs, days in ICU				
2 - 11 years	7.00	-20%	+20%	Tables 32 & 38 of Document B
12 - 55 years	7.00	-20%	+20%	
% of institutionalisation				
Seizure-Free	2.00%	0.00%	10.00%	Table 32 of Document B
≤8 seizures	10.00%	0.00%	20.00%	
>8 - ≤25 seizures	10.00%	0.00%	20.00%	
>25 seizures	10.00%	0.00%	20.00%	
Epilepsy-related Mortality				
SUDEP – RR				
Seizure-Free				
2 - 11 years	0.42	-10%	+10%	Assumption
12 - 55 years	0.42	-10%	+10%	
≤8 seizures				
2 - 11 years	0.60	-10%	+10%	Assumption
12 - 55 years	0.60	-10%	+10%	
>25 seizures				
2 - 11 years	1.40	-10%	+10%	Assumption
12 - 55 years	1.40	-10%	+10%	
SUDEP – Probabilities				
>8 - ≤25 seizures				
2 - 11 years	0.23%	0.11%	0.49%	Based on 98% CIs in Cooper MS, et al. 2016 Epil Res 128:43-7.
12 - 55 years	0.23%	0.11%	0.49%	
Non-SUDEP – RR				
Seizure-Free				
2 - 11 years	0.42	-10%	+10%	Assumption
12 - 55 years	0.42	-10%	+10%	
≤8 seizures				

Parameter	Base Case	Lower Bound	Upper Bound	References
2 - 11 years	0.60	-10%	+10%	Assumption
12 - 55 years	0.60	-10%	+10%	
>25 seizures				
2 - 11 years	1.40	-10%	+10%	Assumption
12 - 55 years	1.40	-10%	+10%	
Non-SUDEP – Probabilities				
>8 - ≤25 seizures				
2 - 11 years	0.16%	0.11%	0.21%	Assumption
12 - 55 years	0.16%	0.11%	0.21%	
Utilities				
Patient utilities				
Seizure-Free; >24 days	[redacted]	[redacted]	[redacted]	Based on standard errors from vignette study Table 25 of Document B
≤8 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
≤8 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
≤8 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
Caregiver utility decrements				
Seizure-Free; >24 days	[redacted]	[redacted]	[redacted]	Based on standard errors from vignette study
≤8 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
≤8 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
Seizure-Free; >24 days	[redacted]	[redacted]	[redacted]	

Figure 1 presents a tornado diagram showing the parameters with the greatest impact on the ICER in descending order of sensitivity. Disaggregated results from the DSA are presented in a tabulated format in Section 6.

Figure 1: Tornado diagram

Probabilistic sensitivity analysis

The parameters included in the probabilistic sensitivity analysis (PSA) were determined based on the results of the one-way deterministic sensitivity analyses (DSA).

The PSA includes transition probabilities (not included in the DSA), patient characteristics (weight), SUDEP rates, patient utilities and disease management costs.

In the updated PSA, the following parameters have been added:

- The long-term treatment discontinuation rates
- Institutionalisation costs for the seizure-free patients
- Caregiver utility decrements.

The inputs that were unlikely to have a significant impact on the ICERs from the DSA were not included. This approach was considered appropriate given the complexity of the model.

The parameters included in the PSA and the corresponding distributions are presented in Table 9.

Table 9: Parameter values for multivariate probabilistic analysis

Parameters		Base case	Min	Max	SE	Alpha	Beta	Distribution
Transition probabilities								
Transition probabilities			Bootstrap from trial data					
Weight								
2 - 5 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
6 - 11 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
12 - 17 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
18 - 55 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Long-term discontinuation								
Seizure-Free		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
≤8 seizures		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
>8 - ≤25 seizures		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
>25 seizures		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
Management Unit Costs								
Visits Costs								
2 - 11 years	Seizure-Free	£275	£138	£413	70,15	15,37	17,90	Gamma
	≤8 seizures	£971	£486	£1,457	247.71	15.37	63.19	Gamma
	>8 - ≤25 seizures	£2,008	£1,004	£3,011	512.13	15.37	130.65	Gamma
	>25 seizures	£3,529	£1,764	£5,293	900.14	15.37	229.63	Gamma
12 - 55 years	Seizure-Free	£106	£53	£160	27.14	15.37	6.92	Gamma
	≤8 seizures	£311	£155	£466	79.31	15.37	20.23	Gamma
	>8 - ≤25 seizures	£560	£280	£839	142.74	15.37	36.42	Gamma
	>25 seizures	£1,192	£596	£1,788	304.15	15.37	77.59	Gamma
Hospitalisation Costs								
2 - 11 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤8 seizures	£1,454	£727	£2,181	370.98	15.37	94.64	Gamma
	>8 - ≤25 seizures	£2,908	£1,454	£4,363	741.96	15.37	189.28	Gamma
	>25 seizures	£5,817	£2,908	£8,725	1483.92	15.37	378.56	Gamma
12 - 55 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤8 seizures	£188	£94	£282	48.02	15.37	12.25	Gamma
	>8 - ≤25 seizures	£376	£188	£565	96.04	15.37	24.50	Gamma
	>25 seizures	£753	£376	£1,129	192.08	15.37	49.00	Gamma
Rescue Med Costs								
2 - 11 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤8 seizures	£102	£51	£153	26.02	15.37	6.64	Gamma
	>8 - ≤25 seizures	£204	£102	£306	52.04	15.37	13.28	Gamma
	>25 seizures	£408	£204	£612	104.08	15.37	26.55	Gamma
12 - 55 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma

Parameters		Base case	Min	Max	SE	Alpha	Beta	Distribution
	≤8 seizures	£51	£26	£77	13.01	15.37	3.32	Gamma
	>8 - ≤25 seizures	£102	£51	£153	26.02	15.37	6.64	Gamma
	>25 seizures	£204	£102	£306	52.04	15.37	13.28	Gamma
Institutionalisation Costs								
18 - 55 years	Seizure-Free	£321	£160	£481	81.86	15.37	20.88	Gamma
	≤8 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
	>8 - ≤25 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
	>25 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
Daily Cost ICU								
Adults		£1,299	£643	£4,482	979.49	1.76	738.39	Gamma
Paediatric		£1,583	£784	£5,867	1296.58	1.49	1061.73	Gamma
Daily Cost General Ward								
Adults		£460	£402	£807	103.43	19.78	23.26	Gamma
Paediatric		£597	£560	£760	51.01	137.00	4.36	Gamma
Emergency Department Visit								
Per episode		£237	£56	£838	199.33	1.41	167.64	Gamma
Epilepsy-related Mortality – SUDEP								
2 – 11 years	>8 - ≤25 seizures	0.23%	0.11%	0.49%	0.00	5.80	0.00	Gamma
12 – 55 years	>8 - ≤25 seizures	0.23%	0.11%	0.49%	0.00	5.80	0.00	Gamma
Utilities								
Patient utilities - Values estimated based on SE								
No seizures	>24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
≤8 seizures	≤18 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>18 - ≤24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
>8 - ≤25 seizures	≤18 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>18 - ≤24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
>25 seizures	≤18 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>18 - ≤24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
Caregiver utility decrements – values based on SE								
>8 - ≤25 seizures	≤18 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Gamma
	>18 - ≤24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Gamma
	>24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Gamma
>25 seizures	≤18 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Gamma
	>18 - ≤24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Gamma
	>24 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Gamma

As the transition probabilities associated with the movement of patients between the different seizure categories are interdependent, the uncertainty around this parameter was estimated by resampling individual patient outcomes from the GWPCARE1, GWPCARE2 and GWPCARE5 studies.

[redacted] bootstrap samples (the same sample size as the trials) were drawn independently from the GWPCARE1 and GWPCARE2 trials to estimate the transition probabilities for the first cycle. A similar number of random samples were independently drawn from the GWPCARE5 study to estimate the probabilities for the subsequent cycles.

The transition probabilities obtained from each bootstrap sample were run one at a time, whilst varying the other parameters included in the PSA simultaneously. This was considered to be the most appropriate approach, as individual patient-level data were available from the Phase 3 trials.

Results from the PSA are presented in Figure 2.

Error! Reference source not found. compares the PSA means to the base case estimates.

Table 10: PSA results compared to base case

	Costs		QALYs		ICERs	
	Base case	**PSA**	**Base case**	**PSA**	**Base case**	**PSA**
CCM + CBD	£227,309	£226,681	4.01	3.98	£34,789	£36,046
CCM	£195,786	£195,578	3.10	3.09	-	-

Figure 2: Cost-effectiveness plane

The incremental cost-effectiveness acceptability curve in Figure 3 shows that there is [redacted] likelihood that cannabidiol + CCM is cost effective when compared to CCM alone at a willingness-to-pay threshold of [redacted] per QALY.

Figure 3: Cost-effectiveness acceptability curve

5 Scenario analyses

Uncertainty around the following structural and parametric assumptions has been tested in scenario analyses:

- **Age groups:** As the base case presents results for all age groups, ICERs were estimated separately for the two age groups used in the model to segregate transition probabilities and costs, i.e. <12 years and ≥12 years.

  In addition, a scenario was tested in which all patients were assumed to be 2-5 years old at model entry. As most patients are diagnosed in this age group, this scenario models the 15-year cost utility in a newly diagnosed incident population. Over time, as the older patients in the prevalent patient population have been treated and discontinue therapy, the ICERs for patients treated in clinical practice will “converge” on this younger population.

- **Dose reduction of drugs included in CCM:** In the base case, the percentage reduction in the dose of the concomitant AEDs was assumed to be 33%. In this scenario, no dose reduction in concomitant AEDs was assumed. See also answers to B25a/b in the ERG clarification questions.

- **Cannabidiol dosage:** A small proportion of patients who have a good response on, and tolerate well, 10mg/kg/day may be escalated to a dose of up to 20 mg/kg/day, in order to target seizure freedom. Therefore, an alternative mean dose was tested that assumes all patients who achieved ≥75% reduction in convulsive seizure frequency on 10mg/kg/day in GWPCARE2 would receive 20 mg/kg/day in the model, whilst those who did not achieve this endpoint would receive 10 mg/kg/day. This was considered a proxy for a good response. The mean dose calculation for this scenario is shown in Table 11. See also answers to A1a/b and B7 of the ERG clarification questions.

Table 11: Cannabidiol dosage by age group in the alternative dose scenario

	<12 years	≥12 years
Patients receiving 10 mg/kg/day (<75% response in GWPCARE2)	[redacted]	[redacted]
Patients receiving 20 mg/kg/day (≥75% response in GWPCARE2)	[redacted]	[redacted]
Average dose per mg/kg/day	[redacted]	[redacted]
Reference: GW 2018 GWEP1414 Data on file		

- **Time horizon:** Alternative horizons of 10 and 20 years were considered.
- **Utilities:** The existing literature provides a number of conversions from VAS scores to TTO and standard gamble (SG); however, there is no consensus on the optimal mapping formula. Therefore, the conversion algorithms that resulted in the lowest and the highest SG utility values were selected for the scenario analysis. See Section B3.4 Table 24 p77 in Document B.

Table 12: Utilities for scenario analyses

	Algorithm 1 (SG3)			Algorithm 2 (SG8)		
Number of Seizures	Number of Days Without Seizures			Number of Days Without Seizures		
	≤18 days	>18 - ≤24 days	>24 days	≤18 days	>18 - ≤24 days	>24 days
Seizure-Free	-	-	[redacted]	-	-	[redacted]
≤8 seizures	-	[redacted]	[redacted]	-	[redacted]	[redacted]
>8 - ≤25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- **No variation in healthcare resource use across seizure groups:** Based on clinical feedback, health resource use within the model is lower in health states with fewer seizures. A scenario that assumes no variation in the resource use (visits, hospitalisations etc.) across different seizure health states has been considered.

- **Discontinuation rates - Cycles 2-9:** These discontinuation rates were estimated for each health state based on data from the GWPCARE5 Open Label Extension study. As the number of patients in each health state was smaller than the ITT population, a scenario that assumes the same discontinuation rate for all seizure groups was implemented. The overall study withdrawal rates, adjusted to a 3-month cycle, for each age group were applied ([redacted] <12 years old and [redacted] ≥12 years old).

- **Long-term discontinuation rates**: Due to the lack of long-term real world data on treatment discontinuations, point estimates and upper and lower bounds were based on assumptions. Scenarios have been run setting these parameters to the top and bottom of their ranges in the PSA.

- **Mortality:** In the base case, patients with a higher number of seizures were assumed to be at a greater risk of death compared to those with fewer seizures. An alternative scenario, in which patients are at the same risk of mortality irrespective of their seizure severity, was implemented.

- **Hospitalisations:** Based on clinical opinion, the majority of the patients (95%) who were hospitalised were assumed to have been so in a general ward; only 5% were admitted into an intensive care unit (ICU). An alternative scenario, assuming that almost all patients (90%) are admitted to an ICU, has been conducted. Additionally, two alternative scenarios, assuming intermediate proportions of ICU admissions (50% and 10%), have also been conducted.

The results of the scenarios tested are shown in Table 13.

Table 13: Scenario analyses (CCM + CBD vs CCM)

			CCM + CBD		CCM		
Parameter	**Base case**	**Scenario analyses**	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case	N/A	N/A	£227,309	4.01	£195,786	3.10	£34,789
Varying the target population							
Target population	All age groups	All patients 2-5 years at model entry	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2-11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		12-55 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the dose reduction of other drugs included in the CCM							
Dose reduction on clobazam, valproic acid and levetiracetam	Clobazam, valproate and levetiracetam dose reduced by a third (-33%)	No dose reduction for AEDs in CCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the cannabidiol dosage							
Cannabidiol dosage	All patients receiving 10 mg/kg/day	20 mg/kg/day if ≥75% response, and 10 mg/kg/day if not, in GWPCARE2. Average dose: [redacted] mg/kg/day See Table 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the time horizon							
Time horizon	15 years	10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the approach to modelling utilities							
Utilities	Table 25 p77 Document B	Algorithm 1 (SG 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Algorithm 2 (SG 8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the resource use in the management of the disease							
Number of visits	Table 30 p85 Document B	No variation across seizure categories Visits for >8 - ≤25 seizures applied to all other seizure groups in the corresponding age group. Seizure-free same as the base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Base case	Scenario analyses	CCM + CBD		CCM		ICER
			Total costs	Total QALYs	Total costs	Total QALYs	
Number of hospital admissions	Table 30 p85 Document B	No variation across seizure categories Hospitalisations for >8 - ≤25 seizures applied to all other seizure groups in the corresponding age group. Seizure-free same as the base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the discontinuation rates							
Subsequent discontinuation	Each health state based on discontinuation rates as observed in GWPCARE5 Table 2	Uniform discontinuation rates across health states [redacted] <12 years and [redacted] ≥12 years old	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-term discontinuations	Table 2	*Both age groups:* Seizure-Free [redacted] ≤8 seizures [redacted] >8 - ≤25 seizures [redacted] >25 seizures [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Both age groups: Seizure-Free [redacted] ≤8 seizures [redacted] >8 - ≤25 seizures [redacted] >25 seizures [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the approach to modelling mortality risk							
Epilepsy-related mortality	Table 3	Uniform mortality rate across health states 0.23% SUDEP; 0.16% non-SUDEP Seizure-free same as base case (0.10%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the proportion for ICU admissions within the hospitalisations							
Ratio ICU/General ward	5% in ICU and 95% in general ward	10% in ICU and 90% in general ward	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		50% in ICU and 50% in general ward	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		90% in ICU and 10% in general ward	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6 Disaggregated results

Model Validation

As the model uses health states defined by absolute convulsive seizure frequencies and not seizure frequency reductions, we validated outcomes from the model against those from the GWPCARE trials for the endpoints of convulsive seizure-freedom and mortality.

Proportion of convulsive seizure-free patients in the cannabidiol arm

The proportion of convulsive seizure-free patients in the cannabidiol arm estimated by the model at 1 year is similar to that observed in the GWPCARE5 Open Label Extension study.

Table 14: Proportion of seizure-free patients in the cannabidiol arm at baseline and at 1 year

	Baseline	1 year
Seizure-free estimates		
Seizure-Free (model)	[redacted]	[redacted]
Seizure-Free (GWPCARE2; 10mg/kg/day)	[redacted]	-
Seizure-Free (GWPCARE5)	[redacted]	[redacted]

Mortality

The disease-specific mortality rate in DS has been reported in the literature at 15.84 per 1000 person-years [Cooper 2016]. The estimated number of deaths in the CCM arm of the model is similar to this.

Table 15: Total number of disease-specific deaths at 10-year in the cannabidiol + CCM and CCM arms

	CBD+CCM	CCM
SUDEP (model)	[redacted]	[redacted]
Non-SUDEP(model)	[redacted]	[redacted]
Total deaths (model)	[redacted]	[redacted]
Total deaths (Cooper 2016)	-	1,584
Reference: Cooper MS, et al. 2016 Epil Res 128:43-7		

Disaggregated results of the base case incremental cost-effectiveness analysis

Table 16: Summary of QALY gain by health state

Health state	QALY comparator (CCM)	QALY intervention (CCM + CBD)	Increment	Absolute increment	% absolute increment
Seizure-Free, >24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤8 seizures, ≤18 days	-	-	-	-	-
≤8 seizures, >18 - ≤24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤8 seizures, >24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>8 - ≤25 seizures, ≤18 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>8 - ≤25 seizures, >18 - ≤24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>8 - ≤25 seizures, >24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>25 seizures, ≤18 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>25 seizures, >18 - ≤24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>25 seizures, >24 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 17: Summary of costs by health state

Health state	Cost intervention (CCM + CBD)	Cost comparator (CCM)	Increment	Absolute Increment	% absolute increment
Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>8 - ≤25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£195,786**	**£227,309**	**£31,522**	**£31,522**	**-**

Table 18: Disaggregated costs for treatment and adverse events per year

	Treatment		Adverse events	
Year	**CCM + CBD**	**CCM**	**CCM + CBD**	**CCM**
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Table 19: Disaggregated costs for mortality per year

	Mortality			
	CCM + CBD		CCM	
Year	Non-SUDEP	SUDEP	Non-SUDEP	SUDEP
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Table 20: Disaggregated costs for management per year

	Visits to HCP		Hospitalisation		Rescue medicine		Institutionalisation		Total management	
Year	**CCM + CBD**	**CCM**	**CCM + CBD**	**CCM**	**CCM + CBD**	**CCM**	**CCM + CBD**	**CCM**	**CCM + CBD**	**CCM**
1	£5,573	£6,295	£7,949	£8,993	£655	£744	£116	£120	£14,294	£16,152
2	£5,028	£6,108	£7,105	£8,750	£584	£721	£108	£114	£12,825	£15,694
3	£4,725	£5,795	£6,646	£8,300	£546	£684	£101	£109	£12,018	£14,888
4	£2,840	£3,653	£3,176	£4,217	£380	£501	£1,278	£1,382	£7,673	£9,754
5	£2,807	£3,466	£3,149	£4,001	£376	£476	£1,598	£1,723	£7,930	£9,665
6	£2,751	£3,288	£3,092	£3,795	£369	£451	£1,524	£1,638	£7,736	£9,173
7	£2,680	£3,119	£3,018	£3,600	£361	£428	£1,454	£1,558	£7,512	£8,706
8	£2,109	£2,393	£1,970	£2,294	£312	£361	£1,386	£1,482	£5,778	£6,530
9	£1,565	£1,728	£978	£1,103	£265	£299	£1,321	£1,409	£4,130	£4,539
10	£1,508	£1,639	£944	£1,047	£256	£284	£2,700	£2,890	£5,408	£5,859
11	£1,450	£1,555	£908	£993	£246	£269	£2,574	£2,748	£5,178	£5,565
12	£1,392	£1,475	£872	£942	£236	£255	£2,453	£2,614	£4,954	£5,286
13	£1,334	£1,399	£837	£893	£227	£242	£2,337	£2,487	£4,735	£5,021
14	£1,277	£1,327	£801	£847	£217	£230	£2,678	£2,846	£4,974	£5,250
15	£1,222	£1,259	£767	£804	£208	£218	£2,985	£3,169	£5,181	£5,449
Total	**£38,264**	**£44,498**	**£42,211**	**£50,581**	**£5,237**	**£6,162**	**£24,614**	**£26,289**	**£110,325**	**£127,529**

Table 21 and **Error! Reference source not found.** below present the impact of cannabidiol on the frequency of seizures when added to CCM. After 15 years, 9.52% of patients who receive cannabidiol in addition to CCM are convulsive seizure-free compared to 0% on CCM alone.

Table 21: Patients' distribution per health state at baseline versus after 15 years

	Baseline		At 15 years	
Health states	**CCM + CBD**	**CCM**	**CCM + CBD**	**CCM**
Seizure-Free	0.00%	0.00%	9.52%	0.00%
≤8 seizures	36.16%	36.16%	33.59%	39.30%
>8 - ≤25 seizures	33.33%	33.33%	29.28%	33.07%
>25 seizures	30.50%	30.50%	27.61%	27.63%

Figure 4: Patients' distribution per health state at baseline versus after 15 years

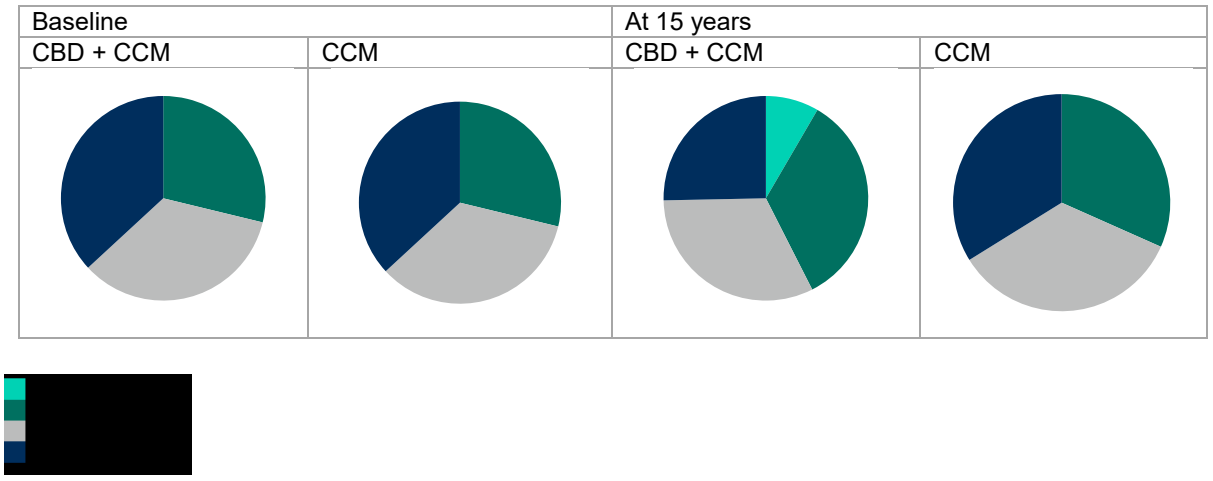


Table 22: Number of deaths after 15 years

	CCM + CBD	CCM	Difference
SUDEP	1,097	1,192	-95
Non-SUDEP	767	833	-66
Background	30	29	0
Total of lives saved	161	-	-

DSA disaggregated results

	CBD + CCM vs. CCM							
Parameter	**Lower limit**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Upper limit**	**Incremental costs**	**Incremental QALYs**	**ICER**
Emergency Department Visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decrements of utilities (caregivers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rates - Outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rates - Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities based on standard errors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUDEP mortality (Probability)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily Cost ICU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily Cost General Ward	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% of institutionalisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-SUDEP mortality (Probability)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phone Call Follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Institutionalisation Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUDEP mortality (RR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rescue Med Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-SUDEP mortality (RR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-SUDEP costs (days in ICU)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7 Appendix

SAS tables on weight of patients with DS

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

Clarification questions

April 2019

File name	Version	Contains confidential information	Date
ID1211 ERG Clarification Answers DS 12Apr19	**Final**	**Yes**	**12 Apr 2019**

General note to ERG: as per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided.

Section A: Clarification on effectiveness data

The decision problem

A1. Priority question: The description of the technology being appraised (Table 2) includes the following statement about dosage: 'The recommended starting dose of cannabidiol (CBD) is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day). Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 20 mg/kg/day, should be made considering individual benefit and risk.' However, the majority of the clinical effectiveness evidence presented relates to the maximum recommended dose (20 mg/kg/day).

a. What proportion of patients do you anticipate will receive the 10mg/kg /day dose and what proportion the 20 mg/kg/day dose in clinical practice?

b. How would patients be identified as being suitable for the 20 mg/kg/day dose? Do you anticipate that all patients will start with the lower dose? If so, what cut-off for inadequate response to the lower dose would be used and when would a response assessment to inform possible dose escalation be made?

c. In the long term do you expect patients to continue taking CBD at the maintenance dose? In the ongoing long-term study (GWPCARE5) it is stated that 'Initially, patients were titrated to 20 mg/kg/day administered in two divided doses, which could then be decreased or increased to 30 mg/kg/day at the investigator's discretion.'

A1a. It is anticipated that all patients will start with the 10mg/kg/day dose.

The latest version of the SmPC states the following: “The recommended starting dose of Epidyolex is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day). Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 20 mg/kg/day, should be made considering individual benefit and risk and with adherence to the full monitoring schedule.”

As the dosage for CBD is patient-specific (i.e. based on patient weight and individual clinical response), an alternative mean dosage of CBD was tested in the scenario analysis. The maximum recommended dose of 20 mg/kg/day is most likely to be received only by a small proportion of patients who have the potential to achieve further seizure reductions and/or seizure-freedom. Therefore, the mean dose of CBD was estimated by assuming that patients who achieve ≥75% reduction in convulsive seizures receive 20 mg/kg/day, while patients experiencing <75% reduction in convulsive seizures receive 10 mg/kg/day. The proportion of responders with ≥75% and <75% reduction in convulsive seizures was obtained from the Phase 3 clinical trial, GWEP1424 (see Table 40 in Document B).

A1b. It is anticipated that all patients will start with the lower maintenance dose. Increasing the dose in patients demonstrating good seizure reduction and tolerability to cannabidiol at 10mg/kg/day who the physician considers may gain additional seizure reduction by dose escalation will be at the physician’s discretion. Patients not achieving good seizure reduction at 10mg/kg/day are unlikely to achieve efficacy by dose escalation.

The decision to escalate would be at the clinician’s discretion, in discussion with the patient and/or caregivers. Feedback suggests that specialist clinicians would be comfortable doing this, especially given their experience in managing existing treatments and the complex set of considerations when making dose adjustments.

GW therefore considers the assumptions made to model the proportion of patients receiving 20mg/kg/day as reasonable (see answer to A1a).

A1c. Yes, in the long term, patients are expected to continue taking CBD at the maintenance dose. This is in line with the anticipated label from EMA. The OLE study protocol was written prior to the maintenance dose being established.

A2. Priority question: The company has added to the population scope 'People with Dravet syndrome where current clinical management is unsuitable or not tolerated'. Does this mean that CBD might be offered earlier in the pathway for this group than that shown in Figure 2 of the company submission?

No. This was added as it is in line with the recommendations in NICE Clinical guideline 137 (CG137). Patients may discontinue AEDs because of tolerability issues, not just lack of seizure control. In addition, certain AEDs are not suitable for DS patients. For example, NICE CG137 states that carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin should not be given to patients with DS as they may worsen seizures.

A3. Priority question: Under 'Placement of CBD within the care pathway' (page 25 of the company submission) and at other points in the document, it is stated that: 'For patients with Dravet syndrome (DS) considered for treatment with CBD, it will be an add-on treatment for refractory seizures in people aged 2 years of age and older once two other appropriate anti-epileptic drugs (AEDs), trialled to a maximally tolerated dose, have failed to achieve seizure freedom.'

a. Does the above statement reflect a narrower use than the expected licence?

b. The above statement does not appear to be consistent with the eligibility criteria for GWPCARE1 and GWPCARE2 given in Table 5 (taking 1 or more AEDs). How many patients had 1 prior AED in each treatment arm of the two trials?

c. The mean number of prior AEDs in both trials was <u>over 4</u> (Tables 6 and 7). Is this a more severe population than might be expected in clinical practice?

d. Please provide a histogram showing the number of patients by number of prior treatments in each arm of the GWPCARE1 and GWPCARE2 trials.

e. How was it established in the trials that patients had failed on their prior treatments and how does this relate to UK practice?

f. The mean number of concurrent treatments in the trials was approximately 3 (Tables 6 and 7). How does this reflect UK clinical practice? Do the concurrent treatments used in the trials reflect UK practice?

A3a. No.

A3b. The number of patients at baseline in each arm of GWPCARE1 and GWPCARE2 on 0, 1, and ≥2 prior AEDs is shown in the table below.

Prior AEDs (no longer taking) at baseline GWPCARE1 and GWPCARE2

		Prior AEDs (no longer taking)		
		10 mg/kg/day	20 mg/kg/day	Placebo
	No. AEDs		n=61	n=59
GWPCARE 1 (1332B)	0		5 (8.2%)	4 (6.8%)
	1		5 (8.2%)	5 (8.5%)
	≥2		51 (83.6%)	50 (84.7%)
		n=64	n=69	n=65
GWPCARE 2 (1424)	0	4 (6.3%)	2 (2.9%)	2 (3.1%)
	1	7 (10.9%)	7 (10.9%)	8 (12.3%)
	≥2	53 (82.8%)	60 (87.0%)	55 (84.6%)

The number of patients in each arm of GWPCARE1 and GWPCARE2 on 1, 2, and ≥3 current AEDs is shown in the table below.

Concomitant AEDs in GWPCARE1 and GWPCARE2

		Concomitant AEDs		
		10 mg/kg/day	20 mg/kg/day	Placebo
	No. AEDs		n=61	n=59
GWPCARE 1 (1332B)	1		4 (6.6%)	4 (6.8%)
	2		15 (24.6%)	15 (25.4%)
	≥3		42 (68.9)%	40 (67.8%)
		n=64	n=69	n=65
GWPCARE 2 (1424)	1	5 (7.8%)	4 (5.8%)	2 (3.1%)
	2	23 (35.9%)	20 (29.0%)	17 (26.2%)
	≥3	36 (56.3%)	45 (65.2%)	46 (70.8%)

A3c. No. Despite the availability of a broad range of AEDs, non-pharmacological interventions and invasive surgery, seizure control in DS remains inadequate, with the majority of patients unresponsive to treatment or unable to tolerate current AEDs. As a result, physicians have used a variety of medical, surgical and dietary approaches in an attempt to control seizures, and polypharmacy on this scale is not uncommon.

The number of previous/concomitant AEDs at baseline in the clinical trials is an artefact of the population that could be recruited and does not reflect the inclusion criteria in studies, or where clinical need lies in treatment practice. Patients with DS are highly drug refractory. As such, the standing population in clinical practice, from which trial patients were recruited, has been extensively treated. Recently diagnosed children with DS will have a high level of clinical need even with existing AEDs, and CBD will be a valuable treatment option in these patients

A3d. Histograms for the number of patients on prior AEDS (no longer taking) at baseline and concomitant AEDs in the DS GWPCARE trials are shown below.

A3e. Patients were having seizures not controlled by their current AEDs. In GWPCARE1, patients were taking at least 1 AED. All medications or interventions for epilepsy were stable for 4 weeks prior to the trial and were to be maintained throughout the trial. Patients had 4 or more convulsive seizures during the first 28 days of the baseline period. In GWPCARE2, patients were taking 1 or more AEDs at a dose that had been stable for at least 4 weeks. Patients had at least 4 convulsive seizures during the first 28 days of the baseline period. All medications or interventions for epilepsy were stable for 4 weeks prior to screening. This reflects UK practice, where refractory epilepsy (as defined by the International League Against Epilepsy) is recognised as failure of adequate trial of two tolerated and appropriately chosen and used AED regimens (as monotherapies or in combination) to achieve sustained freedom from seizures.

A3f. This reflects UK clinical practice. See also A3c above. Despite the availability of a broad range of AEDs, non-pharmacological interventions and invasive surgery, seizure control in DS remains inadequate, with the majority of patients unresponsive to treatment or unable to tolerate current AEDs. As a result, physicians have used a variety of medical, surgical and dietary approaches in an attempt to control seizures, and polypharmacy on this scale is not uncommon.

Systematic review

A4. Appendix D – Identification, selection and synthesis of clinical evidence. This appendix presents a combined systematic review to identify studies for both the Lennox-Gastaut syndrome (LGS) and DS submissions. The PRISMA flow chart appears to indicate that 24 studies were included for clinical effectiveness in the DS population.

a. Please confirm the correct number of included studies (there appear to be 8 in Table 44).

b. Table 43, question 9 (screening algorithm) indicates that randomised controlled trials (RCTs) which did not assess an included intervention (defined as CBD) would be excluded. Please explain why RCTs of other AEDs, which do not include a CBD arm and are not used in the submission, are in the list of included efficacy studies (Table 44).

A4a. Two phase 3 studies of CBD (GWPCARE1 and GWPCARE2) and one ongoing open-label extension study (GWPCARE5) are the only studies included in the clinical effectiveness section of this report. These are reported in a total of 10 publications, which are listed in Table 44.

Table 44 also lists other RCTs of drug treatments for DS, which were identified by our search and have been included here for transparency and completeness. These studies were not included in the model and are not discussed in the clinical effectiveness section. We identified 5 clinical trials of other drug treatments in DS, reported in a total of 10 publications.

A4b. These were listed in the submission for transparency and completeness.

A5. In the systematic review were full papers screened by two reviewers?

Yes.

A6. In the systematic review were ketogenic diet and vagus nerve stimulation also valid comparators?

VNS and ketogenic diet were considered to be part of current clinical management (CCM) of DS. As for the AED therapies that form part of CCM, we did not include RCTs of these interventions in the clinical efficacy section or model.

Literature searching

A7. Please provide the date span for the following database searches reported in Table 42: PubMed, Embase, Cochrane Library (each section), ScHARRHUD, CRD (each section), Clinicaltrials.gov. The date span refers to the inception date of each specific database and the latest segment date, which often differs from the date of search, e.g. Embase (Ovid): 1974-2018/12/28 or Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 1/ Dec 2018: 2016-2018.

PubMed: 1946 to 19 November 2018
Embase:1947 to 19 November 2018
Cochrane: 1992 to 19 November 2018

- Controlled Register of Trials (CENTRAL): CENTRAL first began publication in 1996, but its composite nature means that it does not have an inception (start) date, in the way that other traditional biomedical databases do. (https://www.cochranelibrary.com/central/about-central). Database was searched up to 19 November 2018
- Cochrane Database of Systematic Reviews: 1995 to 19 November 2018

ScHARRHUD: 2008 to 2013

CRD:

- DARE: 1994 to 2014
- NHS EED: 1968 to 2014
- HTA database: 1989 to 31/03/2018

Clinicaltrials.gov: 1999 to 19 November 2018

A8. We have identified a number of issues with the search strategies used to identify relevant studies:

a. Please check the PubMed strategy reported in Table 42 for errors where truncation (*) has been incorrectly applied within specific phrases ("") e.g. "Dravet* syndrome"

b. Please re-run the PubMed strategy with the corrections and screen the missed references.

c. Please explain why the CRD search was limited to title only.

d. Please explain why the term "severe myoclonic epilepsy" was not included in both the Cochrane Library and CRD searches.

e. Please explain why MeSH terms were not included in both the Cochrane Library and CRD searches.

f. Please clarify why the abbreviation "SMEI" was not included in the search for CRD, Heoro, ScHARRHUD, EuroQol or Clinicaltrials.gov.

g. Please confirm whether the 'Condition' or 'other terms' field was searched in clinicaltrials.gov.

h. Please clearly state which sections of the Cochrane Library were searched.

i. Please clarify whether Database of Abstracts of Reviews of Effects (DARE) was searched either via the Cochrane Library or CRD. DARE is not reported as a source in Section D1.1, however it was referred to in Table 42. If DARE was searched, please provide the date span. If DARE was not searched, please clarify how systematic reviews were identified.

A8a. The PubMed search was re-run on 06/02/19. This search identified 19 new papers (after deduplication) that were not found by the original search.

The Embase search was re-run on 11/02/2019 to include the terms LGS, dravet*, "dravet's syndrome", "childhood epileptic encephalopathies", "childhood epilepsy encephalopathies", "childhood epilepsy encephalopathy". This search identified 600 new papers (after deduplication) that were not found by the original search.

These new abstracts were screened by two researchers independently, using the same algorithm provided in the report, and no relevant papers were identified.

A8b. The PubMed search was re-run on the 06/02/19 to correct the truncation issues identified in point A8a. This search identified 19 new papers (after deduplication) that were not originally found by the original search. These 19 new abstracts were screened by two researchers independently, using the same algorithm provided in the report, and no relevant papers were identified.

A8c. This search was re-run on 06/02/2019 with all the original search terms plus “severe myoclonic epilepsy” searched in all fields with no date restrictions. This identified a total of 17 publications, 6 of which had not been previously identified. After screening by two researchers independently, no new papers were considered to be relevant to the review.

A8d. This term was added with relevant MeSH terms to these searches and re-run on 06/02/2019. The outcome of the CRD search identified 6 new publications, none of which were considered relevant after screening by two researchers independently. The search of the Cochrane library identified no additional studies that had not been previously identified.

A8e. Relevant MeSH terms were added to the existing search strategy and the search was re-run on 06/02/2019. The outcome of the CRD search identified 6 new publications, none of which were considered relevant after screening by two researchers independently. The search of the Cochrane library identified no additional studies that had not been previously identified.

A8f. Searches of CRD, ScHARRHUD, EuroQol and clinicaltrials.gov were repeated to include the term SMEI. No additional publications were identified from the search of CRD, ScHARRHUD or EuroQol. The search of Clinicaltrials.gov identified one additional entry, which was added to the database in January 2019 and was therefore unavailable at the time of our original search. The heoro database search was not amended as SMEI is not an entry in the disease ontology.

A8g. We searched the following fields:
Condition or disease: Lennox Gastaut syndrome OR Dravet syndrome.
Study type: Interventional studies (Clinical trials)
Study results: Studies with results
Status: Completed or terminated or suspended or withdrawn.

A8h. We searched the Reviews and Trials sections of the Cochrane library.

A8i. DARE was searched using CRD, no date limit has been applied.

Included trials: methods

A9. Outcomes in the trials could be reported by patient or caregiver.

a. Was any guidance given as to when it was appropriate for the patient to respond or when it should be the caregiver or was this up to the individual patient / caregiver?

b. What training were patients / caregivers given in recognition and recording of seizure type?

c. How do you account for the relatively large placebo response across the trials?

A9a. No specific guidance was given on when a patient should respond versus when a caregiver should complete reporting tools in the trials. This decision was left to the investigator and patient/caregiver to make together. In most cases, it was caregivers, reflecting the fact that patients with DS in the cannabidiol clinical trials were children and young adults with a broad spectrum of abilities, many of whom were unable to communicate effectively, and so would not be able to report outcomes.

A9b. The separate document provided ("QA9b. Collection of the Seizure Data (Primary Endpoint) on the IVRS") details the training given to the caregivers on recording seizure type and PROs.

A9c. Large placebo effects are well documented in epilepsy clinical trials. Although no study has formally assessed placebo effects across DS studies, they have been consistently observed in LGS studies for lamotrigine, topiramate, felbamate, rufinamide and clobazam going back to the early 1990s [Ostendorf 2017].

A comparison of the size of the placebo effect in GWPCARE1 and GWPCARE2 relative to those seen in other studies in DS is not possible, as there is too much heterogeneity in study design between trials. Nonetheless, numerical comparisons have been published for LGS trials. The primary endpoint (median percent change in drop seizure frequency from baseline) in GWPCARE3 (which studied a CBD dose of 10mg/kg/day in patients with LGS) showed a placebo effect that was at the upper end of, but still in line with, those seen with other agents [Ostendorf 2017]. Furthermore, on the key secondary endpoints (percentage of patients achieving a 50% reduction in drop seizure frequency and percentage reduction in total drop seizure frequency), placebo effects that are numerically similar to those of other AEDs were observed [Ostendorf 2017].

The reasons why placebo effects are commonplace in epilepsy trials are unknown. Reasons cited in the literature that may be of particular relevance to cannabidiol include [Goldenholz 2016]:

- Classical conditioning (the psychological expectation of improvement in response to being medicated, especially where there is a high level of "hope")

- Symbol-response (enhanced reaction to attributes in a medication perceived as beneficial or unusual; a drug derived from the cannabis plant might be an unusual example of this)

- Regression to the mean and natural fluctuations in disease natural history (with patients self-selecting themselves into trials during transiently “sicker” periods, and subsequently regressing to their “normal” health state over time).

Of note, placebo effects may be particularly evident in epilepsy trials with high proportions of refractory paediatric patients [Goldenholz 2016], as is true for the cannabidiol studies in DS.

Even with this placebo effect, a robust treatment effect on the primary and all secondary endpoints was achieved at a CBD dose of 10 mg/kg/day. Assessed across the totality of the clinical development plan, this treatment effect was consistently observed across two studies at a dose of10 mg/kg/day and four studies at a dose of 20 mg/kg/day. It was further maintained in the open label extension study.

The hypothesised sources of placebo effects cited in the literature are either an artefact of the clinical trial environment, or a short-term psychological response to “something new” in patients/caregivers with a high level of clinical need. These effects are unlikely to apply and persist in clinical practice, especially given the highly drug-resistant nature of DS patients.

Nonetheless, in order to ensure any clinical effectiveness of CCM was captured, we applied transition probabilities in the first cycle of the Markov model derived from the placebo arms of the studies.

A10. For GWPCARE2, please justify why the primary endpoint analysis was changed. Please could you provide the results of the statistical analysis comparing % change from baseline between the groups using the Wilcoxon rank-sum test.

The primary endpoint in GWPCARE2 analysed using the Wilcoxon Rank Sum Test method is shown in Table 8.2.2 of the CSR Tables, and reproduced in the table

below. This was a pre-specified sensitivity analysis in the statistical analysis plan (SAP).

A negative binomial regression (NBR) was introduced as the primary analysis method as part of a protocol amendment for the GWPCARE2 study implemented prior to database lock. The rationale for this amendment was that the NBR would provide a superior modelling approach for over-dispersed seizure count data than the non-parametric Wilcoxon rank-sum test, as it allows estimates of effect size that can incorporate age as a stratification variable and time, treatment arm and treatment arm-by-time interaction as effect-modifying co-variables. An analysis of previous epilepsy trials in DS and LGS indicated that modelling of seizure counts implemented within the framework of general linear models, using the negative binomial response distribution, might provide a more optimal fit to the data. Moreover, an NBR model accounts for the number of days over which each patient is evaluated, and so adjusts for variable periods of patient follow-up in the analysis.

This methodology has been accepted by the EMA.

Percent change from baseline in convulsive seizure frequency treatment period for the ITT analysis set in GWPCARE2 using the Wilcoxon rank sum test with Hodges-Lehmann estimate

	N	Mean	SD	Q1	Median	Q4	Min	Max	Median dif.	95%CI	p-value
10mg/kg/day	66	-23.67	87.947	-80.95	-41.21	-2.99	-100	483.2	-15.74	(-31.27, 3.68)	0.1051
20mg/kg/day	67	-34.74	53.757	-71.43	-46.98	-10.46	-100	185	-19.88	(-33.92, -5.29)	0.0082
Placebo	65	-8.02	80.474	-51.88	-24.48	4.62	-100	367.6			

Included trials: patient characteristics

A11. Priority question: Please comment on the apparent baseline imbalance, in convulsive seizure frequency, between study arms in GWPCARE2, and in all seizure frequency, between study arms in GWPCARE2 and GWPCARE 1 (Tables 6 and 7 in the company submission). Please provide ranges not just median values, for all baseline characteristics. Please also comment on whether these imbalances would be expected to affect response rates.

The full data for seizure numbers at baseline is shown in the table below.

Although there are numerical differences in the mean values for convulsive seizures at baseline, the medians are similar whilst the standard deviations and ranges are large. These trends are also seen for total seizures, albeit with much larger ranges.

This reflects a very heavy right-skew and over-dispersion in the distribution of seizures as a count variable for all study arms: 86% and 89% of patients on placebo and 10mg/kg/day respectively in GWPCARE2 had a baseline count within a 70% boundary above the mean, even though the upper bound of the standard deviation is over 200% above the mean. This skew negates a casual inspection of statistical significance versus placebo for the treatment arms.

Due to these properties in the distributions, seizure counts were considered generally balanced at baseline between arms. Moreover, the primary and key secondary endpoints all analyse a change from baseline, which would not be expected to be affected by baseline criteria. To test this hypothesis, pre-specified sensitivity analyses were conducted on the primary endpoint in GWPCARE1 and GWPCARE2 using ANCOVA, Rank ANCOVA, and ANCOVA of the log transformed outcomes, with baseline convulsive seizure frequency. In GWPCARE2, a statistically significant treatment effect was observed in the 10mg/kg/day arm that was similar to the primary analysis in all cases except one (ANCOVA of percent change from baseline). The same outcomes were seen for the 20mg/kg/day arm across both GWPCARE1 and GWPCARE2.

The equivalent (key secondary) endpoint for total seizure count was analysed in the same way. For the key secondary efficacy endpoint of ≥50% reduction in convulsive seizure frequency, outcomes were modelled using logistic regression including treatment arm as a covariate. These outcomes were also positive.

The EMA has accepted these data.

Seizure numbers in the 28-day baseline period in the ITT analysis sets for GWPCARE1 and GWPCARE2

			Seizures							
			Convulsive				Total			
		n	Mean	Median	SD	Range	Mean	Median	SD	Range
GWPCARE1	Placebo	59	60.61	14.88	129.766	3.7-718.0	331.48	41.48	671.765	4.0-3170.0
	20 mg/kg/day	61	67.28	12.44	230.595	3.9-1716.7	234.24	24.00	503.996	4.1-2712.5
GWPCARE2	Placebo	65	64.65	16.63	127.771	3.0-770.5	246.96	46.34	499.072	4.0-2659.0
	10 mg/kg/day	66	40.51	13.53	82.923	0.0-467.0	152.52	34.50	296.607	3.7-1541.0
	20 mg/kg/day	67	38.13	9.03	95.031	3.9-661.2	274.54	26.00	681.812	3.9-4141.0

Source: Table 3.2.2 1424 CSR Tables; Table 3.2.2B 1332B CSR Tables; Table 9.4.1.1B 1332B CSR Tables.

A12. Priority question: How many UK centres and patients were included in GWPCARE1? How similar does the company consider the trials to be to patients seen in practice in England and Wales? Have you sought any clinical expert input on this issue?

There were 4 UK sites in GWPCARE1, of which 3 recruited, and none in GWPCARE2. Overall there were 16 UK patients in GWPCARE1.

It is expected that the patients in these studies will be very similar to those seen in practice in England and Wales.

GWPCARE1 included patients from the UK, the USA, France and Poland.

GWPCARE2 included patients from the USA, Spain, Poland, Australia, Israel and the Netherlands.

GWPCARE5 is an ongoing, open-label extension of GWPCARE1 (Dravet syndrome), GWPCARE2 (Dravet syndrome), GWPCARE3 (LGS) and GWPCARE4 (LGS).

A13. Please provide baseline characteristics and efficacy results for the UK patients included in GWPCARE1.

The baseline characteristics of UK patients in GWPCARE1 are shown in the table below.

There are too few UK patients in the trial to provide efficacy outcomes for UK patients specifically, or to draw conclusions about how similar this subpopulation is to the ITT population of the trials.

Clinical experts in the UK have confirmed that the trial populations are similar to those seen in clinical practice.

Baseline characteristics of UK patients in GWPCARE1

GWPCARE1 UK patients	20 mg/kg/day	Placebo
N	[redacted]	[redacted]
Age (years)	[redacted]	[redacted]
Gender (% male)	[redacted]	[redacted]
Ethnicity (% Caucasian)	[redacted]	[redacted]
Seizure frequency (28 day median)	[redacted]	[redacted]
Prior AED use	[redacted]	[redacted]
Concurrent AED use	[redacted]	[redacted]

A14. Is there evidence that suggests an association between baseline seizure frequency and the patient's current clinical management?

In general, the data support the conclusion that existing prescribing is highly heterogeneous and patients are refractory to existing treatment modalities.

Due to the orphan nature of the disease, no formal pre-specified or post-hoc analysis to assess the association between baseline seizure frequency and CCM treatment was done.

Based on an informal analysis of the patient level data in GWPCARE1 and GWPCARE2 combined, there is a strong correlation between baseline seizure burden and number of concomitant AEDs, as is to be expected (see the figure below). A descriptive analysis of drug proportions amongst patients stratified by seizure frequency at baseline (also in the figure below) for the most commonly used pharmacological agents does not show any obvious trends.

A) Spearman's correlation for seizure count (over 28-days) and number of concomitant AEDs at baseline.
B) Proportion of patients on each AED at baseline.

C) & D) Proportion of patients on each AED in each sextile of (convulsive/total) seizure count at baseline (for the most commonly used AEDs only).

A. Spearman's Correlation

Seizures:	*Convulsive*	*Total*
r_s	0.457	0.460
H0	0	0
n	318	318
df	316	316
SE	0.050027349	0.049935886
t	9.141267405	9.221051852
alpha	0.05	0.05
t-crit	1.967499519	1.967499519
p	7.70274E-18	4.29156E-18
rho-crit	<0.362	<0.362

Value for n=30 at 0.05 alpha level 2T

B. Percentage patients at baseline on:

Agent	
Valproate	65.1%
Clobazam	64.2%
Stiripentol	38.4%
Levetiracetam	27.4%
Topiramate	24.2%
Clonazepam	13.2%
Zonisamide	10.7%
Bromides	6.3%
Phenobarbital	6.0%
Ethosuximide	4.7%
Others	<4%

C. Convulsive Seizures (sextiles)

	N Seizures	0-14	15-29	30-43	44-58	59-72	≥73
	N (%) Pts	75	40	44	53	55	51
VAL	65.1%	69.33%	72.50%	65.91%	69.81%	58.18%	54.90%
CLB	64.2%	69.33%	60.00%	59.09%	64.15%	67.27%	60.78%
STI	38.4%	48.00%	35.00%	40.91%	35.85%	36.36%	29.41%
LEV	27.4%	28.00%	30.00%	20.45%	26.42%	20.00%	39.22%
TOP	24.2%	26.67%	27.50%	13.64%	24.53%	25.45%	25.49%
CLON	13.2%	10.67%	7.50%	9.09%	13.21%	18.18%	19.61%
ZON	10.7%	13.33%	7.50%	18.18%	9.43%	7.27%	7.84%

D. Total seizures (sextiles)

	N Seizures	0-57	58-114	115-170	171-227	228-284	≥285
	N (%) Pts	56	52	51	54	51	54
VAL	65.1%	71.43%	75.00%	68.63%	61.11%	54.90%	59.26%
CLB	64.2%	66.07%	63.46%	70.59%	59.26%	64.71%	61.11%
STI	38.4%	51.79%	44.23%	37.25%	35.19%	39.22%	22.22%
LEV	27.4%	26.79%	28.85%	19.61%	24.07%	25.49%	38.89%
TOP	24.2%	26.79%	17.31%	27.45%	33.33%	17.65%	22.22%
CLON	13.2%	5.36%	11.54%	11.76%	16.67%	23.53%	11.11%
ZON	10.7%	14.29%	11.54%	11.76%	9.26%	3.92%	12.96%

A15. Priority question: Could you provide patient level data showing baseline total seizure frequency and concurrent AEDs at baseline for each patient in each treatment group of GWPCARE 1 and GWPCARE2. An example table using fictional data is given below.

See the separate document provided ("Patient Level Data LGS DS.xlsx").

A16. Priority question: Both of the two main trials (GWPCARE1 and GWPCARE2) exclude adult (>18 years) patients. What are the implications of this, given that the expected licenced indication is for patients 2 years of age and older with no upper age limit mentioned?

This reflects the demographics of the DS population. Patients are diagnosed at a young age and mortality rates are high. Premature mortality is a major issue in DS, with most deaths occurring before 10 years of age. For these reasons, the number of adults with DS is very low compared with the number of children.

Included trials: efficacy results

A17. Priority question: Please provide full results, for all outcomes assessed, for GWPCARE1 and GWPCARE2.

Please refer to CSRs and separate document provided ("Detailed Responses A17, A18, A19, A24 and A26").

A18. Priority question: The results provided in Tables 10 and 11 are incomplete. Baseline and endpoint (e.g. 14 weeks) measures are needed for all outcomes. Please ensure that all medians (including baseline data) are presented with an associated interquartile range (IQR).

Please refer to CSRs and separate document provided ("Detailed Responses A17, A18, A19, A24 and A26").

A19. Priority question: Please ensure that all outcomes are reported clearly indicating whether differences between treatment groups are statistically

significant. Please provide full statistical measures (e.g. median/mean difference or odds ratio with 95% confidence intervals).

Please refer to CSRs and separate document provided ("Detailed Responses A17, A18, A19, A24 and A26").

A20. Priority question: For GWPCARE2, please provide results of comparisons between the 20 mg and 10 mg CBD groups, for all outcomes where these are available.

No formal pre-specified test for significance between the CBD groups was included in the SAPs.

A21. Priority question: On page 36 of the company submission it is stated that 'no subgroup analyses were conducted.' However, on page 51 it is stated that '<u>treatment effect was not significantly different across the patient subgroups stratified by age, gender, number of AEDs previously taken and use of specific AED (such as clobazam or valproic acid)</u>.' Please could you provide these subgroup analyses?

The primary and key secondary endpoints were analysed in the following pre-specified subgroups for GWPCARE2. Very similar subgroups were analysed in GWPCARE1. The sources are shown in the table below.

- Age group (2-5 years, 6-12 years and 13-18 years)
- Sex (Male, Female)
- Region (US, Rest of the World)
- Clobazam use (Yes, No)
- Valproate use (Yes, No)
- Stiripentol use (Yes, No)
- Clobazam and Stiripentol use (Yes, No)
- Levetiracetam use (Yes, No)
- Topiramate use (Yes, No)
- Baseline average convulsive seizure frequency per 28 days (≤ observed tertile 1, > observed tertile 1 to ≤ observed tertile 2, > observed tertile 2) The observed tertile values were rounded to the nearest 5
- Number of current AEDs (<3, ≥3)
- Number of prior AEDs (<8, ≥8).

These outcomes were not included in the Evidence Submission as they are not relevant to clinical prescribing or the cost-utility analysis. They are standard demographic subgroup analyses that are done as part of any SAP. Furthermore, as an orphan indication, these subgroups have small population numbers with low statistical powering.

For the recommended 10 mg/kg/day dose, no clinically relevant trends were seen in these subgroup analyses; the point estimates were similar to that for the ITT population, and CIs between them heavily overlapped.

References for subgroup analyses

Trial	Source
GWPCARE1	CSR Figure 8.4.1.1.2-1 p129 Table 8.4.1.2.1-2 p132
GWPCARE2	CSR Figure 8.4.1.4.1-1 p186 CSR Figure 8.4.1.4.1-2 p188 CSR Figure 8.4.1.4.2-1 p190 CSR Figure 8.4.1.4.2-2p192

A22. The company notes, in the clinical section (p25), that: "A subset of 18 patients in the GWPCARE1 study had never experienced seizure reduction from any previous AEDs. Of these, 9 patients were on CBD (20 mg/kg/day) and 9 were on current clinical management (CCM) + placebo. The patients on CBD saw a 70% median reduction in convulsive seizures while those on CCM saw a median increase in convulsive seizures of 11%" Please provide detailed efficacy results and baseline characteristics for these patients.

These data are reported in the poster Wilfong *et al* 2018. A copy of this reference is provided as a separate document. Baseline characteristics and efficacy outcomes are reported in full in this source.

A23. Priority question: In the company submission page 82 it is stated that 'the percentage reduction in the dose of the concomitant AEDs was based on clinical opinion and was assumed to be 33%.' Do you have any data on reduction in medication use from GWPCARE1, GWPCARE2 or GWPCARE 5? If so, could you provide this?

In GWPCARE1 and GWPCARE2, all medications or interventions for epilepsy were required to be stable for 4 weeks prior to screening and patients had to be willing to maintain a stable regimen throughout the study. The percentage reduction in the dose of the concomitant AEDs was based on clinical opinion.

Included trials: safety results

A24. Priority question: Appendix F provides a full breakdown of adverse events for GWPCARE2. Please provide the same for GWPCARE1 and any adverse events (including serious adverse events) data from GWPCARE5 from the latest available data set.

Please refer to CSRs and separate document provided ("Detailed Responses A17, A18, A19, A24 and A26").

A25. Priority question: Please provide a detailed breakdown of the serious adverse events (SAEs) (i.e. any untoward medical occurrence that at any dose that results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in significant disability or incapacity) occurring in GWPCARE1, GWPCARE2 and GWPCARE5 including their relationship to treatment.

Please see the CSRs/Tables now provided for GWPCARE1, GWPCARE2 and GWPCARE5.

A26. Priority question: Figures 9 and 10 of the company submission give the participant flow through the trials. Please provide full detail of the discontinuations (specific adverse events leading to discontinuation, reasons for withdrawal).

Please refer to CSRs and separate document provided ("Detailed Responses A17, A18, A19, A24 and A26").

Ongoing studies

A27. Priority question: When are interim and end of trial results anticipated to be published in full for GWPCARE5?

The GWPCARE5 trial is estimated to complete in [redacted].

Interim data cuts of the GWPCARE5 study, as submitted to the regulatory authorities for registration, have been published as follows:

- The GWPCARE5 DS cohort: Devinsky O, *et al.* Epilepsia 2018;1-9.
- The GWPCARE5 LGS cohort: Thiele E, *et al.* Epilepsia. 2019;1-10.

This data cut is earlier than the one presented at the [redacted] The final cut is targeted for publication in [redacted].

A28. Priority question: Are there any other ongoing studies that would provide relevant information for this submission (such as longer-term follow-up data relating to changes in mortality including sudden unexpected death in epilepsy (SUDEP))? If so, when will data become available for these studies?

No.

Section B: Clarification on cost-effectiveness data

Model structure

B1. Priority question: In the model, health states are defined based on number of absolute convulsive seizures and (convulsive) seizure-free days per 28 days. However, based on the clinical data (i.e., GWPCARE1, GWPCARE2, and GWPCARE5), a substantial number of non-convulsive seizures is reported for both CBD and the current clinical management (CCM) group. Non-convulsive seizures appear to be ignored in the model (e.g. in terms of estimated utility values, costs, and transition probabilities).

a. Please justify this assumption and elaborate on the potential implications.

b. If non-convulsive seizures are still occurring in patients in the (convulsive) seizure-free condition, they are still prone to SUDEP, non-SUDEP, and hospitalisations. Therefore, it seems highly implausible to assume that patients in the seizure-free condition have the same mortality risk as the general population, especially in patients with DS. Please adjust the model accordingly.

c. Please justify whether the model structure still adequately represents the natural course of the disease. Focus in your response on, for example, cognitive decline (e.g. would patients with a reduction in convulsive seizures but a high frequency of non-convulsive seizures still be expected to be at higher risk of cognitive decline) and the likelihood of becoming seizure-free over time.

B1a. Reduction in convulsive seizures was the primary endpoint of the trial.

The presence of severe, treatment-intractable convulsive seizures, primarily featuring generalized tonic-clonic and clonic seizures, as well as myoclonic, atypical absence, and focal seizures, is a salient feature of DS. Risk for status epilepticus is elevated, and patients suffer from injuries due to falls associated with these types of seizures.

These seizures drive the physical morbidity and complications of the condition. As such, the GWPCARE studies were designed to investigate the impact of CBD on convulsive seizures; the effect on non-convulsive seizure types was an exploratory endpoint only. The model thus necessarily assesses utility gains deriving from health states linked to the primary endpoint of the clinical studies, which are also most relevant to both clinical and patient outcomes.

It is reasonable to assume that there would be utility gains associated with improvements in non-convulsive seizures. Cannabidiol showed a statistically significant mean percentage reduction in total seizures, and an improvement in non-convulsive seizures (not tested for statistical significance as an exploratory endpoint). Furthermore, as the table below shows, within the treatment period the median number of non-convulsive seizures decreases substantially across convulsive seizure-based health states (the median is the most relevant measure

due to outliers). As patients spend more time in lower convulsive seizure frequency health states on CBD versus CCM alone, they will accrue QALYs associated with fewer types of other seizures, which is a potential benefit for patients not captured in the model.

Summary of non-convulsive seizures across convulsive seizure-frequency defined health states (treatment period)

	Non-convulsive seizures					
Convulsive seizures	**N**	**Mean**	**SD**	**Median**	**Min**	**Max**
Seizure-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>8 - ≤25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B1b. We acknowledge that patients in the convulsive seizure-free category may not be fully exempt from the risk of death due to SUDEP and non-SUDEP causes. This was also discussed with and acknowledged by clinical experts, who stated that it is possible but would be rare.

As per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided. A change to this assumption has been implemented in this new economic evaluation and model.

B1c. The current cost-utility model still accurately captures the most important clinical and patient benefits, even though it does not attempt to capture the contribution to utilities of non-convulsive seizures:

- Convulsive seizures are accepted as the most clinically relevant seizure type in DS, driving the physical morbidity and complications of the disease over time
- Patients with DS rarely achieve complete freedom from all seizures, no matter how good their response is to any given treatment; seizure types not associated with generalised prolonged convulsions often persist. However, achieving freedom from convulsive seizures is still a highly meaningful clinical and patient/caregiver relevant outcome

- Reduced exposure to non-convulsive seizures, and the consequential gain in QALYs, would be likely on CBD; this is a “hidden” upside in the cost-utility outcomes

- Children with DS usually develop cognitive and psychomotor retardation with attention deficit and hyperactivity and absent language skills by the age of 2 years. However, the correlation between outcomes for these co-morbidities and seizure control are unknown. Given this complexity, we have not attempted to measure the utility-gains from improving these outcomes over time, in line with other cost-utility studies in the literature; these outcomes also constitute a “hidden” upside.

Healthcare resource utilisation levels would be similar whether non-convulsive seizures are considered or not. The non-convulsive seizure types do not generally result in hospitalisation, and they would be managed as part of the same set of specialist consultations already captured for convulsive seizures. As such, costs for non-convulsive seizures are already captured in the model.

B2. Priority question: Patients in the CCM group transfer back to their baseline seizure frequency after the first cycle. As a result, there are no patients in the CCM group who achieve seizure freedom. The assumption that baseline seizure rates are representative of the efficacy associated with CCM without placebo after the first cycle is questionable. It might be reasonable to assume that patients in CCM would be offered alternative treatments which would than potentially lead to a sustained “placebo” effect. At the very least, patients in the CCM group should be able to stay in their current health state and keep their reduced/increased seizure frequency after the first cycle (as assumed for CBD after the ninth cycle). Please modify the model to incorporate this assumption and perform a scenario analysis based on this assumption.

We have not provided a scenario to model the maintenance of health states after the first cycle in the CCM group, nor one that maintains the transition probabilities from placebo groups in the clinical trials after the first cycle.

In the GWPCARE studies, all patients had to be receiving a stable dose of ≥1 AED for at least 4 weeks prior to screening. As such, it is reasonable to assume that the baseline health states reflect outcomes in clinical practice associated with CCM.

A placebo response was observed in both GWPCARE1 and GWPCARE2. As outlined in the response to question A9c, this is a common phenomenon in epilepsy trials, for which the cannabidiol trials were adequately powered. The reasons for this phenomenon are unknown, but are likely to arise from artefacts of the clinical trial environment and/or a psychological response to starting a new treatment in patients with a high level of unmet clinical need [Goldenholz 2016]. It is not reasonable to assume that these effects would be sustained in clinical practice. Clinical experts have validated this assumption.

In the GWPCARE1 and GWPCARE2 trials, it was necessary to maintain baseline medication consistently throughout the studies in order to assess the treatment effect of CBD in isolation. In clinical practice, by comparison, patients who continue CCM may receive new treatments over time. However, it is not reasonable to assume that over a 15-year time horizon this will result in significant and durable improvement of seizure status. A feature of DS is that treatment with AEDs is unlikely to control seizures completely, and patients retain a relatively high seizure burden despite treatment with multiple AEDs (as seen in the baseline characteristics of the cannabidiol trials).

It is unlikely that there would be any sustained benefit with CCM in this group of patients, even if new drugs were to be added. It can be assumed that health states in real world practice would not improve from baseline. Nonetheless, to be conservative we have utilised the transition probabilities from the placebo arms in the trials in the first cycle of the model, which provides benefits associated with the observed placebo effect. Of note, the assumption that patients revert to their baseline health state has also been applied to CBD patients discontinuing treatment in the model.

B3. The time horizon in the base-case of the model is 15 years. However, we prefer analyses based on a lifetime time horizon. This is especially important as patients with DS are at risk of higher mortality depending on their seizure

frequency. Additionally, the use of a half-cycle correction is not discussed in the company submission.

a. Please extend the time horizon of the model to lifetime.

b. Please justify why the half-cycle correction is not used.

B3a. DS is a chronic and life-threatening disease. However, given the lack of long-term data on the natural history of the disease and the unpredictability of seizure patterns, it is difficult to extrapolate seizure frequency over a lifetime horizon, especially for young patients. A 15-year time horizon was considered appropriate to provide insights on the future costs and benefits, and capture the increased risk of deaths in children and young adults. In addition, previous economic models in epilepsy (as described in Appendix G of the dossier) did not use a lifetime horizon.

B3b. Given that the cycle length used in the analyses is quite short (3 months) it was deemed not useful to apply a half-cycle correction.

B4. Clinical effects of drugs are frequently known to wane over time.

a. Please justify why no treatment waning was assumed for CBD.

b. Please add a scenario in which the efficacy of CBD is assumed to decrease over time.

B4a/b. No treatment waning assumption has been built into the transition probabilities for CBD treatment for two reasons:

- There is [redacted], which is used to model transition probabilities from cycle 2-9 in the model. The document “Transition probabilities over cycles DS.xlsx” shows how transition probabilities change over cycles. A visual inspection shows that the probabilities for transitioning to a better health state [redacted]. (Note: cycles 2-9 are derived from outcomes observed in the GWPCARE5 open label extension study). By comparison, the probabilities of transitioning from a better to a worse health state, or staying in the same health state, [redacted].

- The discontinuation rate assumptions in the model already account in part for patients who are not responding to treatment. The CBD discontinuation rates applied from cycles 2-9 are those observed in the GWPCARE5 open label extension study. These mostly reflect withdrawals due to a lack of efficacy (although withdrawals were rare, of those patients who did discontinue in GWPCARE5, the majority were unrelated to an adverse event). As discontinuers are assigned to their baseline health state for all subsequent cycles, these patients attenuate the observed outcomes over time in the model for all patients starting on CBD, creating a *de facto* waning effect. Implementing an additional and unevidenced waning assumption into the model for CBD-continuers would constitute "double counting".

Population

B5. The target population in the model is specified as people with DS whose seizures are inadequately controlled by current or prior established clinical management. This is in line with the final scope issued by NICE. The company has extended the scope to include people with DS where current clinical management is unsuitable or not tolerated (see question A2).

a. The two phase 3 trials and the open-label extension study all target children or adolescents ≤18 years old. Please justify whether the evidence base is sufficient to justify the broader target population specified in the company submission (i.e. all patients with DS) and elaborate on the implications.

b. Please justify the use of age category "18-55 years" in calculating treatment costs given that the estimations for this category are based on a small number of patients (1.89%) and an implausible mean weight (49.70 kg, which is lower than the patients in category 12-17 years; and lower compared to category 18-55 years in the LGS submission which is 64.46 kg).

c. In the model, treatment costs are based on the average weight by age group (Table 32). Please justify whether the weight per age group in the model is representative for the DS patient population in the UK?

d. Please validate the mean weight for each age category in the model (e.g. using UK specific data).

B5a. These age ranges at baseline reflect the demographics of the DS population in clinical practice. Patients are diagnosed at a young age and mortality rates are high. Premature mortality is a major issue in DS, with most deaths occurring before 10 years of age. For these reasons, the number of adults with DS is very low compared with the number of children.

It is reasonable to use the transition probabilities observed for the entire population over 11 years old in all patients meeting this age criterion in the model, including adults.

B5b. The weight for adult patients was applied as observed for those who are 18 years old at baseline in the clinical trials, despite the small sample size (n=6). Of note, children with DS tend to be underweight [Eschbach 2017]. There was an asymmetric distribution of weights within this small sample and, as such, in the new economic analysis we have utilised the median ([redacted]) and not mean weight ([redacted]). This addresses the face-validity issue in the prior assumptions. Baseline weights have been tested in the sensitivity analyses.

B5c/d. It is not possible to definitively conclude whether the mean weights at baseline in the clinical trials are representative of those for the DS population in the UK. No data were identified in the literature and, due to the orphan nature of the disease, there were too few UK patients in the GWPCARE1 and GWPCARE2 trials (16 overall) to use only this subgroup in the model.

However, it is recognised that patients with DS are generally underweight relative to the general population. As only 16 patients out of 318 were from UK centres, UK-specific data have not been used in the model.

The table below provides the mean and median weight of UK patients versus all patients in the trials. However, the small sample of UK patients does not allow a statistical assessment of the difference.

UK clinical experts have validated our weight assumptions for the UK population.

The median weight from baseline across age groups has been used in the updated economic analysis, given the asymmetric distribution due to outliers.

Mean and median weight of patients in the CBD Phase 3 trials

	UK PATIENTS			OVERALL			Proportion of UK patients
	N	Mean	Median	N	Mean	Median	
2 - 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 - 11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 - 17 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 - 55 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B6. It is unclear how the different age cohorts (i.e. 2 - 5 years, 6 - 11 years, 12 - 17 years, 18 - 55 years) flow through the model. It appears as if the cohorts are modelled in four separate Markov traces (see for example Sheet "PM CDB10" in the model).

a. Please elaborate on whether this assumption is correct and which transition probabilities were used for each age subgroup.

b. Please provide the starting age of the cohort (if applicable for all four age categories).

B6a. This is correct; the cohorts are modelled in four separate Markov traces. This allows us to have more granularity on the starting ages and weights of the cohort. The transition probabilities for 2-11 years old patients (as derived from the trials) are used for the cohorts 2-5 years and 6 -11 years; the transition probabilities for 12-55 year old patients are used for the last two cohorts; 12-17 years and 18-55 years.

B6b. The starting age of the cohorts are displayed in the cohort definition sheet of the model as well as in section B.3.3 "Clinical parameters and variables" of Document B (Table 15 on page 58). Please find them also in the table below.

Mean starting age in the CBD Phase 3 trials

	Mean age
2 - 5 years	[redacted]
6 - 11 years	[redacted]
12 - 17 years	[redacted]
18 - 55 years	[redacted]

Intervention

B7. Priority question: In the base-case analysis of the model, it is assumed that the intervention consists of CBD 10 mg/kg/day in addition to CCM. However, in both GWPCARE1 and the open label study, the focus appears to be on substantially higher dosages (20 mg/kg/day or more).

a. Please add an incremental analysis to the model comparing 10 mg/kg/day in addition to CCM to 20 mg/kg/day with CCM. Please use treatment-specific effectiveness, resource use, and adverse event data.

b. It is stated in the company submission that some patients benefit from CBD 20 mg/kg/day. Which patients (e.g. what characteristics, what proportion) are expected to benefit from this higher dosage?

B7a. We have not done an incremental analysis comparing patients on 10 mg/kg/day and 20 mg/kg/day doses of CBD. This is not clinically meaningful.

The model does not assess outcomes for 10 mg/kg/day and 20 mg/kg/day doses separately, nor does it focus its analysis on doses above 10 mg/kg/day. The SmPC defines 10 mg/kg/day as the maintenance dose in clinical practice, with a small proportion of patients benefiting from escalation up to 20 mg/kg/day. This is supported by clinical expert feedback.

It is therefore not clinically meaningful to consider outcomes separately and relative to each other for each dose, as physicians are not “choosing” between them for an individual patient ahead of drug initiation, and few patients will receive the higher dose. Instead, the model estimates outcomes overall across a population being treated entirely (in the base case) or mostly (for the alternative scenario analysis) with 10 mg/kg/day, with a small contribution from a minority of patients escalating to

a higher maintenance dose of between 10 and 20 mg/kg/day (who are modelled using outcomes from the 20 mg/kg/day arms in cycle 1). Page 108 of Document B outlines how the average dose assumption in the alternative scenario was calculated.

For cycles 2-9 the model uses transition probabilities derived from the overall DS population in GWPCARE5, which are assigned equally to patients irrespective of starting dose in cycle 1. GWPCARE5 allowed patients to be titrated up to an optimal maintenance dose. The transition probabilities derived from GWPCARE5 are considered to be a good approximation for those that would have been observed on 10 to 20 mg/kg/day. This assumption is considered to be reasonable given the lack of a broad dose response on efficacy endpoints between the two doses in GWPCARE2 (also seen in LGS patients in GWPCARE3), and the greater validity of using real long-term data from a clinical study rather than extrapolating 14 week outcomes (from GWPCARE1 and GWPCARE2) to more than 2 years in the model.

B7b. See A1a and A1b above.

B8. In the scenario analysis varying the CBD dosage (company submission Table 41), patients receive 10 mg/kg/day if they experience <75% response, and 20 mg/kg/day if they experience ≥75% response.

a. Please clarify how response was defined for this analysis.

b. Please justify the ≥75% response threshold that was used to determine the CBD dosage (i.e. 10 mg/kg/day or 20 mg/kg/day).

B7a. The responder definition in this analysis comes from the clinical trials.

A tertiary endpoint in the clinical trials was the percentage of patients achieving a ≥75% reduction in convulsive seizure frequency from baseline during the treatment period (measured as the 28-day mean during the treatment period versus the daily mean during the baseline period). This was analysed per treatment group using a Cochran-Mantel-Haenszel test stratified by age group.

B7b. The calculation that was used to give the average dose (mg/kg/day) of CBD is shown in the table below (and is also explained on page 108 of Document B).

Proportions were used as reported for the endpoint in the CSR tables for the maintenance period in the ITT populations from GWPCARE1 and GWPCARE2, in line with the definition above.

Calculation of mean doses for the scenario analysis

	DS			Weighted mean mg/kg/day
	1424		1332	
	10mg	20mg	20mg	
n	66	67	61	
75%-responders	[redacted]	[redacted]	[redacted]	[redacted]

The average dose was calculated assuming that all patients who achieved the 75% responder outcome in GWPCARE2 ([redacted]) were moved to a maintenance dose of 20 mg/kg/day, and all others ([redacted]) were retained on a maintenance dose of 10 mg/kg/day. No titration was assumed in this calculation.

The SmPC states that the recommended maintenance dose is 5 mg/kg twice daily (10 mg/kg/day) and that, based on individual clinical response and tolerability, each dose can be further increased up to a maximum maintenance dose of 10 mg/kg twice daily (20 mg/kg/day). It further states that any dose increases above 10 mg/kg/day should be made considering individual benefit and risk, and with adherence to the full monitoring schedule as defined in the label.

The clinical data do not support a broad dose response on efficacy outcomes within the trials. They do, however, suggest that a minority of patients may achieve seizure-freedom on the higher dose. As such, the expectation in clinical practice is that most patients will be maintained on 10 mg/kg/day, with a small proportion (who show a strong response on seizures at this dose, and who have good tolerability) being escalated to between 10 and 20 mg/kg/day in order to target seizure-freedom. This is supported by feedback from clinical experts, and reflected in the intent of the SmPC.

We have used the 75%-responder outcome from the trials as a threshold to estimate the proportion of patients who would qualify for escalation. This is an outcome for which we have evidence. In such a refractory population it represents a very good response in clinical practice, signalling that further improvements may be achievable.

It is also likely that the actual proportion of patients who would be dose-escalated is smaller than this, as it assumes that all patients titrate up to and tolerate 20 mg/kg/day and none de-escalate.

Comparator

B9. Priority question: In the company submission, CCM (including several combinations of AEDs) plus CBD was compared to CCM only. Contrary to the final scope issued by NICE, different (combinations of) AEDs were not considered as separate comparators. This implies that the effectiveness of CBD is assumed to not vary with the combination to which it is added. However, the Clinical Study Reports (CSRs) for the key trials (GWPCARE1 and GWPCARE2) indicate that the company has also conducted a number of subgroup analyses that show an effect on the primary outcome of the presence of a specific AED or number of AEDs in the CCM combination. The company also claim that patients in both the intervention and comparator arm receive the same clinical management, but in fact a dose reduction of 33% is applied to a proportion of patients taking only some AEDs in those taking CBD plus CCM. Therefore, even if effectiveness does not vary by combination, which is a strong assumption, cost will vary as the dose reduction only applies to some AEDs.

a. Please justify why all AEDs and combinations of AEDs were combined (as CCM) and were not compared to the intervention as individual combinations.

b. Please justify whether the AED proportions, as shown in Table 16 of the company submission, are representative of UK clinical practice in this population.

c. Please perform a set of subgroup analyses based on all combinations of AEDs for which there are any trial data as per NICE scope.

d. CCM was determined based on primary research on AED prescription patterns in the UK and the final NICE scope. However, reference 44 of the company submission is missing. Please provide the content of this reference and in addition provide more detail on:

i. The aim of the market research

ii. The methodology used (e.g. how were participants selected and approached, what questions were asked)?

iii. Detailed results of the market research.

iv. Why data from the market research was preferred above the pivotal trials to inform the AEDs proportions (as shown in Table 16 of the company submission) in the economic model.

B8a. As per the NICE scope, the intervention is “cannabidiol in addition to current clinical management”. Current clinical management varies due to the refractory nature of DS, and is also defined in the NICE scope as “combinations of” the various AEDs/interventions. Given the orphan nature of the condition and the heterogeneous nature of the patients, it is not clinically or statistically meaningful to compare the intervention to individual or specific combinations of AEDs.

B8b. The AEDs considered in the submission are in line with published evidence on current clinical practice and the final scope published by NICE, and were also validated by clinical experts to be appropriate and representative of the UK clinical setting.

B8c. See answer to B8a. Given the orphan nature of the condition and the heterogeneous nature of the patients, it is not clinically or statistically meaningful to compare the intervention to individual or specific combinations of AEDs. As such, these subgroup analyses have not been performed.

B8d. To summarise the methodology for this market research, [redacted] clinicians (neurologists and paediatricians with an epilepsy specialism, paediatric neurologists and epileptologists) were interviewed across the EU5, with minimum of [redacted] in each country (N=[redacted] in the UK). Physicians had to manage at least one of three childhood epilepsy syndromes (DS, LGS or tuberous sclerosis complex - TSC) and have a minimum caseload of 100 paediatric or 200 adult epilepsy cases per year.

The objectives of the research were to gather insights on:

[redacted]

[redacted]. Findings were based on physician feedback in interviews.

Current treatment behaviour was based on clinician reporting. In this context, respondents were asked questions on which combinations of AEDs they currently use, and in what proportion of patients. These data were used to determine the proportion of patients on each AED at model entry, which sets the drug-mix for concurrent CCM within the cost utility analysis.

Table 16 in Section B3.3 of Document B shows the results of this research with UK respondents in terms of the treatment basket for CCM. Table 6.3 (page 93) of the Unblinded Final Tables in the GWPCARE2 (1424) CSR show usage levels of AEDs amongst patients at baseline in the clinical trial. There are differences: in 1424 the most commonly used agents (clobazam, valproate, stiripentol and topiramate) are somewhat under-represented versus clinical practice as reported in the market research. This lack of congruence suggests that a single source should be used to define the CCM mix in the UK. GWPCARE1 and GWPCARE2 included 16 UK patients, whereas this research included findings from [redacted] treating clinicians with a combined caseload of over 420 patients. It was thus considered to be more reflective of the treatment basket in UK clinical practice.

Of note, the model is not sensitive to the precise mix of agents within CCM given their low cost such that any uncertainty in the CCM mix from the market research is not material.

B10. Priority question: Contrary to the final scope issued by NICE, (combinations including) ketogenic diet and vagus nerve stimulation were not considered as comparators in the cost effectiveness model.

Please include ketogenic diet and vagus nerve stimulation as comparators in a full incremental analysis (non-adherence and/or complications is not a valid justification to exclude comparators).

Ketogenic diet: As per Figures 1 and 2 in Document B, ketogenic diet (KD) is an established part of the treatment pathway for DS, and therefore part of the CCM mix into which CBD would be added.

Use of KD was not an exclusion criterion in the clinical trials for cannabidiol. Approximately 9% of patients were on a KD at baseline in GWPCARE2 and 10% in GWPCARE1. These patients continued their dietary regimen throughout the treatment period in all trial arms.

Therefore, KD in already included in the comparator by virtue of its contribution to transition probabilities in both cohorts of the model as part of the CCM mix.

KD is a routine part of clinical care for a subset of eligible drug-refractory epilepsy patients within paediatric tertiary care in the UK [NICE CG137]. There is no reason to assume that levels of use would differ greatly between patients receiving and not receiving CBD. For simplicity, neither costs of the diet, nor disutilities associated with its adverse events, have been included in the model, as they would apply equally to both cohorts. Furthermore, the costs of KD from an NHS perspective would be difficult to define, as most are borne out-of-pocket by families.

Vagus nerve stimulation: As per Figures 1 and 2 in Document B, vagus nerve stimulation (VNS) is an established part of the treatment pathway for DS, and therefore part of the CCM mix into which CBD would be added.

VNS was not excluded at baseline in the CBD clinical trials. Overall, about 14% of patients in GWPCARE2 had previously received a VNS implant. Proportions were similar for GWPCARE1. Patients were not permitted to have VNS during the studies.

As the effects of VNS are durable, these interventions are already included in the comparator by virtue of their contribution to transition probabilities in both cohorts of the model as part of the CCM mix.

In theory, the adjunctive use of CBD could reduce the incidence of VNS as part of ongoing CCM versus CCM alone, which would reduce both costs and disutilities associated with long-term complications of this intervention. However, there is no evidence to quantify this, nor any data from the literature to model disutilities. It is reasonable to assume that these effects would apply equally to both cohorts, so they have not been factored into the model.

It would not be appropriate to consider these interventions in isolation as comparators to CBD, given their tight eligibility criteria and restricted use. NICE positions VNS secondarily to surgical resection in drug-resistant paediatric patients [NICE CG137], and NHS England estimates in its clinical commissioning policy that only 1% of epilepsy patients are eligible for resective surgery [NHSE NHSCB/D04/P/d]. Furthermore, restrictive eligibility criteria are imposed on VNS in clinical commissioning guidance [NHSE NHSCB/D04/P/d]. The level of use of this procedure in the UK is thus unlikely to be high enough to justify it as a comparator in isolation.

Effectiveness

B11. Priority question: Question A11 considers baseline imbalances in convulsive seizure frequency and in all seizure frequency between study arms in GWPCARE1 and GWPCARE2 (Tables 6 and 7 in the company submission).

a. Please elaborate on the implications of these potential imbalances on the estimated transition probabilities.

b. Please elaborate on the implications of these potential imbalances on the cost effectiveness results.

c. Please provide a scenario analyses where transition probabilities have been adjusted for convulsive seizure frequency at baseline.

B11a/b. The difference in the mean baseline seizure count between the active and placebo arms in the GWPCARE1 and GWPCARE2 trials is not anticipated to impact transition probabilities.

As described in the answer to A11, baseline seizure counts (both convulsive and total) show a very wide range, heavy left skew and over-dispersion. Most observations are concentrated in a small band at the lower end of the range. Medians are broadly similar, and even more so when outliers are removed. As such, these baseline criteria were considered generally balanced in the statistical analysis, and no effect on outcomes was expected. Sensitivity analyses on the primary endpoint confirmed this (see A11). If trial endpoints are not affected, it is reasonable to assume that transition probabilities will not be affected either.

Transition probabilities reflect only the probability of moving from one convulsive seizure frequency grouping to another between two timepoints for a given treatment arm and age group (the timepoint was baseline for the first cycle, and the prior 3 months of follow-up for all subsequent cycles). It is reasonable to assume that this will not be affected by any differences in seizure frequency between the treatment arms at baseline.

Furthermore, any hypothetical bias would only be applied in the first cycle of the model, as patients on CCM alone go back to their baseline health state as of cycle 2.

If the transition probabilities are not expected to be affected by these numerical imbalances, then the cost utility outcomes would not be either.

B11c. In line with the answers to B11a/b, no scenario analyses have been performed.

B12. Priority question: According to the company submission (section B.3.2), the proposed licensed indication for CBD (oral solution) consists of a recommended starting dose of 2.5 mg/kg twice daily (5 mg/kg/day), increased to a maintenance dose of 10 mg/kg/day.

a. Please justify why the GWPCARE1 trial is used to inform the model parameters, given that this trial only considers CBD 20 mg/kg/day (i.e. not the recommended dosage of CBD 10 mg/kg/day).

b. In the open label extension study (GWPCARE5), patients were initially titrated to 20 mg/kg/day, which could then be either decreased or increased to 30 mg/kg/day at the investigator's discretion. This does not reflect the recommended dosage of CBD 10 mg/kg/day. Please justify why the open label extension study (GWPCARE5) is used to inform the model parameters, given that this study has a mean modal dose during treatment of 23 mg/kg/day (min=2.5, max=30; n=364).

c. Please provide a scenario analysis using the GWPCARE2 trial only. Please use similar assumptions for CBD after the first cycle, as is done after cycle nine in the base-case (i.e. that patients remain in their corresponding health

state unless they discontinue from treatment or die). Please extrapolate the treatment discontinuation from the GWPCARE2 trial beyond the first cycle.

d. Please provide a scenario analysis using the GWPCARE2 trial only. Please use similar assumptions for both CBD and CCM after the first cycle, as is done after cycle nine in the base-case for CBD (i.e. that patients remain in their corresponding health state unless they discontinue from treatment or die). Please extrapolate the treatment discontinuation from the GWPCARE2 trial beyond the first cycle.

B12a. The GWPCARE1 trial is used because it is necessary to model scenarios in which a minority of patients are escalated to a maintenance dose of up to 20 mg/kg/day.

As described in the answer to B7b, it is anticipated that, in clinical practice, most patients will be maintained on the recommended dose of 10 mg/kg/day, with a minority escalated to a dose of up to 20 mg/kg/day. Consequently, whilst the base case assumes all patients are on the former, an alternative scenario does consider outcomes when a small proportion are on the latter. The outcomes from GWPCARE1 are material to this scenario analysis.

B12b. The GWPCARE5 study protocol was written prior to the maintenance dose being established. Although the dosing in GWPCARE5 is not fully aligned to the labelled posology, this study was used to inform model parameters for cycles 2-9, as it provides actual data on long-term outcomes for CBD from a well-designed clinical trial. This was considered methodologically preferable to extrapolating 14-week outcomes from GWPCARE1 and GWPCARE2 over 2 years.

It is reasonable to assume that GWPCARE5 is a good proxy for long-term outcomes on the labelled dose. In GWPCARE2 (and GWPCARE3 for LGS), no broad dose response was observed between the 10 and 20 mg/kg/day treatment arms on efficacy endpoints. As such, the higher average dose used in GWPCARE5 is unlikely to offer a significant gain in clinical effectiveness. In addition, [redacted] is observed in the transition probabilities between cycle 1 (derived from GWPCARE1 and GWPCARE2) and cycle 2 (GWPCARE5) for the 10 mg/kg/dose, as well as between cycles 2 and 9 (see separate document “Transition probabilities

over cycles DS.xlsx"). Thus, the higher average dose in GWPCARE5 is not likely to be benefiting cost-utility outcomes in the model.

B12c/d. We have not conducted these scenario analyses. We feel that it is not reasonable to extrapolate outcomes at 14 weeks from GWPCARE2 over a 15-year time horizon, especially when actual long-term data exists that is a better proxy for clinical effectiveness at the labelled posology (see B12b).

As per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided. This analysis revises discontinuation assumptions. Discontinuation rates in the first cycle are made uniform and aligned to overall withdrawal rates observed in the GWPCARE1 and GWPCARE2 studies. This reflects the fact that early discontinuations would be largely driven by tolerability, consistent with the Phase 3 trial outcomes.

Over cycles 2-9, discontinuations would be expected to be driven by a mixture of adverse events and a lack of efficacy. This is reflected in the reasons for withdrawal in the GWPCARE5 study. Furthermore, the expected gradient of increasing discontinuation rates with worsening health state is observed in these data. As such, we have not applied discontinuation rates from GWPCARE1 and GWPCARE2 beyond the first cycle. Instead, we have retained discontinuation rate assumptions per health state as observed in the extension study. These are likely to provide the best evidence available for medium-term persistence on CBD.

B13. Company submission Table 17 provides an overview of transition probabilities. Please explain how CBD treatment discontinuation is incorporated in this overview. If this is not incorporated, please provide an overview including CBD treatment discontinuation.

To compute the transition probabilities we used the LOCF (last observation carried forward) method for imputing missing data for all patients withdrawing from the trials prior to the end of follow-up.

Whilst it cannot be excluded that this may overestimate transition probability assumptions, pre-specified sensitivity analyses done on the primary endpoint in the clinical trials would suggest otherwise. In particular, sensitivity analyses were performed on the primary endpoint in GWPCARE1 and GWPCARE2 to impute for

missing data using the highest of the LOCF, next observation carried backward (NOCB) and the mean from the non-missing data for each patient. This would be expected to be a more stringent test than LOCF alone. Despite this, outcomes under these scenarios were almost identical to those for the main analysis. Furthermore, time-course analyses of the same endpoint in GWPCARE5 for the data-as-observed and under the LOCF method confirmed that discontinuations did not affect the outcome [Scheffer 2018]. If using the LOCF method does not bias outcomes in the clinical trials, it is reasonable to assume it does not do so for transition probabilities.

B14. CBD treatment discontinuation (company submission Table 19) is assumed to be dependent on health state.

a. Please justify the assumption that treatment discontinuation is dependent on health state, given that the treatment discontinuation probabilities might lack face validity (e.g. treatment discontinuation does not always increase with higher convulsive seizure frequencies) and are based on a small sample size.

b. Treatment discontinuation reported in company submission Table 19 seems inconsistent with the 27% (40/147) reported by Laux et al, (2017)[1]. Please clarify this inconsistency.

c. Please provide the median and mean study duration used by Laux et al, (2017)[1] to calculate the above mentioned 27% for LGS and DS patients.

d. Only an abstract is provided for the Laux et al, (2017).[1] Please provide a digital copy of the poster presented at the American Epilepsy Society.

e. Please justify that the 0% CBD treatment discontinuation probabilities provided in Table 19 are clinically plausible.

f. Please provide a scenario analysis using the average treatment discontinuation probability across the health states.

B14a. The discontinuation rates were computed for each health state as observed in the trial data. It is expected that they would differ over the short-to-medium term by both treatment arm and health state, as withdrawals would be driven by both

adverse events (related to treatment assignment) and perceived lack of efficacy (linked to being in high seizure health states).

As per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided. The assumptions for treatment discontinuation rates are revised in this new model. Face-validity inconsistencies in discontinuation rate assumptions between health states have been corrected in the new analysis. For cycles 2-9, discontinuation rates are retained from those observed in GWPCARE5. These data show the expected gradient of increasing discontinuations levels with worsening health state, and are considered likely to provide the best evidence available for medium-term persistence on CBD.

B14b/c/d. As per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided. The assumptions for treatment discontinuation rates are revised in this new model. A copy of the Laux et al 2017 poster is provided separately. Median follow-up in this study is reported in this source.

B14e. As per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided. The assumptions for treatment discontinuation rates are revised. A uniform discontinuation rate equal to the average across health states has been applied to the first cycle. This reflects that most treatment withdrawals in the first 3 months will be due to tolerability and adverse events. As highlighted in the answer to B14a, variable discontinuation rates per health state, as observed in the GWPCARE5 study, are retained for cycles 2-9.

B15. The number of days without seizures is provided in company submission Table 18 and is assumed to be dependent on both treatment allocation and health state.

a. Please justify why the number of days without seizures is assumed to be dependent on both treatment allocation and health state instead of being dependent on health state only.

b. Please provide a scenario analysis where the probability of number of days without seizures is equal across treatment allocation (i.e. assuming the

number of days without seizures probabilities are only dependent on health state).

B15a/b. As explained in section B.2.6 of Document B ("Clinical effectiveness results of the relevant trials"), CBD has a significant impact on both the frequency of convulsive seizures and the number of convulsive seizure-free days per month over the treatment period. Therefore, the number of days without seizures is dependent on the treatment allocation.

The scenario analysis proposed would assume no treatment effect by CBD on the number of seizure-free days, which contradicts the evidence from the trials. We have therefore not performed this analysis.

B16. The calculation of epilepsy-related mortality rates provided in company submission Table 20 is unclear. Specifically, how the three-month probability was converted to the mortality probabilities for the four health states. Please provide a detailed explanation of how the epilepsy-related mortality rates are calculated and provide evidence and/or justifications for all assumptions or data used (e.g. the assumed annual risk ratios)

Please refer to the original explanation in Document B (page 65-66) of the Company's Evidence Submission for an explanation of how mortality rates were derived. These assumptions were discussed with clinical experts and were deemed reasonable.

As per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided. New mortality estimates have been provided as part of this.

Adverse events

B17. According to the company submission: 'The most frequently occurring (events reported in ≥3% of patients treated with CBD and ≥1% of patients in the

placebo arm) treatment-emergent adverse events of special interest were included in the base case analysis'.

a. Please justify why different thresholds (i.e. ≥3% and ≥1% for CBD and placebo respectively) were used to select adverse events for the base-case.

b. Please clarify what the implications, including the expected impact on the cost-effectiveness, are of using different thresholds to select adverse events for the base-case.

B17a. In the cost-utility model, we have included only adverse events of special interest (AESI). To correct the definition of AESIs as reported in the Company's Evidence Submission, these were defined *a priori* in the SAP for the MAA submission and are based on complex clinical criteria that are not related to observed incidences in the clinical trials. These AEs are the most relevant to capturing costs in the model and have been retained. As per the answer to B21 below, disutilities associated with AEs have been ignored.

B17b. The impact of adverse events is minimal in the model. They constitute less than 1% of the total cost difference between the two treatment arms in the existing analysis. Any assessment altering the AE basket and incidences will have no material effect on the ICERs in the model.

Quality of life

B18. Priority question: In the model, health states are defined based on the number of absolute convulsive seizures and convulsive seizure-free days per 28 days. However, based on the clinical data (i.e., GWPCARE1, GWPCARE2, and GWPCARE5), a substantial number of non-convulsive seizures is reported for both CBD and the CCM group. Please clarify what the number of non-convulsive seizures is per subgroup based on the classification used for the health states (i.e. seizure-free, ≤8 seizures, >8 - ≤25 seizures and >25 seizures).

The table below displays the mean and median number of non-convulsive seizures across health states defined by convulsive seizure frequencies for the treatment period. As explained previously, the mean number of non-convulsive seizures is

lower in health states with fewer convulsive seizures. This can be expected to provide a utility gain not measured in the model.

Summary of non-convulsive seizures across convulsive-seizure frequency-defined health states (treatment period)

	Non-Convulsive seizures					
Convulsive seizures	**N**	**Mean**	**SD**	**Median**	**Min**	**Max**
Seizure-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>8 - ≤25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B19. Priority question: Utility values were determined based on a vignette study which only focused on convulsive seizure frequency and seizure-free days in accordance with the health states in the model.

a. Please justify whether the vignette study incorporated all relevant domains of quality of life (i.e. not merely condition-related factors). For example, seizure severity or other relevant domains such as mobility, self-care, anxiety/depression, social activities.

b. Please elaborate on the implications if the vignette study did not incorporate all relevant domains of quality of life.

c. The utility values associated with the seizure free health state appear to be relatively high for patients with DS, especially given the likelihood of remaining non-convulsive seizures. Please justify why utility values are not adjusted for non-convulsive seizures.

d. Please elaborate on the fact that the vignette study for DS included less health states than the vignette study for LGS.

e. In the vignette study, three additional vignettes for carers of patients with DS were included. Please elaborate on how these vignettes were used in determining utility values for the model.

f. Public preferences are different from patient preferences (e.g. the proportion of individuals that have experience with specific health states)[2]. In general, health state valuations are preferably obtained from the general public. Please justify why patients and caregivers were used to obtain valuations for the vignettes.

g. In the GWPCARE1 and GWPCARE2 studies, quality of life was assessed using the Quality of Life in Childhood Epilepsy (QOLCE) instrument (company submission Table 22).

> **i. Please justify why this instrument was not used to estimate utilities for the base-case.**
>
> **ii. Please add a scenario analysis in which utilities are based on the QOLCE instrument from the phase 3 trials.**

h. In appendix H, several sources for utilities are mentioned. It is unclear why these were not used. Please justify why these sources were considered to be inappropriate.

> **i. In absence of quality of life estimates, proxy estimates from previous studies can be used. Please justify why this was not considered as a source to calculate utilities (see for example De Kinderen et al.,[3]).**

B19a/b. For methodological purposes, the vignette study could not formally measure the impact on utilities beyond condition-related factors. However, this is still clinically meaningful, and the use of a “live” population partially overcomes this limitation. Furthermore, our methodology is likely to underestimate the long-term utility gains associated with non-condition-related factors that are improved with better seizure control.

Given the rarity of DS, a limited study sample size ([redacted] in the final result) was possible for the vignette study, and thus the health states that could be presented were limited. Consequently, it was considered appropriate to focus the study only on seizure burden, which clinical experts are clear is the essential clinical feature driving physical morbidity and disutility in the disease. In this context, measuring the two

parameters related to our model health states (monthly convulsive seizure frequency and seizure-free days) generated 23 descriptive vignettes in total. An example is given in the figure below. Whilst this was a manageable number, testing more than this would have imposed a high respondent burden. To test sufficiency, we piloted the questionnaire with caregivers and patients, who confirmed that the information on the health condition provided in the main descriptive vignette was sufficient.

Given the above restrictions, other domains of potential relevance could not be methodologically incorporated into the study. Nonetheless, the most important features are captured, as evidenced by the high utility differential between health states. The model does not attempt to model utilities associated with the wider long-term behavioural, cognitive and social impacts of DS, which may be improved with better seizure control (and which can be considered a “hidden” upside in the ICERs). Furthermore a “live” population would be likely to have an intrinsic understanding of the broader morbidities and quality-of-life implications associated with the vignette descriptions (in a way that the general population would not). Descriptions around intellectual and behavioural impairments are incorporated into the vignette narratives in order to trigger these considerations. As such, utilities associated with these wider QoL domains are already integrated into the valuations to a degree.

Main narrative vignette on a patient's current condition

David *is 11 years old and has had Dravet Syndrome (rare form of epilepsy) from early infancy.*

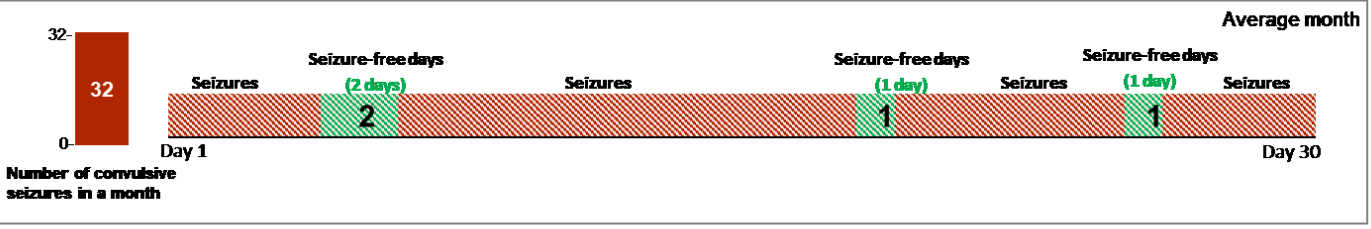
Due to the multiple seizures, he is intellectually and developmentally delayed, and is prone to fevers that may result in convulsive seizures lasting between 15 and 30 minutes.

He has previously been treated with more than 6 antiepileptic drugs and is currently being treated with 3 antiepileptic drugs, but continues to have multiple ***convulsive*** *seizures.*

Imagine you are David and the scenario above describes your current health status.

David has **approximatively 32 convulsive seizures in a month** and **4 seizure-free days in a month**.

Reminder: You are David and the scenario above describes your current health status.

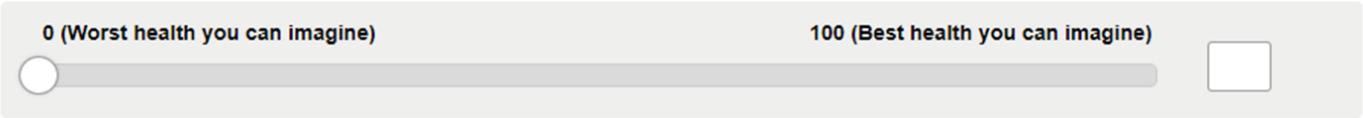


We would like to know what your **quality of life** (QoL) is assuming you are David. Below there is a scale numbered from 0 to 100.

100 means the best QoL you can imagine

0 means the worst QoL you can imagine

Please select the number that indicates how **you rate this health status**. (Use the slider or write the number in the box below)



B19c. Only 3 studies were identified in the literature that report utility measures for DS patients specifically. One of these (Strzelczyk 2018) does not report figures. The other two (Campbell 2018 & Lagae 2017/Irwin 2017) report average EQ-5D-5L index values only, making it difficult to compare with the health state-linked measures in our own study. Of the latter, the figure reported in Lagae 2017/Irwin 2017 (0.42±0.29) is broadly in line with those seen for the intermediate health state in our own study (>8 - ≤25 seizures per month, [redacted]. Those reported in Campbell *et al* 2018 (0.78±0.17, VAS 0.67 [range 11-94]) are unrealistically high given the utilities reported for LGS, which is a similar (and possibly less severe) epileptic condition (see below).

Given that other cost utility analyses in DS have used utilities reported for LGS patients as an analogue [e.g. Elliot 2018], it is relevant to consider how these compare to those reported for DS patients in our own study. We note that the VAS score for the convulsive seizure-free health state from our study ([redacted]) is higher than the utility values reported by Clements *et al.* (0.699) [Clements 2013]. This study obtained QoL estimates from Verdian *et al.* [Verdian 2010], who measured utilities in a UK setting. Clements *et al.* conservatively assumed that the utility in the seizure-

free health state was the same as the lowest health state with seizures as reported by Verdian *et al.* This assumption was made because the latter did not include a seizure-free health state in their analysis. It is therefore reasonable that our utility estimates are higher than those in the literature.

We have not corrected the VAS scores for the disutilities that may be associated with other seizure types. Convulsive seizures drive the physical morbidity and complications of DS. Achieving convulsive seizure freedom is a hugely significant and rarely achieved treatment milestone that was attained by some patients in the clinical studies for CBD. As such, it is reasonable to conclude that a high quality-of-life would be assigned to being and remaining convulsive seizure-free, even if other seizure types persist. Of note, even in the convulsive seizure-free health state, a utility of much less than full health was still measured.

B19d. The number of convulsive seizures in DS is lower than the number of drop seizures per month in LGS. This creates an “impossible” health state for DS.

Seizures are a discrete count outcome. It is not possible to have a health state in which you have fewer seizures in a month than you have days with seizures (as it is not possible to have fewer than one seizure per day). For this reason, the lowest health state with seizures for DS (≤8 seizures and >12 days with seizures per month) is not possible. The equivalent health state for LGS by comparison is numerically possible.

B19e. As per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided. Caregiver disutilities as measured in the vignette study are integrated into this revised analysis. We have conservatively assumed that each patient has only one caregiver.

B19f. Whilst it is recognised that the NICE Reference Case prefers public preferences, in this case health state valuations by the general public would be unlikely to be meaningful. The highly complex, onerous and distressing nature of DS would make it impossible for someone with no experience of the condition to fully understand, empathise with and appreciate its implications, even with a detailed health state description (which would be methodologically hard to accommodate in a utility study). Valuations by the general public would run the risk of being

considerably under- or over-valued, and this uncertainty would be difficult to measure.

Furthermore, as described in the answer to B19a/b, the limited sample size possible for the vignette study meant that we had to focus on measuring the utility impacts of seizure burden alone. By studying a “live” population, we could recruit respondents who had an intrinsic understanding of the implications and challenges of living with DS, meaning that the wider QoL domains are more likely to be integrated into valuations without the need for detailed explanation or a large (and unrecruitable) sample size.

B19g. Please see responses below to each of the sub-questions:

ii. QOLCE scores were not used to estimate utilities for the base-case for the following reasons:

- The response rate was low in the trials ([redacted]). This is not unusual for severe refractory epilepsy, where most patients are unable to participate in surveys due to intellectual impairment and/or age
- Lack of an appropriate mapping algorithm to convert the QOLCE scores to EQ-5D values
- It was not possible to estimate the QOLCE scores based on both seizure frequency and seizure-free days

iii. As per the reasons above, a scenario analysis based on utilities derived from the QOLCE outcomes has not been done.

B19.h None of the current published studies evaluate how health states based on convulsive seizure frequency and seizure-free days impact quality of life, and therefore do not report appropriate proxy estimates for utilities. As such, they could

not be considered for our analysis, and utilities were derived *de novo* using the vignette study as described.

The study by De Kinderen *et al*. does not consider seizure-free days in its health state valuations. Therefore, it is not possible to derive utility scores that are reflective of our model health states using the algorithm published in this study.

B20. The SLR for utilities was restricted to English language only.

a. Please elaborate on the implications of this restriction.

b. Please present the studies that were excluded based on language use in the SLR and elaborate per excluded study on whether it could potentially inform utilities for the health states in the economic model.

B20a/b. Overall, 18 studies were excluded based on language. Citations for these excluded abstracts are provided below. None of these studies were relevant to inform utility values or cost and resource use for the economic model.

1. Alva-Moncayo, E. and A. Ruiz-Ruiz (2003). The value of topiramate used with conventional schemes as an adjunctive therapy in the treatment of Lennox-Gastaut syndrome. Revista de Neurologia 36(5): 453-457.
2. Bertamino, F., et al. (1988). Observations about the rate of psychopathological symptoms in epilepsy in childhood. Bollettino - Lega Italiana contro l'Epilessia(62-63): 349-351.
3. Ernst, J.-P. (2008). Long-term courses of West and Lennox-Gastaut syndrome. Zeitschrift fur Epileptologie 21(1): 26-29.
4. Gonzalez-De la Rosa, M. G. and E. Alva-Moncayo (2017). "[Lafora disease presentation, two cases in a Mexican family]." Rev Med Inst Mex Seguro Soc 55(2): 252-256.
5. Grioni, D., et al. (2011). Clinical evidence of a possible synergy between Rufinamide and Vagus Nerve Stimulation in a drug-resistant case of Lennox Gastaut Syndrome. Bollettino - Lega Italiana contro l'Epilessia(142): 176-178.
6. H. R. Hirt (1996). "[Nosology of Lennox-Gastaut syndrome]." Nervenarzt 67(2): 109-22.
7. Hortiguela-Saeta, M. M., et al. (2015). [Descriptive statistical analysis of the treatment of status epilepticus in a referral hospital]. Rev Neurol 60(10): 433-438.
8. Li, W. H., et al. (2017). "[Novel compound heterozygous TBC1D24 mutations in a boy with infantile focal myoclonic epilepsy and literature review]." Zhonghua Er Ke Za Zhi 55(1): 50-53.
9. Liu, A. J., et al. (2017). "[Study on mosaicism of SCN1A gene mutation in parents of children with Dravet syndrome]." Zhonghua Er Ke Za Zhi 55(11): 818-823.
10. Mengarelli, C., et al (2017). [Stiripentol for the treatment of severe myoclonic epilepsy in infants (dravet's syndrome)]. https://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32017000287&UserID=0
11. A. Miyamoto, S. Takahashi and J. Oki (1999). "[A successful treatment with intravenous lidocaine followed by oral mexiletine in a patient with Lennox-Gastaut syndrome]." No To Hattatsu 31(5): 459-64.
12. Parmeggiani, A., et al. (1996). Antiepileptic treatment in age-related epileptic encephalopathies: Severe myoclonic epilepsy and Lennox-Gastaut syndrome. Bollettino - Lega Italiana contro l'Epilessia(95-96): 155-156.

13. Z. P. Qu (1991). "[Auto-cholinergic synapse dysfunction in patients with generalized epileptic seizures. A preliminary report]." Zhonghua Shen Jing Jing Shen Ke Za Zhi 24(3): 160-1, 188-9.
14. A. A. Sharkov, I. V. Sharkova, E. D. Belousova and E. L. Dadali (2016). "[Genetics and treatment of early infantile epileptic encephalopathies]." Zh Nevrol Psikhiatr Im S S Korsakova 116(9. Vyp. 2): 67-73.
15. Tian, X. J., et al. (2017). "[Clinical and neuroimaging features of acute encephalopathy after status epilepticus in Dravet syndrome]." Zhonghua Er Ke Za Zhi 55(4): 277-282.
16. F. Vassella, A. Rudeberg, S. V. Da and E. Pavlincova (1978). "Double-blind crossover trial of the anticonvulsive effect of phenobarbital and valproate in Lennox syndrome. DOPPERTBLIND-UNTERSUCHUNG UBER DIE ANTIKONVULSIVE WIRKUNG VON PHENOBARBITAL UND VALPROAT BEIM LENNOX-SYNDROM." Schweizerische medizinische wochenschrift 108(19)
17. Vicentini, R., et al. (2013). Epileptic encephalopaty Lennox-Like, clinical picture about a rufinamide responsive patient. Bollettino - Lega Italiana contro l'Epilessia(145): 287-289.
18. Zeng, Q., et al. (2017). "[Analysis of SCN1A deletions or duplications in patients with Dravet syndrome]." Zhonghua Yi Xue Yi Chuan Xue Za Zhi 34(6): 787-791.

B21. In the model, the occurrence of adverse events is not accompanied with loss in QALYs. This seems implausible. Please adjust the model accordingly (e.g., based on De Kinderen et al.,[3])

The clinical trials have established a well-defined and consistent safety profile for CBD, which is considered to be well tolerated and manageable. 76% of AEs in the pooled safety set from controlled trials were reported as mild-to-moderate in severity. They were generally transient: 36% and 56% resolved within 4 and 14 weeks respectively. Furthermore, the majority occurred during the first 6 weeks: 82% of patients had ≥1 AE with onset in the first 6 weeks, versus 7% in weeks 7-14.

On this basis, the contribution to disutilities from AEs associated with CBD is likely to be small relative to those from worsening health states. Furthermore, AEs on CBD are happening against a background of those from drugs in the CCM basket, which may “dilute” their incremental impact. There are also no data from the literature on which to base disutility assumptions for the set of adverse events of special interest (AESI) identified for CBD. Therefore, AE disutilities have not been included in the model, and only costs captured.

Utility decrements for side-effects from De Kinderen *et al*. are based on their severity and not type of side-effect experienced. Therefore, it is not possible to apply these decrements to our analysis.

Costs and resource use

B22. Priority question: The company states that the decline in cognitive functioning in DS patients is likely associated with the symptomatic level of epileptic activity in early age, and patients in the convulsive seizure-free group were therefore not considered to be at risk of being institutionalised. However, cognitive functioning of these patients could still decline as a result of other aspects of DS, including non-convulsive seizures.

a. Please justify whether the assumption of convulsive-seizure free patients not being at risk to be institutionalised is appropriate.

b. Please include the institutionalisation risk and costs for this patient group in the cost effectiveness model.

B22a/b. As per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided. The assumptions for institutionalisation are updated in this analysis.

B23. Mortality costs were subdivided into costs associated with SUDEP and non-SUDEP deaths.

a. Please justify why no costs for SUDEP deaths were included in the cost effectiveness model.

b. Please elaborate on the methodology used to determine non-SUDEP costs (e.g. what were the questions asked) as well as the plausibility of the non-SUDEP costs that were included in the economic model.

B23a/b. SUDEP deaths are, by definition, sudden and unexpected. Clinicians reported that they usually occur at home, and incur no health resource (see separate document provided: “UK KOL interview reports - DS”). Therefore, no costs were included for SUDEP in the cost-utility analysis.

Regarding non-SUDEP deaths, we asked clinicians to describe the possible patient pathways where a complication could lead to death, such as status epilepticus, asphyxia, ventilator-associated pneumonia or drowning as described in the source for mortality rates in the model (Cooper 2016). See the separate document provided

("UK KOL interview reports - DS") for these findings. These health resource utilisation estimates have been carried through into the model for non-SUDEP deaths.

B24. Health-state unit costs and resource use were mainly based on expert opinion. In addition, the SLR for costs and resource use was restricted to English language only, and the methodology used to retrieve expert opinion on health-state costs and resource use was not provided in detail.

a. Please present the studies that were excluded based on language use in the SLR and elaborate per excluded study on whether it could potentially inform cost and resource use in the economic model.

.**b. Please provide more detail on the methodology that was used to derive health-state unit costs and resource use from expert opinion and elaborate on the plausibility of the obtained results for the UK context (e.g. unit costs and resource use related to visits, hospitalisation, rescue medicine and institutionalisation).**

B24a. Overall 18 studies were excluded based on language. Citations for these excluded abstracts are provided in the answer to question B20. None of these studies were relevant to inform utility values or cost and resource use for the economic model. See B20 above for the list of studies.

B24b. The report and questionnaire for UK KOL interviews is provided separately (see "UK KOL interview reports - DS"). Unit cost sources are shown on pages 83-86 of Document B.

B25. In the base-case analysis of the cost effectiveness model, patients receiving CBD had a 33% reduction in dose of concomitant AEDs. This assumption was justified by suggesting that some patients receiving CBD may benefit from this dose reduction of concomitant AEDs.

a. Please justify why a 33% dose reduction of concomitant AEDs was assumed in the company's base case by providing DS-specific evidence (e.g. from the pivotal trials) to support this assumption.

b. Please include a scenario assuming a 0% dose reduction of concomitant AEDs.

B22a/b. The reduction of one third of the dose was an estimate made by clinical experts in their feedback (see the separate document provided: “UK KOL interview reports - DS”). KOLs reported that physicians strive to use the lowest possible dose in an effort to reduce the drug burden and adverse events, and that the addition of CBD may provide that opportunity.

Nonetheless, as requested, we have incorporated a scenario analysis assuming a 0% dose reduction in the revised economic assessment and model. There is very little effect on costs.

Validation and transparency

B26. Priority question: The model is programmed in Visual Basic for Applications (VBA) with an Excel user interface. The variables used in the VBA code are not defined, nor linked to the company submission report. This severely hampers the transparency of the model.

a. Please provide a full list of all parameter names used in the model.

b. In addition, for each parameter in this list, provide the name used in the VBA code, the name used in the Excel sheet, cell reference in Excel sheet, a description, the value if applicable, se (standard error) and if applicable the corresponding name/description used in the company submission report.

The model used 333 names ranges. An additional Excel sheet was created in the model to report the description tables for all parameters, classified as follows:

- Parameters used in VBA calculations (Parameters defined in Modules A2_GetValuesInputs, A3_TransitionMatrix, A4_PatientTraces, A5_QALYTraces and A6_CostsTraces)
- Parameters used in Excel calculations (not used in VBA calculations)
- Parameters used to restore default values (not used in VBA calculations)

- Parameters used for user friendly features (not used in VBA calculations)
- Parameters used in DSA.

Please see [redacted] in the cost utility model for the list of parameters as requested.

B27. Priority question: The calculations of the results are not well documented. For instance, it is unclear why the cohort analyses (see for instance the worksheet "PM PLB") consist of multiple sections (e.g. rows 8:67, rows 71:130, rows 134:193 and rows 197:256), similar for the accompanying cost and effect calculation sheets (see for instance the worksheets "DQM PLB" and "DCM PLB").

a. Please explain why the cohort analyses consist of multiple sections (e.g. is this due to the different age categories).

b. For the "PM", "PM2", "DQM" and the "DCM" worksheets, it is often unclear what the columns (or numbers in the columns) actually represent (e.g. column A in the worksheet "PM PLB") and how these are exactly calculated (given the calculations are performed in VBA; see also previous question). Please provide a detailed explanation of what the columns in the "PM", "PM2", "DQM" and the "DCM" worksheets represent and how these are calculated.

B27a. The multiple sections represent the 4 age categories.

B27b.

"PM" worksheets

- Numbers in column A in worksheets "PM PLB", "PM CBD10" and "PM CBD20" represent the current age group of patients. As patients get older this number changes from 1 to 4.
- Columns B to V in "PM" worksheets represent the 21 different health states considered in the model. Column W represent the total number of patients in one cycle (i.e. one row).

"PM2" and "DQM" worksheets

- Columns B to AW in "PM2" and "DQM" worksheets represent the 21 different health states considered in the model. For each health state, the 3 columns represent the category of the number of days without seizures (i.e. ≤ 3 days, > 3 - ≤ 15 days and > 15 days). Labels have been added.

- Columns AX to BB represent the death health states.

"DCM" worksheets

- Columns B to ER in "DCM" worksheets represent the 21 different health states considered in the model. For each health state, the 7 columns represent the category of costs (i.e. Treatment Costs, Visit Costs, Hospitalisation Costs, Rescue Med Costs, Total Management Costs, AEs Costs and Societal Costs (=0)).

- The main macro of the model is in the module "A1_Main" and runs the following instructions:

    - For each age group (2-5, 6-11, 12-17 and 18-55 years)

    - For each treatment arm (CBD 10 mg + CCM, CBD 20mg + CCM and Placebo)

        1- Create the transition matrix

        2- Create the patient matrices (*patientMatrix* and *patientMatrix2*)

        3- Create the QALY matrices (*QALYMatrix*, *discQALYMatrix*, *QALYMatrix_CG* and *discQALYMatrix_CG*)

        4- Create the costs matrices (*costMatrix* and *discCostMatrix*)

        5- Print matrices to the corresponding worksheets ("PM", "PM2", "DQM", "DQM-CG" and "DCM")

1- A transition matrix, representing the probabilities for a patient to move from one health state to another, is calculated for the given age group and treatment arm. In VBA this matrix (variable *transitionMatrix*) is represented by an Array of 3

dimensions [*nbHealthStates*; *nbHealthStates*; *nCycles*]. The transition matrix is computed based on the data from the worksheet “Transition matrices” (the matrix TM and the list of transition probabilities TP). The list of transition probabilities is computed from the data defined in worksheets “# SEIZURES”, “DISCONTINUATION” and “MORTALITY”.

Based on TM and TP, the macro in module “A3_TransitionMatrix” creates one transition matrix per age group, treatment arm and model cycle.

2- The patient matrix (VBA variable: *patientMatrix*) lists the number of patients in each health state for each model cycle. It is represented by an array of 2 dimensions [*nCycles*; *nbHealthStates*].

In Module “A4_PatientTraces”, one patient matrix is calculated by age group and treatment arm.

The patient matrix is initialized (Cycle 1) with the frequency of seizures at baseline. Patients are placed in health states 3 (SeizureCat1 1st cycle, column D), 5 (SeizureCat2 1st cycle, column F) or 7 (SeizureCat3 1st cycle, column H). The number of patients in other health states is set to 0.

For each following cycles, the number of patients is calculated by multiplying *patientMatrix*(iCycle - 1) with *transitionMatrix*(iCycle). Patients who discontinue treatment are assumed to revert to the baseline seizure rates after 1 cycle. Similarly the placebo effect is stopped after 1 cycle and patients are assumed to revert to baseline efficacy and continue to experience baseline efficacy for the remaining duration of the analysis.

The result is printed in the corresponding “PM” worksheet.

patientMatrix2 lists the number of patients in each health state (x3 for each category of number of days without seizures [≤ 3 days, > 3 - ≤ 15 days, > 15 days]) for each model cycle. *patientMatrix2* is an array of 2 dimensions [*nCycles*; *(nbHealthStates - 5) x 3 + 5*]. (Each health state is multiplied by 3 to have the 3 days categories; the 5 health states related to death are not multiplied by 3.)

patientMatrix2 is initialized with the frequency of seizures at baseline and the frequency of number of days without seizures at baseline. The number of patients in other health states is set to 0.

For each following cycles, the number of patients is calculated by multiplying *patientMatrix* with *daysInputs*. The VBA variable *daysInputs* lists the number of days without seizures as defined in worksheet "# DAYS".

The result is printed in the corresponding "PM2" worksheet.

3- The QALY matrix contains the total QALYs per cycle and per health state. In Module "A5_QALYTraces", one QALY matrix is calculated by age group and treatment arm. The VBA parameter *QALYMatrix* is represented by an array of 2 dimensions [*nCycles*; *(nbHealthStates - 5) x 3 + 5*].

QALYMatrix is calculated by multiplying *patientMatrix2* with *utilityVector*. The VBA variable *utilityVector* lists the utility values associated with each health states as defined in worksheet "UTILITIES".

The discounted QALYs (VBA variable *discQALYMatrix*) are calculated by multiplying *QALYMatrix* with the outcomes discount factors.

The result is printed in the corresponding "DQM" worksheet.

discQALYMatrix_CG is calculated in the same but using caregivers' decrements of utilities instead of patient utilities.

The result is printed in the corresponding "DQM-CG" worksheet.

4- The cost matrix contains the total costs per cycle and per health state. In Module "A6_CostsTraces", one cost matrix is calculated by age group and treatment arm. Costs are split into 7 different categories (Treatment Costs, Visit Costs, Hospitalisation Costs, Rescue Med Costs, Total Management Costs, AEs Costs and Societal Costs (=0)).

The VBA variable *costMatrix* is calculated by multiplying *patientMatrix* with *costVectors*. The VBA variable *costVectors* contains all unit costs per patient. It is

computed from the data defined in worksheets “COHORT DEFINITION”, “SAFETY” and “COSTS”.

The *costMatrix* is then multiplied by the costs discount factors to obtain the discounted costs matrix (VBA variable *discCostMatrix*).

The result is printed in the corresponding “DCM” worksheet.

B28. Questions related to the implementation of the probabilistic sensitivity analysis (PSA):

a. Transition probabilities were included in the PSA using a bootstrapping method. This was justified by the company by stating that the movement of patients between the different health states are interdependent, and all transition probabilities would have to be changed simultaneously in order to ensure clinically meaningful results. However, bootstrapping is not the recommended approach to incorporate interdependent transition probabilities (see for instance Briggs et al.,[4]). Please, provide an updated version of the economic model, incorporating the transition probabilities in the PSA by sampling from the Dirichlet distribution.[4]

b. The PSA run time is vastly longer than would be expected (given it is a cohort simulation and has a relatively simple model structure). Please speed up the PSA run time (e.g. by removing all components from the VBA code that are not essential to run the PSA).

c. The company provided a model file restricted to a maximum of 1,000 PSA iterations. Please justify that 1,000 simulations or 500 (as used by the company) are sufficient to provide stable results. Alternatively, increase the maximum allowed iterations to enable PSA analyses that provide stable results.

d. Based on company submission Table 38 some parameters (e.g. non-SUDEP costs) are not included in the PSA. Please include all relevant parameters in the PSA.

B28a. The bootstrapping method was preferred to the Dirichlet distribution as the transition probabilities are not only interdependent, but also time dependent. Indeed, we have 9 sets of the transition probabilities covering the trial data. We are sampling with replacement and running [redacted] samples to get a reasonable approximation of the "true" sample population mean and variance. The sampling of the patients is done at the trial initiation, avoiding oversampling. A Dirichlet distribution would assess the uncertainty around transition probabilities at each time point, but without considering the previous cycles. We would have used the Dirichlet if only one set of transition probabilities by treatment arm was used.

B28b. The PSA running time has been decreased by setting the Excel calculation mode to manual (instead of automatic) where necessary.

B28c. We have increased the simulation number to [redacted]. With the observed shape of this new distribution in the cost-effectiveness plane, we are confident of the stability of the PSA analyses.

B28d. The parameters that had a minor impact on the results were not included in the PSA.

The cost of ICU is included in the updated PSA, which directly impacts the non-SUDEP costs.

B29. Questions related to the scenario analyses:

a. The deterministic sensitivity analysis in which the impact of long-term discontinuation was examined is relatively favourable for CBD (e.g. low discontinuation rates; 0.93% for 2-11 years and 0.00% for 12-55 years). Please add a scenario in which higher discontinuation rates are assumed (e.g. 1.33% for 2-11 years and 1.33% for 12-55 years).

b. When performing PSA analyses of scenarios (i.e. with different parameter values than the base-case), the adjusted parameters are automatically changed back to the default (i.e. base-case) values before starting the PSA. Please provide instructions on how to adjust (default) parameter values to be used in the PSA.

B26a. As per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided. The assumptions for treatment discontinuation rates are revised in this new model.

B26b. No parameters are changed back to default values before running the PSA. Please note that uncertainty parameters are only relevant for the current base case values. If you decide to change the base case values, you will need to update the PSA parameters (green cells in columns G to O) before running the PSA.

B30. Priority question: The cost effectiveness model has a 15-year time horizon. The base-case total QALYs, as reported in company submission Table 34, exceed this time horizon (i.e. are larger than 15). This is not plausible and brings into question the internal validity of the model.

a. Please explain how the calculated QALYs can exceed 15.

b. Please correct this error in the cost effectiveness model and provide updated results of the results presented in the company submission (company submission sections B.3.6, B.3.7, B.3.8 and B.3.9).

c. Please provide a detailed description of the internal validation performed (e.g. what specific steps / tests are performed), ensuring that the model is internally valid.

B30a/b. As per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided.

B30c. An overview of the QA checks performed on the revised model and economic analysis are included in a separate document ("QA Checks").

For the revised model, we used two modellers, one who developed the VBA code, and one who verified the VBA code and ran the standard QA process. The VBA modeller will carry out their own QA before the model is handed over to the second modeller for the formal QA process. An external QA has also been performed on the face-validity, input assumptions and VBA coding.

B31. The cost effectiveness model has a 3-month cycle time. In this company submission this is justified by stating: "The model was based on a cycle length of 3 months as the clinical outcomes in the Phase 3 trials for DS (GWEP1332 Part B and GWEP1424) and the open-label extension study (GWEP1415) were reported at 12-week intervals." However, 3 months represent 13 weeks (i.e. 365.25 / 7 / 4) and the Phase 3 trials for DS consists of a 14-week treatment period (2 weeks of dose escalation and 12 weeks of dose maintenance).

a. Please clarify that the input parameters (e.g. transition probabilities, utility values, resource use and costs) are consistent with the 3 months cycle time.

b. Please elaborate on the implications if the input parameters are not consistent with the 3 months cycle time.

B31a/b. The 3-month transition probabilities were assessed based on a 14-week treatment period (from the Phase 3 trials) and on 12-week assessment periods from the extension study. This was considered as a sufficient estimation of how patients will transition over a 3-month period (±1 week).

Resource use was adjusted to reflect a 3-month period based on what was reported by the clinicians (they either used an annual reference, or a 6-month reference). Annual mortality rates were also all adjusted to a 3-month period. Annual utilities obtained from the vignette study are adjusted for 3-monthly cycles.

Section C: Textual clarification and additional points

Missing documents

C1. Priority question: Please provide all tables and appendices for the clinical study reports (CSRs) of GWPCARE1 and GWPCARE2.

Full CSRs with tables and appendices are provided.

C2. Priority question: If a full CSR is not available for the ongoing open-label extension study (GWPCARE5), please provide the study protocol and all available results to-date (not just the published conference abstracts).

The CSR for the interim analysis of GWPCARE5 is provided.

C3: Priority question: Please provide a new copy of the evidence submission, ensuring that all references are numbered correctly and that they refer to the correct PDFs. We note, in table 44, all references after McCoy (93) are incorrect, as are subsequent PDFs. Please ensure that all PDFs of references are provided.

The updated version with Table 44 corrected is provided as a separate document.

References

[1] Laux L, Bebin M, Checketts D, Chez M, Flamini R, Marsh E, et al. *Long-term safety and treatment effect of cannabidiol in children and adults with treatment-resistant Lennox-Gastaut Syndrome or Dravet Syndrome: expanded access program (EAP) results (Abst. 1.434) [Word document supplied with the company's submission]. Poster presented at the American Epilepsy Society; 1-5 December 2018; Washington: US* 2017

[2] Versteegh MM, Brouwer WBF. Patient and general public preferences for health states: a call to reconsider current guidelines. *Soc Sci Med* 2016;165:66-74.

[3] de Kinderen RJ, Wijnen BF, van Breukelen G, Postulart D, Majoie MH, Aldenkamp AP, et al. From clinically relevant outcome measures to quality of life in epilepsy: a time trade-off study. *Epilepsy Res* 2016;125:24-31.

[4] Briggs A, Claxton K, Sculpher M. *Decision modelling for health economic evaluation: handbooks for health economic evaluation*. Oxford: Oxford University Press, 2006.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Epilepsy Action
3. Job title or position	Senior Policy & Campaigns Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Epilepsy Action is the UK's leading epilepsy organisation and exists to improve the lives of everyone affected by the condition. As a member-led organisation, we are led by and represent people with epilepsy, their friends, families and healthcare professionals. Epilepsy can affect anyone at any age and from any walk of life. Epilepsy Action is funded by individual donations from members and supporters. As of November 2018 Epilepsy Action has 9,917 members.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Email communications to relevant members and supporters.** **Social media requests – Twitter and Instagram.**

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	It became clear from the responses we received from carers and parents that caring for a person with Dravet syndrome is often incredibly challenging. This is due in large part to the high needs of people with Dravet syndrome. These needs centre on the number and severity of seizures associated with Dravet syndrome. One parent carer noted that their son experiences a variety of seizure types up to 50 times day. 'He experiences tonic clonic, focal, partial and absent seizures (sometimes 30-50 of these per day)'. They went on to highlight the severity of some of these seizures and the associated risks – '[their son] is hospitalised every 5 weeks on average due to a prolonged seizure'. During these hospitalisations, their son will often have to be intubated and placed in PICU at the children's hospital. Another carer whose son has Dravet syndrome noted that he required '24 hour care and 24 hour monitoring for seizures'. The severe needs of many people with Dravet syndrome can have a major impact of the personal life of parents, carers and other family members. These include financial pressures, strain on relationships and an impact of the health of parents and carers. One parent carer noted that 'the first thing I had to do on [his son's] diagnosis (at 8 months) was give up work. My wife had to extend her maternity leave. Immediately we took a huge hit financially.' It is not just financial pressures, another parent carer highlighted the impact of caring for a child with Dravet on their own health and family life noting that 'it has been a real toll on our health and family life'. This was echoed by other respondents, 'we haven't had a night out in over two years, we live in darkness, and communicate in whispers for fear of waking [their son] up.' The same parent carer went on to note that the burden of caring for their son has made them suicidal. Another parent carer noted the intense medication regime that their child required and the potential consequences if a mistake is made with administering the medications. 'Each morning, it's so important that we administer the correct AEDs as we are aware of the consequences if this doesn't happen. Having 3 AEDs, morning and night, plus a 3-day course of antibiotics each week, is now set as a routine'. The

	potential impact of Dravet syndrome was also succinctly noted by another parent carer, 'SUDEP is never far from our thoughts'.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There was a mixed response from parents and carers to this question. Two respondents were pleased with the current treatments and care provided by the NHS. One parent carer was particularly pleased with the community care provision – 'At-home care services were exceptionally good.' Another parent carer highlighted the quality of healthcare professionals involved in their child's care and the availability of new treatments – 'we have seen very good doctors and neurologists who are quick to prescribe new treatments or refer for specialist care!' Another parent carer thought that current treatments available on the NHS were 'limited'. A similar point was made by another parent carer who noted that 'there are generally wider available treatments available in the [United] States especially that I think could benefit [my child].' The same parent highlighted that they are yet to seen an Epilepsy Specialist Nurse despite (ESN) their child being diagnosed with Dravet syndrome two and a half years ago.
8. Is there an unmet need for patients with this condition?	A variety of responses and opinions were shared in response to this question. One parent carer categorically stated 'yes [there is an unmet need for patients with this condition] because it is rare and patients present differently.' Two respondents commented on the time it takes for new treatments and medicines to be licensed and subsequently made available to patients. One parent carer said 'I certainly feel that, as an advanced country with medicines, we could be approving and allowing trials of medications a lot quicker.' This view was echoed by another parent carer – 'whilst I understand that various tests have to and should be carried out, it takes too long for new treatments to be licensed and available for patients.'

	A respondent also highlighted issues with the time it took to access appropriate at-home care. They noted that 'in our experience it took too long for the at-home care to care kick in…over a year!'
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	One parent carer noted that they are currently trying CBD at home without a prescription (no additional information was provided about form, strength or dosage) – '[CBD] has helped with sleep and spasms and [we] have seen a reduction in seizures'. They went on to highlight that they believe cannabis-based treatments are working for children in the United States. Another parent carer had similar opinions and although they did not specify whether they had used CBD, they said that 'I personally think that CBD would benefit my [child]'. They went on to add that this assumption was based on personal research into this technology – 'looking at statistics, results and public feedback from other users of CBD, this is certainly something I would like for him to try as an add-on treatment.' The same parent also noted an apparent lack of severe side effects as an advantage of the technology - 'if there is a treatment option available for anyone that doesn't have severe side effects, they should have the option to have it made available.' The same respondent noted earlier that their child is currently taking a number or AEDs on a twice daily basis, a weekly 3-day course of antibiotics and rescue medications (Buccal Midazolam) when needed. It is the opinion of Epilepsy Action that there is some, albeit limited, good quality clinical evidence, including placebo controlled trials that have shown cannabidiol as safe and efficacious as an adjuvant treatment for seizures associated with Dravet syndrome. In light of available clinical evidence, the often uncontrolled and severe nature of seizures associated with Dravet syndrome and the increased risk of premature mortality associated with this high seizure frequency and severity, Epilepsy Action believes this technology should be made available in the capacity set out in the terms of this appraisal.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The parent carer who is currently trying CBD for their child at home raised concerns about the currently available, unlicensed CBD products. They noted that at present 'the compounds available are not pharmaceutical, exact compositions and dosages are not known, no certainty of product quality.' Another respondent who cares for their child with Dravet was sceptical about the efficacy of CBD for the treatment of seizures associated with the syndrome. They highlighted that a neurologist was 'sceptical about them [CBD] being beneficial for [my child]. I suspect he was sceptical about there use in general.' The same respondent also referenced clinical trials of Fenfluramine and the potential benefits that this adjunctive treatment had shown for people with Dravet. Another parent raised a similar point about scepticism around CBD as an adjuvant treatment for seizures associated with Dravet, this was also informed by the apparent scepticism of some clinicians to this technology. They noted 'Doctors and specialists are sceptical about it and I don't blame them!'
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	N/A

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**N/A**
Other issues	
13. Are there any other issues that you would like the committee to consider?	In light of the inherently political nature of the UK debate around cannabis derived medicinal products, including cannabidiol, necessary consideration should be given to this during the appraisal process and as part of any next steps. Half of the parent and carer responses received by Epilepsy Action (two out of four) note an apparent scepticism shown by clinicians towards this technology. In light of this, if the appraisal is successful, consideration should be given to ensuring relevant clinicians are adequately informed and supported around prescribing this technology where it may be beneficial.
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: • Dravet syndrome is a severe and complex condition that can make life very difficult for patients, carers and families affected.	

- Half of the parents and carers we spoke too (two out of four) currently use or would like to try cannabidiol as an adjunctive treatment for seizures associated with Dravet syndrome.
- Important to further explore potential side effects of this technology and compare their severity, if any, to those of existing treatment options.
- Half of the parents and carers we spoke too (two out of four) noted the scepticism or concerns expressed by medical professionals in relation to this technology.
- The necessary focus on cannabidiol as an adjuvant treatment for seizures associated with Dravet should not come at the expense of other emerging technologies and treatments.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Neurologists (Epilepsy Advisory Group)**

3. Job title or position	**Professor of Neurology, Honorary Consultant Neurologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists is a non for profit membership association for Neurologists whose mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	Prevention of seizures and their consequences. There are many other comorbidities in Dravet Syndrome (cognitive impairment, behavioural difficulties, speech and swallowing difficulties, deterioration in gait etc), some of which, such as cognitive function, may be partly influenced by seizure frequency. We do not understand the full causation of many of the associated comorbidities.

disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The ideal is freedom from seizures, but this is rarely achieved with current treatments. Cessation of generalised tonic-clonic seizures (one type of seizure seen in this condition) has benefits, for example in reduction of risk of sudden death. Cessation of episodes of status epilepticus is also of value. The commonly used measures of a50% reduction in frequency of seizures, or types of seizures, though of undoubted help, should be acknowledged to be the arbitrary measure it is, and does not necessarily reduce risks (eg of sudden death) or improve quality of life
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – most patients with Dravet Syndrome do not become seizure-free with currently available treatments
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Primary treatments: antiepileptic drugs (AEDs) Ketogenic diets and vagus nerve stimulation also considered
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE cg137

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is not a well-defined pathway for care of all aspects. NICE cg137 offers some guidance on drug treatment: 1.9.9 Pharmacological treatment ofDravet syndrome *First-line treatment in children with Dravet syndrome* 1.9.9.1 Discuss with, or refer to, a tertiary paediatric epilepsy specialist when a child presents with suspected Dravet syndrome. [new2012] 1.9.9.2 Consider sodium valproate or topiramate[15]as first-line treatment in children with Dravet syndrome. Follow the MHRA safety advice on sodium valproate. [2018] *Adjunctive treatment in children, young people and adults with Dravet syndrome* 1.9.9.3 Discuss with a tertiary epilepsy specialist if first-line treatments (see recommendation 1.9.9.2) in children, young people and adults with Dravet syndrome are ineffective or not tolerated, and consider clobazam[15] or stiripentol as adjunctive treatment. [new 2012] 1.9.9.4 Do not offer carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new2012]
• What impact would the technology have on the current pathway of care?	An additional drug to be tried as adjunctive therapy
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, as another AED
• How does healthcare resource use differ	Should not be different – is another AED, potentially with a different mechanism of action.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nothing specific – it will be another antiepileptic drug, so same investment as needed for a typical such drug.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There are limited data, including an RCT (Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S; Cannabidiol in Dravet Syndrome Study Group. N Engl J Med. 2017 May 25;376(21):2011-2020), and an overview of cannabidiol in general (J Neurol Neurosurg Psychiatry. 2018 Jul;89(7):741-753.)
• Do you expect the technology to increase length of life more than current care?	Yes, if seizure freedom is achieved.
• Do you expect the technology to increase health-related quality of	Yes, if seizure freedom is achieved.

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The group (patients should have Dravet Syndrome) has already been selected - adults and children are both suitable candidates, neither should be excluded on age grounds alone.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional	It will require monitoring (eg of liver profile) and may require dose adjustments for co-prescribed AEDs. Its use will need the level of monitoring typically employed with a new AED with known adverse reaction profile. Its teratogenic and neurodevelopmental toxicity profiles in humans will need consideration. Like all AEDs, there are adverse reactions that may limit use.

tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	See 13 for additional tests. The same rules should be in place as for any other new AED. Its place in the treatment pathway will only become clear with time as it is actually used for people with epilepsy due to Dravet Syndrome as for any other AED.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Anecdotal reports suggest improvement in features such as alertness. There is insufficient information to be clear about such aspects currently. A reduction in risk of sudden death may ensue if seizure freedom (especially from generalised tonic-clonic seizures) is achieved.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes as judged by RCT evidence.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No, it is another antiepileptic drug.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, as per Q8
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This was partly addressed in the RCT: "Adverse events that occurred more frequently in the cannabidiol group than in the placebo group included diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests. There were more withdrawals from the trial in the cannabidiol group." (Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S; Cannabidiol in Dravet Syndrome Study Group. N Engl J Med. 2017 May 25;376(21):2011-2020)
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, reasonably, except that the inclusion criteria included a particular threshold for generalised tonic-clonic seizures, and only people up to the age of 18 were included.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in frequency of seizures, especially convulsive seizures – these were measured in the trial
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the	These are too limited/biased for cannabidiol to give a reliable opinion

trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Dravet Syndrome affects all populations and ages and treatment availability should not be restricted to any particular subgroup within the population of patients with Dravet Syndrome
22b. Consider whether these issues are different from issues with current care and why.	No difference.
Key messages	
24. In up to 5 bullet points, please summarise the key messages of your submission. • CBD adds to the treatment options for Dravet Syndrome • Freedom from convulsive seizures is a valuable achievement in this syndrome • CBD has not been compared directly to other AEDs yet • CBD needs to be considered and treated like any other AED •	

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NICE National Institute for Health and Care Excellence

Template for NHS England submission

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

NHS England statement

Cannabidiol for adjuvant treatment of seizures associated with:

- **Dravet syndrome [ID1211]**
- **Lennox-Gastaut syndrome [ID1308]**

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

Background

1. Dravet and Lennox-Gastaut syndromes are rare and devastating forms of epilepsy that present early in childhood. They result in progressive dysfunction of the brain with associated cognitive and behavioural difficulties that prevent children from achieving independence in adult life. This has a profound impact on the quality of life experienced not only by those with the syndromes but also by their families and carers. In England, it is estimated that there are 3,000 people with Dravet syndrome and 5,000 people with Lennox-Gastaut syndrome.

2. Dravet syndrome is primarily a clinical diagnosis, although patients often have an associated genetic mutation in the SCN1A (sodium channel) gene. It manifests with seizure onset in the first year of life, often prolonged in duration and triggered by fever. In the second year of life, the child demonstrates a range of seizure types that are difficult to treat. Over time, there is progressive neurological, cognitive and behavioural decline. The mortality rate is approximately 15% before adult life as a result of recurrent status epilepticus or sudden unexpected death in epilepsy (SUDEP).

3. Lennox-Gastaut syndrome is a clinical condition characterised by: multiple seizure types, often refractory; frequent moderate to severe cognitive impairment and a distinctive electro-encephalographic (EEG) pattern. The causes of Lennox-Gastaut are broad, including hypoxic ischaemic brain damage, genetic disorders, neuro-cutaneous disorders and various infections. Sometimes, no cause is identified. The age at onset is around 2-3 years of age, after previous normal development, or it may evolve from a previous earlier presentation with infantile spasms. The range of seizures varies widely, are usually frequent and difficult to treat. The most common type is the atonic seizure, or drop attack, that can occur many times a day resulting in suddenly falling to the floor and causing subsequent injury. Children with Lennox-Gastaut syndrome have neuro-developmental slowing that develops into severe intellectual disabilities.

4. The most common treatment used to treat epilepsy in UK clinical practice is anti-seizure medication (known as anti-epileptic drugs, AEDs). According to NICE clinical guideline 137, the AED treatment strategy should be individualised according to the epilepsy syndrome, seizure type, co-medication, co-morbidity, the person's lifestyle, and the preferences of the person and their family and/or carers. People with either Dravet syndrome or Lennox-Gastaut syndrome should have specialist input into their management.

5. A high proportion of patients with either Dravet syndrome or Lennox-Gastaut are often on a variety of AEDs reflecting the complexity of the conditions and are termed drug-resistant epilepsies. The International League Against Epilepsy define drug-resistant epilepsy as failure of adequate trials of two tolerated, appropriately chosen and used AEDs (whether as monotherapies or in combination) to achieve sustained seizure freedom.

6. Non-pharmacological treatment options include a ketogenic diet, vagus nerve stimulation and various other surgical procedures such as a surgical resection of an abnormal area of brain or performing a corpus callosotomy (a surgical procedure that disrupts the connection between the left and right sides of the brain to prevent the spread of abnormal electrical activity).

7. Epidiolex® is a liquid formulation of pure plant-derived Cannabidiol (CBD), with <0.1% □9-THC (tetrahydrocannabinol), that has been assessed for the treatment in two rare and difficult to treat childhood-onset epilepsy disorders: Dravet syndrome and Lennox-Gastaut syndrome. Epidiolex® has shown some benefit in the treatment of these two syndromes, with few side effects over and above appetite suppression and diarrhoea. Epidiolex® is currently unlicensed for treating any type seizure in the England but its use in refractory seizures associated with Dravet syndrome and Lennox-Gastaut Syndrome is under further evaluation with the European Medicines Agency.

8. The decision to start cannabidiol must be discussed with a tertiary paediatric or adult epilepsy specialist within a specialised neurosciences centre.

9. The commissioned services should collect outcome data locally on this treatment modality and provide an annual report on numbers

treated and outcomes and upload this to the Quality Surveillance Information System (QSIS) at NHS England. This should include:

- The number of patients started on cannabidiol
- The dose of cannabidiol that patients are using
- Change in seizure frequency
- Reductions in concomitant medication(s)
- Adverse events

10. Clinicians will be required to register patients with the NHS Blueteq system to develop an auditable trail of whom and how many people are using CBD and to ensure that the starting and continuation criteria are being met.

11. The view of NHS England is that the clinical trial data is generalisable to the UK population.

Implementing a positive NICE recommendation

NICE recognises that in the event of a positive recommendation, more prescriptive clinical commissioning criteria for treatments commissioned via Specialised Services will be implemented by NHS England to ensure appropriate use within the NHS.

NHS England is responsible for ensuring that the final clinical commissioning criteria are aligned with final guidance (section 1 – recommendation and section 3 – committee discussion).

Draft commissioning criteria

12. If cannabidiol for treating Dravet's or Lennox Gastaut Syndrome is recommended for use within its marketing authorisation, NHS England proposes to use the following commissioning criteria:

If this technology is recommended for routine commissioning in a subpopulation or with certain specifications (for example, a treatment continuation rule), the final commissioning criteria will reflect these conditions.

13. NHS England will expect stopping and/or continuation rules to be part of the recommendations. If that is not the case then the following will be put in place as part of the Blueteq application:

Criteria for continuation of cannabidiol:

Cannabidiol treatment could continue, if at least one of the following criteria are met:

- If the frequency of all countable seizures has reduced by 25% based on seizure diaries collected by patients, parents or carers OR
- If the frequency of target seizure types (i.e. drop seizures in Lennox Gastaut syndrome, convulsive seizures in Dravet syndrome) have reduced by 30% compared to baseline.

Criteria for stopping cannabidiol:

- If the continuation criteria are not met OR
- If unacceptable toxicity or side effects with cannabidiol is experienced OR
- If derangement of liver function tests is encountered after the commencement of cannabidiol, specifically:
    - a greater than three times increase in transaminases AND
    - above two times increase in serum bilirubin AND
    - without an alternative explanation for these increasing levels

Issues for discussion

14. None – SPC is not currently available

Issues for decision

15. NHS England would wish the committee to discuss and agree specific starting criteria which will be slightly different for the two syndromes and specific continuation and stopping criteria as part of their recommendations.

Equality

16. No equality or diversity issues were identified when considering the implementation of the proposed commissioning criteria (see section 4) in clinical practice.

Author: [redacted], NHS England

23/04/2019

NICE National Institute for Health and Care Excellence

Patient expert statement

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Galia Wilson**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☒ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Dravet Syndrome UK
4. Did your nominating organisation submit a submission?	☐ yes, they did ☒ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☒ I have other relevant personal experience. Please specify what other experience: *Chair of Dravet Syndrome UK Charity* ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	My son Arlo was born in late October 2007, on his due date. He was a good size and we were thrilled to meet our little boy and take him home. For our first Christmas, we went to my parents' and spent a wonderful day with the family. On Boxing Day, Arlo woke up and wasn't himself, he had a cold, was very clingy and sleepy. I knew something wasn't right, so when I went to have a shower I asked my husband to stay with him rather than just listen through the baby monitor. While I was in the shower Arlo had his first tonic clonic seizure (a type that affects the whole brain) – it lasted 20 minutes. At first, my husband asked my mother if his shaking was normal. She turned as white as a sheet and said 'no!'. We called an ambulance. This was the first of our many trips to the hospital. There was no follow-up

	medical attention as a result of this first seizure; Arlo had used what the doctors called his 'get out of jail free' first seizure card, dismissing it as a one-off irregularity. Arlo continued to have what we later learned were called 'focal seizures'. His eyes would deviate to one side and I couldn't draw his attention. He had a seizure of this type about once a fortnight. The episodes would often last 30 minutes and I would take the bus up to the hospital, but by the time I was seen he had returned to normal. This recurred, until one day when he was five months old he had another tonic clonic seizure, this time lasting about 30 minutes. After this, Arlo started to be treated for epilepsy. He was sent for an EEG and MRI scans as well as blood tests. Our care was transferred to Great Ormond Street Hospital. They worked hard to establish a cause, and although they were very open with us at all stages, all of the presented possible causes were depressing. At this point all of his seizures were triggered by fever or infection and his temperature didn't have to be particularly high to cause a seizure onset. During this period, Arlo would suffer very serious seizures resulting in status epilepticus about once a month. Often these seizures would last for over an hour and a half. I have lost count of the number he endured. By the time Arlo was two, I had independently researched complex epilepsies and discovered Dravet syndrome. I became convinced that this was Arlo's condition. Receiving the official diagnosis of Dravet syndrome was neither quick nor easy. Arlo's doctors were convinced that he was still developing and therefore it couldn't be Dravet syndrome. After the genetic analysis of his blood revealed that he had an exon deletion in the SCN1A gene the doctors tried to say he had generalized epilepsy with febrile seizures plus (GEFS+). However, 18 months after his bloods were taken, when Arlo had just turned three and a half, we received a call from his

	consultant at GOSH who told us that Arlo had tested positive for the SCN1A gene mutation. He had an exon deletion. He did have Dravet syndrome! At first, the diagnosis was a relief. As strange as it may seem, to know the cause of these terrible seizures was a relief. One of our first actions was to contact the Dravet Syndrome UK charity. It was about a month before the annual Center Parcs trip so we thought we would go along and meet other families. Being surrounded by families whose children and teenagers had and were going through similar experiences and to compare notes and experiences was refreshing, enlightening and comforting. To these other families what we were going through wasn't weird, they simply understood. It also helped us come to terms with facing the future, and to learn a little of the anticipated progress of the condition. Arlo has always been a fussy eater and we were warned by his doctor that he may need a feeding tube at some point. We were horrified and in denial about the very prospect. But when he was five, he stopped eating altogether and had to have an emergency gastrostomy to fit a tube. I can categorically say that this was the single best decision we have made for him. It took away the stress and worry of him eating and in particular getting his medicine in him when needed. Especially after a rough night of seizures for him. Arlo started crawling at five months and was walking and talking by a year old. It wasn't until he was 14 months that I started to notice differences between him and his peers. By the time Arlo was two, it was clear that he wasn't developing at the rate of the other children. For us, this was one of the hardest parts of the condition to come to terms with. To see all his peers overtaking him and leaving him behind was extremely stressful. But it was only us that found it painful to realise he was on a different track to his friends, he was not bothered one bit. But we minded.

	There is a kind of grief associated with the discovery your child will never live independently. After meeting other families with Dravet, and once Arlo was in a safe and appropriate environment for him at his special school, we came to terms with the delay. Arlo is now 11, but is at the developmental stage of an 18-24 month old, his prolonged seizures have subsided, but he has seizures every night and is still awake for many hours each night. He is very onerous to care for and requires one-on-one care 24 hours a day, which is difficult to resource and relentless. We are very worried about how puberty will affect his seizures and behaviour and there is always lurking the latent risk of sudden unexpected death in epilepsy (SUDEP). But he is the most wonderful, happy, loving, funny boy. He enjoys watching his iPad, swimming and listening to nursery rhymes and trying to blow out candles on birthday cakes (whether or not it's his birthday). When he's happy he can't contain his joy and it spills out of him in the form of flapping his arms. He has a younger sister, Coco, who absolutely adores her older brother, she is now eight but he still calls her 'baby'. We love him! In addition to my story, I would to add that the condition does change and is progressive in many cases. It is unpredictable which makes caring very challenging. Living with the constant threat that your child might die, either from a seizure or SUDEP is terrifying and often the first thing a parent will do in the morning upon waking is to check that their child is still breathing. Living in a heightened state of emergency and never being able to switch off in case a seizure occurs, never knowing if it will be short, prolonged or fatal is something that no one will ever get used to.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Carers are always looking to improve the seizure control whilst balancing the drug side effects. Some children are better controlled than others but that can always change, the symptoms of the condition don't stay static for long. Better seizure control is paramount, and, as with most conditions, Dravet Syndrome is a spectrum disorder. It's complex and not everyone responds the same way to treatments. Therefore, most of the treatments and treatment combinations are on a trial and error basis, which is taxing on the children and the carers. Very few children/adults experience a seizure free existence. Most are on three AED's, each of which bring with them side effects such as suppression of appetite, aggression, insomnia, somnolence, etc. Many have tried the Ketogenic diet and VNS with limited success, again dependent on the child.
10. Is there an unmet need for patients with this condition?	Absolutely, there is a massive unmet need. As I have said above most children still have regular seizures. There needs to be more treatment options to improve control and to reduce the side effects. It is important to understand that Dravet Syndrome is not just seizures, the co-morbidities associated with the condition can often be harder to manage than the seizures. These include: • Anorexia • Insomnia • Gait and mobility issues • ASD/ADHD • SUDEP Side effects from treatments can increase some of the symptoms of the co-morbidities.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	There is great hope for this new treatment. Initially, there was much hype surrounding CBD and the fact that it will cure Dravet Syndrome. There was a lot of debate on forums a few years ago but over time that has subsided as the reality has proven it will not cure. There have been many very positive stories from our community about children becoming seizure free or improved seizure control. Resulting in their children being able to participant more in family life, some have described it as their children have woken up. But conversely there have also been people not noticing a difference or that that their child/adult was drowsy and not themselves. Like all Dravet medications it works for some and not for others. Most people would be willing to give it a go, who wouldn't if your child is having regular seizures and there was a possibility to have them better controlled?
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	• It not being efficacious • An increase in side effects • They won't be able to access the treatment – this is a big concern
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Any child/adult whose seizures aren't controlled could benefit from trying this new medication. Most of these child/adults have tried many drugs before and still have seizures. Any reduction in seizure activity is a benefit. For example, if you have a child who has 5 seizures a night and the medication is reduced that to 3 a night, that would be considered by a family to an improvement. Or a child was having daily seizures reduces to two seizures a week, then that would be considered a success.

	One thing that needs consideration is the reduction in length of seizure. For example a child who has three seizures a week and each seizure normally last 5 mins and after starting treatment they still have those three seizures week but they have been reduced down to 1 minute each, that is a huge difference. If a child had less seizures and side effects from medication it can positively affect their development and improve their comorbidities and ultimately improve their quality of life. Which can often be quite poor. It also will reduce the time they spend at hospital which will improve the lives of the whole family. Simply put, if seizure control can be achieved or improved it affect the whole aspect of looking after a child with this devastating condition.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	I think all is outlined above.
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement:	

• Seizure control is very poor in most people living with the condition • People living with Dravet Syndrome are in desperate need of more treatment options • Dravet Syndrome is not just seizures – co-morbidities can often be more a problematic to manage than the seizures • Dravet Syndrome is a devastating condition that effects the entire family • The hope is needed,….

Thank you for your time.

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……

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ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Declared competing interests of the authors

None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Marie Westwood acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Willem Witlox, Ben Wijnen, Steve Ryder, Titas Buksnys and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Kate Misso acted as information specialist, critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ABN	Association of British Neurologists
AE	Adverse events
AED	Anti-epileptic drug
BI	Budget impact
BIC	Bayesian information criterion
CBD	Cannabidiol
CCM	Current clinical management
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CG	Clinical guideline
CGIC	Caregiver global impression of change
CGICSD	Caregiver global impression of change in seizure duration
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
DS	Dravet syndrome
EEG	Electroencephalogram
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
ERG	Evidence Review Group
FDA	Food and Drug Administration
HR	Hazard ratio
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LGS	Lennox-Gastaut syndrome.
LYS	Life year saved
MAH	Marketing authorisation holder
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
mg	Milligram
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
OR	Odds ratio
PAS	Patient access scheme
PCT	Primary Care Trust
PRESS	Peer review of electronic search strategies
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
RCT	Randomised controlled trial

RR	Relative risk; risk ratio
SAE	Serious adverse events
SD	Standard deviation
SF-36	Short form 36
SGEs	Symptomatic generalised epilepsies
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SSW	Slow spike-wave
STA	Single technology appraisal
SUDEP	Sudden unexplained death in epilepsy
TEAEs	Treatment-emergent adverse events
TESAEs	Treatment-emergent serious adverse events
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
WTP	Willingness to pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population defined in the NICE scope is 'people with Dravet syndrome (DS) whose seizures are inadequately controlled by established clinical management'. The company extended the scope to 'people with DS where current clinical management is unsuitable or not tolerated'. This addition is consistent with the pathway outlined in the relevant NICE guidance (CG137).

The submission relied, primarily, on two randomised controlled trials (RCTs) (GWPCARE1 and GWPCARE2) of cannabidiol (CBD) (Epidyolex®) as an add-on treatment to current clinical management (CCM). Although the decision problem did not specify any age restriction and the expected licenced indication for Epidyolex® is for patients two years of age and older, neither of the key trials in the submission included adult patients (over the age of 18 years). Although DS has its onset in childhood, it is expected that patients will continue taking cannabidiol into adulthood.

The treatment pathway proposed by the company placed CBD as a third-line treatment (i.e. for patients who have inadequate seizure control with first-line and at least one adjunctive anti-epileptic drug (AED)). However, the baseline characteristics for GWPCARE1 and GWPCARE2 indicated that approximately 16% of participants included in these studies had previously tried and discontinued fewer than two prior AED. It should be noted that these patients may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled.

The description of the comparators in the company submission (CS) is in line with the NICE scope (established clinical management without cannabidiol), which may include combinations of: sodium valproate, topiramate, clobazam, stiripentol, levetiracetam, ketogenic diet and vagus nerve stimulation. The comparator used in the key trials (GWPCARE1 and GWPCARE2) was current clinical management (CCM), which includes various combinations of different AEDs. Different combinations of AEDs were not considered as separate comparators. It should be noted that the use of a 'mixed' CCM comparator assumes that the effectiveness of CBD does not vary with the combinations of AEDs to which it is added. The Evidence Review Group (ERG) questions the validity of this assumption.

The CS focused primarily on convulsive seizures as these were the primary outcome in the two main trials. Although mortality was investigated, the two main randomised trials were of 14 weeks' duration so could not provide long-term data on sudden unexpected death in epilepsy (SUDEP) and other deaths.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS identified two international RCTs of cannabidiol (GWPCARE 1, GWPCARE2) and an ongoing open-label extension study (GWPCARE5) as relevant to the submission. Both RCTs were conducted in patients aged 2 to 18 years with DS, whose seizures were incompletely controlled with previous AEDs and who had had at least four convulsive seizures per week in the past 28 days. The intervention was cannabidiol in addition to current clinical management (CCM) and the comparator was CCM without cannabidiol (i.e. CCM plus placebo). GWPCARE1 compared cannabidiol (20 mg/kg/day) in addition to CCM and CCM plus placebo. GWPCARE2 was a three-arm study, comparing two doses of cannabidiol (10 mg/kg/day and 20 mg/kg/day) in addition to CCM and CCM plus placebo. Both randomised trials had a dose escalation phase (14 days in GWPCARE1 and seven or 11 days in GWPCARE2) followed by a 12-week treatment period. GWPCARE1 included patients from the UK (three centres recruited 16 patients overall) but GWPCARE2 did not include patients from the UK.

GWPCARE1 had a total of 120 patients and GWPCARE2 198. Patients had used on average four or five prior anti-epileptic drugs (AEDs).

Patients in GWPCARE2, who received 10 mg/kg/day CBD in addition to CCM, achieved better convulsive seizure frequency outcomes than those who received CCM + Placebo ([redacted] A higher proportion of patients in the 10 mg/kg/day CBD group achieved at least a 50% reduction in convulsive seizures, during the treatment period, than in the placebo group ([redacted]). [redacted] patients in the CBD group of GWPCARE2 and [redacted] in the placebo group achieved freedom from convulsive seizures for the whole 14-week treatment period. Patients in the 10 mg/kg/day CBD group of GWPCARE2 experienced fewer seizures overall, during the 14-week treatment period, than those in the placebo group ([redacted]). Safety data appeared to indicate a pattern of gastrointestinal and 'tiredness'-related adverse events (AEs) in patients taking CBD, as well as a detrimental effect on markers of liver function. With respect to markers of liver function, the company noted that '*cases of raised liver transaminases resolved either spontaneously or with dose adjustments of CBD or concomitant AEDs'.* The rates of individual, treatment-related AEs were generally higher in the 20 mg/kg/day CBD groups than in the 10 mg/kg/day CBD group.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS included a systematic review of the evidence of CBD for DS. The submission and response to clarification provided sufficient details for the evidence review group (ERG) to appraise most of the literature searches. A range of databases were searched, and additional searches of conference proceedings and trials registers were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. Errors and omissions in the search strategies were queried during clarification, and as corrected strategies were not provided in the clarification response, the ERG remains concerned about potentially relevant missed evidence.

Although the CS included two international RCTs and an open-label extension study, there are some limitations in applying this evidence to UK practice. Firstly, as has been mentioned in section 1.1, the randomised trials did not include any adult patients. Secondly, the ERG notes that three UK sites recruited a total of 16 patients to GWPCARE1, and that GWPCARE2 did not have any UK patients. This is most relevant when considering the nature of background current clinical management, which is the comparator in the trials. Current clinical management is considered to be a 'basket' of choices of AED and although the company conducted a number of subgroup analyses based on the presence or absence of various AEDs, they assumed that there were no treatment interaction effects. The ERG questions this assumption.

In addition, a major limitation of the evidence is the small size of the data set relating to the 10 mg cannabidiol dose to be used in practice. Just [redacted] patients in GWPCARE 2 and none in GWPCARE1 received the 10 mg/kg/day dose (this trial compared 20 mg/kg/day CBD to placebo). In the open-label extension study, GWPCARE5, the average dose was [redacted] with patients receiving [redacted] making this study less relevant to the decision problem.

A further limitation was the short-term nature of the RCTs (14 weeks including a 1one to two-week titration followed by a treatment maintenance phase of 12 weeks). There is a lack of long-term efficacy and safety data particularly based on the 10 mg/kg/day CBD dose. Any observations of reduction in seizures in the short-term trials, particularly convulsive seizures, may not be sustained in the long-term and the effects on outcomes relating to mortality (especially SUDEP) are unknown. Any long-term or rarer adverse events for the 10 mg/kg/day dose are unclear.

1.4 Summary of cost effectiveness submitted evidence by the company

The company developed a cohort state transition model using Microsoft Excel®. The model consisted of five health states, that were mainly based on the convulsive seizure frequency and the number of convulsive seizure-free days.

In line with its anticipated marketing authorisation and the final scope issued by NICE, CBD was considered in the cost effectiveness model for the treatment of patients with DS who are aged two years or older and in whom the condition is inadequately controlled by the established current clinical management (CCM) in the UK.

In the CS, the base-case analysis utilises the maintenance dose of 10 mg/kg/day as the company assumes that the majority of patients will receive this dose in clinical practice.

The analysis takes an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was three months with a 15-year time horizon.

The main sources of evidence on treatment effectiveness are the pivotal clinical trials (GWPCARE1 and GWPCARE2) and the open label extension study (GWPCARE5). It should be noted that GWPCARE1 is not used in the base-case analyses, only in the scenario analyses that used CBD 20 mg/kg/day. These studies are used to obtain evidence for the frequency of convulsive seizures, number of days without convulsive seizures, discontinuation rates and adverse events for both CCM plus CBD and CCM. GWPCARE2 was mainly used to inform treatment effectiveness during cycle one, while GWPCARE5 (in combination with assumptions) was used for subsequent cycles. Moreover, treatment effectiveness was estimated separately for patient subgroups <12 years and ≥12 years. Long-term treatment effectiveness was extrapolated assuming a constant treatment effect by assuming that CBD patients remain in the same health state until CBD discontinuation or death.

Adverse events were based on a pooled analysis considering both the DS and Lennox-Gastaut syndrome (LGS) phase III trials (GWPCARE1, GWPCARE2, GWPCARE3 and GWPCARE4).

Health state utilities were estimated using patient vignettes using a visual analogue scale. Health state utilities were assumed to be treatment dependent due to differences in number of days without convulsive seizures between CBD and CCM. The impact of adverse events on health-related quality of life was not incorporated in the model.

The cost categories included in the model were costs associated with treatment (drug acquisition costs included concomitant therapies and costs associated with treatment-related AEs), health state costs and mortality costs. Unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and clinical opinion.

CBD resulted in higher costs and quality-adjusted life year(s) (QALYs) than CCM resulting in an incremental cost effectiveness ratio (ICER) of [redacted], the company's revised analysis, resulted in an ICER of £36,046.

The company performed face validity, internal validity and external validity checks.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The submission and response to clarification provided sufficient details for the ERG to appraise most of the literature searches. A range of databases were searched, and additional searches of conference proceedings and trials registers were conducted. Searches were carried out in accordance with the NICE

guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. Errors and omissions in the search strategies were queried during clarification, and as corrected strategies were not provided in the clarification response, the ERG remains concerned about potentially relevant missed evidence.

The ERG considered that the economic model and base-case analyses described in the CS only partly met the NICE reference case. Deviations from the NICE reference case included the restricted time horizon of 15 years and the method used to estimate utilities.

The main concern of the ERG related to the model structure was the assumption that patients receiving CCM transfer back to their baseline convulsive seizure frequency after the first cycle. The company clarified that this was done as a placebo effect was observed in both the GWPCARE1 and GWPCARE2 studies and argued it was not reasonable to assume that these effects would be sustained in clinical practice. The ERG disagrees with the approach as it may be the case that the placebo effect is also present in the CBD group (and hence is part of the demonstrated effects) and these patients do not transfer back to their baseline seizure frequency after the first cycle. Removing the placebo effect for CCM while not removing this for CBD would most likely induced bias (similar to that which might be expected with pre-post comparisons) and thus might result in an overestimated treatment effect for CBD.

The ERG had multiple concerns related to the estimation of treatment effectiveness in the CS. These issues mainly concerned the extrapolation of treatment effectiveness. Firstly, extrapolation of evidence from GWPCARE5, using CBD 20 mg/kg/day as maintenance dose (mean modal dose during treatment was [redacted]) to model the effectiveness of CBD 10 mg/kg/day beyond three months. It is debatable whether this evidence is representative for a CBD maintenance dose of 10 mg/kg/day. Secondly, the extrapolation after 27 months is uncertain due to the lack of evidence beyond this time period. After 27 months the company assumed a constant treatment effectiveness, i.e. assuming that CBD patients remain in the same health state until CBD discontinuation or death while assuming a constant CBD discontinuation probability. Thirdly, it is questionable whether the evidence can be extrapolated to patients aged 18 year above given the large majority of patients in the trials ([redacted] based on GWPCARE1 and GWPCARE2) is aged below 18 year. The uncertainty related to extrapolation is, in part, reflected in the ERG base-case ICER range.

Another source of uncertainty was the estimated health state utility values. In addition to the use of methodology that is not in line the NICE reference case, the (implicit) use of treatment dependent health state utility values is not considered appropriate by the ERG. Particularly for patients that, after CBD discontinuation, reverted back to their baseline frequency of convulsive seizures, the treatment benefit (compared with CCM) potentially induced by the difference in number of days without convulsive seizures between the treatments, is questionable.

The model validity and transparency can be regarded as a major limitation of the current assessment. Despite the company attempting to resolve validity issues (e.g. estimated QALYs that are larger than the time horizon) during the clarification phase, the ERG still considered the model validity of the revised model to be problematic. Particularly because the model failed to provide the expected results to internal validity tests performed by the ERG. For instance, changing the clinical effectiveness input parameters for CBD 10 mg/kg/day to the clinical effectiveness input parameters for CCM still resulted in a QALY benefit of 0.36 for CBD (while 0.00 would be expected). Accordingly, the ERG believes, there are fundamental problems with the economic model that potentially induce a QALY gain for CBD 10 mg/kg/day. Consequently, the cost effectiveness results, calculated using the economic model submitted by the company, lack credibility. Due to the complexity and limited transparency of the

model, the ERG was unable to satisfactory resolve these validation issues within the available timeframe.

Due to the abovementioned validity issues, the ERG considers the original CS ICER ([redacted] per QALY gained) as well as the revised base-case ICER submitted by the company (£36,046 per QALY gained, including QALYs gained by caregivers) as not credible given the validity issues and adjustments (to the model structure and inputs that were not requested by the ERG) made by the company.

The ERG base-case consisted of an ICER range reflecting the uncertainty surrounding the extrapolation of treatment effectiveness. The probabilistic ERG base-case indicated that the ICER, for CBD compared with CCM, would range between £76,013 per QALY gained (assuming a constant treatment effect after 27 months) and £477,476 per QALY gained (assuming no treatment effect after 27 months).

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

In the company base-case (probabilistic), the ICER of CBD compared with CCM was estimated to be [redacted] per QALY gained. However, this ICER was based on technically implausible QALY estimates and is, according to the ERG, not informative/seriously flawed. Similarly, the revised base-case ICER submitted by the company ([redacted]) should be interpreted with extreme caution given the validity issues and adjustments (model structure and input) made by the company. The ERG has incorporated various adjustments to the CS base-case (using the revised economic model with input parameters from the original CS as starting point). The ERG base-case consisted of an ICER range, reflecting the uncertainty surrounding the long-term extrapolation of treatment effectiveness. The ERG base-case (probabilistic) indicated that the probabilistic ICER, for CBD compared with CCM, would range between [redacted] per QALY gained and [redacted] per QALY gained. However, it should be reiterated that some of the abovementioned potential biases (model structure, validity) could not be explored by the ERG. Consequently, the ICERs reported are likely to be underestimations of the true ICERs.

2. BACKGROUND

In this report the ERG provides a review of the evidence submitted by GW Research Ltd. in support of cannabidiol, trade name Epidyolex®, for the treatment of patients with Dravet syndrome. In this section we outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken from section B.1.3 of the company submission (CS) with subsections referenced as appropriate.

2.1 Critique of company's description of underlying health problem.

The underlying health problem of this appraisal is Dravet syndrome, a severe form of epilepsy affecting children and adults.

Dravet syndrome, previously known as severe myoclonic epilepsy of infancy (SMEI), is a rare disease. The CS cited a prevalence of 0.4 in 10,000 people.[1] We note that at the time of designation of cannabidiol as an orphan drug the EMA accepted that Dravet syndrome affected fewer than 0.5 in 10,000 people in the European Union (EU).[2] Extrapolating this to a UK population gives approximately 3,300 people potentially affected by Dravet syndrome. Even among epilepsy patients the syndrome is rare.

The role of genetic mutation in Dravet syndrome is highlighted in the CS and the company cited sources indicating that *'70-85% of individuals with clinical features of DS test positive for mutations of the SCN1A gene*'.[1] We further add that in Dravet syndrome, the gene mutation nearly always arises spontaneously. However, some people with Dravet syndrome may have some history of febrile seizures or epilepsy in their extended family.[3]

The company explained that DS typically starts '*in the first year of life with prolonged, repeated clonic or unilateral seizures in developmentally normal children, associated in many instances (estimates range from 39-72%) with a fever*.' The company considered the development of multiple types of seizure over time. '*Patients with DS present with different seizure patterns, but most include combinations of severe convulsive seizures, including generalised tonic-clonic and clonic seizures, as well as myoclonic, atypical absence and focal seizures*.'[1]

The burden of disease was highlighted by the company '*Children with DS experience severe symptoms including prolonged convulsive seizures, resulting in emergency hospital visits.*'[1] The company detailed the cognitive, functional and neuromotor impairments that can arise with Dravet syndrome. The role of seizures on the development of the young brain was mentioned.

The company cited a DS mortality rate of 20% with most deaths occurring before the age of 10. They further stated that '*Patients with DS are at high risk of SUDEP and status epilepticus, which cause around a half and a third of deaths in DS respectively*'.[1] These data are from a review that found that 73% of deaths were before the age of 10. This review also provided a breakdown of cause of death based on 177 deaths: 87 (49%) SUDEP, 56 (32%) status epilepticus, 14 (8%) drowning/accidents, nine (5%) fatal infections and six (3%) other causes with the remainder unknown.[4]

The company stated that '*High seizure frequency is a significant predictor of early death (18), with persistent seizures strongly related to excess mortality (19). Standardised mortality ratios are especially high among those with convulsive seizures (20).*' The references cited are from general epilepsy populations. The company stated that '*Clinical opinion recommends that the most effective prevention strategy for death related to epilepsy, and especially SUDEP, is to reduce the frequency of seizures*'.[1]

The impact on family and caregivers is made explicit. '*DS is also associated with many consequences and comorbidities that can result in lifelong impairment, so that patients are completely dependent upon caregivers for daily activities.*'[1] The company referenced surveys including a European survey of caregivers of patients with DS which captured about 15% of the DS patient population under the age of 18 in France, Germany, Italy, Spain, and the UK.[5] This survey found that '*more than a third (34%) were unemployed, of whom 81% had given up their job due to their role as a caregiver.*'[1]

ERG comment: The company provided a good overview of the underlying health problem of Dravet syndrome illustrating the seriousness of the condition and its impact on patients and their families. The ERG checked the references provided to support the statements in the company submission. In general, these were appropriately referenced. Where citations did not match an alternative source was checked.

However the CS did not explicitly mention the stages of Dravet syndrome described by Dravet '(1) the febrile or diagnostic stage in the first year; (2) the worsening (preferred to ''catastrophic'') stage between one and five years: period with frequent seizures and statuses, behavioural deterioration, and neurologic signs; and (3) the stabilisation stage after five years: convulsive seizures decrease and occur mainly in sleep, myoclonic and absence seizures can disappear, focal seizures persist or decrease; mental development and behaviour tend to improve but cognitive impairment persists, although of variable degree.'[6] The stabilisation and decrease in convulsive seizures after five years is relevant to this submission.

There was brief mention in the CS of adolescence and adulthood in relation to nocturnal seizures and risk of SUDEP. However, it is important to emphasise that DS is not just a childhood condition. In October 2018 a US Dravet Syndrome Foundation survey found that 80% of children with DS survive to adulthood.[7] Therefore a high proportion of those eligible for cannabidiol are not fully represented in the main trials which included patients only up to age 18 years.

2.2 Critique of company's overview of current service provision

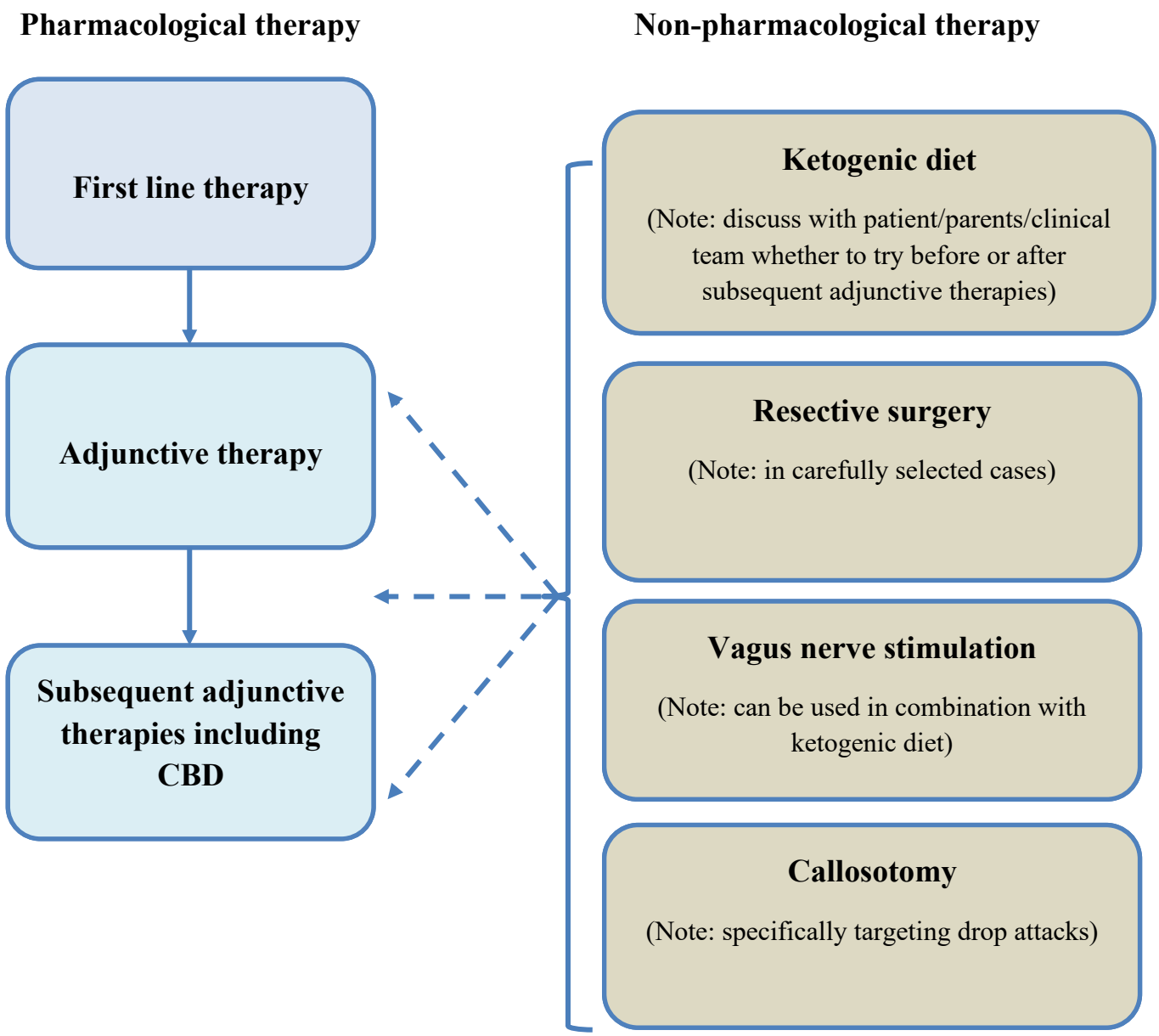
The main clinical guideline relevant to this submission is CG137. This NICE guideline (referred to in the CS) recommends consideration of sodium valproate or topiramate as a first-line treatment for DS and if seizures are inadequately controlled, clobazam or stiripentol as an adjunctive treatment.[8] The company also referred to a North American consensus panel set of recommendations[9] which are not discussed as they are less relevant to a UK population.

The company highlighted the current unmet need for treatment to reduce seizure frequency and severity and to improve the overall condition of patients with DS. This is due to existing medications being only partially effective. As part of the submission we received a statement from Professor Sisodiya from the Association of British Neurologists (Epilepsy Advisory Group) who stated that '*most patients with Dravet syndrome do not become seizure-free with currently available treatments*'.[10] In practice patients with DS need to take a combination of anti-epileptic drugs in an attempt to control their seizures. The company cited a study illustrating how physicians have '*to balance seizure control effectiveness, adverse event burden, and the side-effect profile of combinations*'.[11]

The place of CBD in the current pathway, according to the company, is as '*an add-on treatment for refractory seizures in people aged 2 years of age and older once two other appropriate AEDs, trialled to a maximum tolerated dose, have failed to achieve seizure-freedom*'.[1] Figure 2.1 shows the proposed treatment pathway for patients with Dravet syndrome.

The company stated that '*The introduction of cannabidiol in the DS treatment pathway aligns with current clinical management. No service design will be required.*'[1]

Figure 2.1: Proposed treatment pathway for DS including CBD (Source Figure 2 of CS)



ERG comment: The company's overview of the current pathway is appropriate. However the ERG asked a number of questions relating to the place of CBD in the pathway.[12] The questions are given below with the company's responses and our interpretation.

ERG question A2: The company has added to the population scope '*People with Dravet syndrome where current clinical management is unsuitable or not tolerated*'. Does this mean that CBD might be offered earlier in the pathway for this group than that shown in Figure 2 of the company submission?

Company response: *'No. This was added as it is in line with the recommendations in NICE Clinical guideline 137 (CG137). Patients may discontinue AEDs because of tolerability issues, not just lack of seizure control. In addition, certain AEDs are not suitable for DS patients. For example, NICE CG137 states that carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin should not be given to patients with DS as they may worsen seizures.*'[12]

ERG interpretation: The ERG agrees with the response provided and notes that the additional wording '*People with Dravet syndrome where current clinical management is unsuitable or not tolerated*' is consistent with the wording around recommendations for third-line AEDs in CG137.[8]

ERG question A3: Under 'Placement of CBD within the care pathway' (page 25 of the company submission) and at other points in the document, it is stated that: '*For patients with Dravet syndrome (DS) considered for treatment with CBD, it will be an add-on treatment for refractory seizures in people aged 2 years of age and older once two other appropriate anti-epileptic drugs (AEDs), trialled to a maximally tolerated dose, have failed to achieve seizure freedom*.'[13]

a. Does the above statement reflect a narrower use than the expected license?

Company response: '*No'*

ERG interpretation: The company did not elaborate on this response. However it appears to be inconsistent with the therapeutic indications stated in the submitted summary of product characteristics (SmPC), which does not include any limitation based on prior trials of other AEDs:'Epidyolex is indicated for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.' [10]

b. The above statement does not appear to be consistent with the eligibility criteria for GWPCARE1 and GWPCARE2 given in Table 5 (of the CS) (taking one or more AEDs). How many patients had one prior AED in each treatment arm of the two trials?

Company response: '*The number of patients at baseline in each arm of GWPCARE1 and GWPCARE 2 on 0, 1, and ≥2 prior AEDs is shown in the table below*.'

Table 2.1: Prior AEDs at baseline in GWPCARE1 and GWPCARE2

		Prior AEDs (no longer taking)		
		10 mg/kg/day	20 mg/kg/day	Placebo
	No. AEDs		n=61	n=59
GWPCARE1	0		5 (8.2%)	4 (6.8%)
	1		5 (8.2%)	5 (8.5%)
	≥2		51 (83.6%)	50 (84.7%)
GWPCARE2		n=64	n=69	n=65
	0	4 (6.3%)	2 (2.9%)	2 (3.1%)
	1	7 (10.9%)	7 (10.9%)	8 (12.3%)
	≥2	53 (82.8%)	60 (87.0%)	55 (84.6%)
Source: Clarification response, page 5[12]				

ERG interpretation: The ERG notes that the proportion of participants in the key trials, who had discontinued fewer than two prior AEDs was 16% in GWPCARE1[14] and was 15% in GWPCARE2.[15] The ERG considers that, with respect to prior AED treatments, the data of most (over 80%), but not all, of the trial participants clearly reflect the placement of CBD in the care pathway, as described in the CS. It should be noted that the remaining participants may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled.

We also asked a number of questions regarding the patient characteristics in the main trials given the proposed placement of CBD in the pathway at third-line. These are discussed in more detail in sections 3 and 4 of this report.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale	ERG comment
Population	People with Dravet syndrome whose seizures are inadequately controlled by established clinical management.	People with Dravet syndrome (DS) whose seizures are inadequately controlled by current or prior established clinical management. People with DS where current clinical management is unsuitable or not tolerated. Rationale: This is in line with recommendations in NICE Clinical guideline 137 (CG137)[8]	The population addressed, (people aged two years and over with Dravet syndrome (DS) whose seizures are inadequately controlled by current or prior established clinical management) is consistent with the final scope issued by NICE and with the expected licenced indication for Epidyolex®. The addition of people with DS where current clinical management is unsuitable or not tolerated is consistent with the pathway outlined in NICE CG137.[8] The two main trials in the submission excluded adult (> 18) patients. There are therefore no clinical data relevant to adult patients.
Intervention	Cannabidiol in addition to current clinical management	Cannabidiol in addition to current clinical management	In line with the scope.
Comparator(s)	Established clinical management without cannabidiol, which may include combinations of: • sodium valproate • topiramate • clobazam • stiripentol • levetiracetam • ketogenic diet	Established clinical management without cannabidiol, which may include combinations of: • sodium valproate • topiramate • clobazam • stiripentol • levetiracetam • ketogenic diet	In line with the scope. The comparator used in the submission is CCM, which includes various combinations of different AEDs. Different combinations of AEDs were not considered as separate comparators, as indicated by the NICE scope. It should be noted that the use of a 'mixed' CCM comparator assumes that the effectiveness of CBD does not vary with the combination of drugs to which it is added.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale	ERG comment
	• vagus nerve stimulation	• vagus nerve stimulation	Issues relating to how well the trials in the submission might reflect current clinical management in England and Wales in terms of concurrent treatments are discussed within this report.
Outcomes	The outcome measures to be considered include: • seizure frequency (overall and by seizure type) • response rate (overall and by seizure type) • seizure severity • incidence of status epilepticus • mortality • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • seizure frequency (convulsive seizures and overall) • proportion of people convulsive seizure-free • number of people with episodes of status epilepticus • mortality • adverse effects of treatment • health-related quality of life • CGIC (Caregiver Global Impression of Change) • CGICSD (Caregiver Global Impression of Change in Seizure Duration) Rationale: The primary endpoint of the pivotal clinical trials was change in convulsive seizure frequency. A seizure severity proxy (duration of seizures) was measured through the caregiver surveys as an impression of seizure duration change rather than as a defined metric. The clinical trial patients were a highly refractory group of patients with status epilepticus as part of their disease. In the	The outcomes presented in the CS do not completely match the outcomes identified in the NICE scope. However, this is due to the design of the two main trials. An important point is that although mortality is investigated, the two main trials are of 14 weeks' duration so cannot provide long-term data on SUDEP and other deaths. The exact link between reduction in convulsive seizures and any associated reductions in mortality cannot be determined from the two main randomised trials. The ongoing open label GWPCARE5 trial did not list either SUDEP or overall mortality in the effectiveness outcomes to be assessed.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale	ERG comment
		trials, the number of people with episodes of status epilepticus was reported, not the incidence.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope	Deviations from the NICE reference case included the restricted time horizon of 15 years and the method used to estimate utilities.
Subgroups to be considered	Not applicable	Not applicable	Not applicable
Special considerations including issues related to equity or equality	Not applicable	Not applicable	Not applicable

Source: Table 1, Section B.1.1 of the CS[1]

AED = anti-epileptic drug; CG = clinical guideline; CS = company submission; DS = Dravet syndrome; ERG = Evidence Review Group; SUDEP = Sudden death in epilepsy

3.1 Population

The population defined in the scope is 'people with Dravet syndrome (DS) whose seizures are inadequately controlled by established clinical management'.[16] The company has added to this '*people with DS where current clinical management is unsuitable or not tolerated*'.[1] This addition is consistent with the pathway outlined in NICE CG137.[8]

The submission relied, primarily, on two randomised controlled trials (RCTs) of CBD as an add-on treatment to current clinical management (GWPCARE1[14] and GWPCARE2[15]). Both RCTs (GWPCARE1 and GWPCARE2) were conducted in patients aged two to 18 years with DS, whose seizures were incompletely controlled with previous AEDs and who had had at least four convulsive seizures per week in the past 28 days. Although the decision problem did not specify any age restriction and the expected licenced indication for Epidyolex® is for patients two years of age and older, neither of the key trials used in the submission (GWPCARE1 and GWPCARE2) included adult patients (over the age of 18 years).

The number of previous or current AEDs in relation to CBD was not specified in the NICE scope. However, the treatment pathway proposed by the company (see Figure 2.1 of our report) placed CBD as a third-line treatment (i.e. for patients who have inadequate seizure control with first-line and at least one adjunctive AED). The baseline characteristics for GWPCARE1 and GWPCARE2, reported in the CS (Tables 6 and 7) indicated that some participants included in these studies may have been treatment naïve or have tried only one prior AED.[1]

Of the two main trials, GWPCARE1 included patients from the UK ([redacted] patients from [redacted] centres) but GWPCARE2 did not include patients from the UK.

The CS (Section B.2.7) stated that '*no subgroup analyses were conducted.*' However, the CSRs for both key trials (GWPCARE1[14] and GWPCARE2[15]) reported a number of subgroup analyses, which are further discussed in this report.

ERG comment: The ERG asked a number of questions relating to the population defined in the decision problem and the populations included in the key trials, GWPCARE1 and GWPCARE2. The questions are given below with the company's responses and our interpretation.[12]

ERG question A16: Both of the two main trials (GWPCARE1 and GWPCARE2) excluded adult (>18 years) patients. What are the implications of this, given that the expected licensed indication is for patients two years of age and older with no upper age limit mentioned?

Company response: '*This reflects the demographics of the DS population. Patients are diagnosed at a young age and mortality rates are high. Premature mortality is a major issue in DS, with most deaths occurring before 10 years of age. For these reasons, the number of adults with DS is very low compared with the number of children.*'

ERG interpretation: Around 80% of people with Dravet syndrome can survive into adulthood.[7] Therefore a high proportion of those eligible for cannabidiol are not fully represented in the main trials given the inclusion of patients only up to age 18.

ERG question A3: Under 'Placement of CBD within the care pathway' (page 25 of the company submission) and at other points in the document, it is stated that: '*For patients with Dravet syndrome (DS) considered for treatment with CBD, it will be an add-on treatment for refractory seizures in people*

aged 2 years of age and older once two other appropriate anti-epileptic drugs (AEDs), trialled to a maximally tolerated dose, have failed to achieve seizure freedom.'[12]

c. The mean number of prior AEDs in both trials was over four... Is this a more severe population than might be expected in clinical practice?

Company response: 'No. Despite the availability of a broad range of AEDs, non-pharmacological interventions and invasive surgery, seizure control in DS remains inadequate, with the majority of patients unresponsive to treatment or unable to tolerate current AEDs. As a result, physicians have used a variety of medical, surgical and dietary approaches in an attempt to control seizures, and polypharmacy on this scale is not uncommon.

The number of previous/concomitant AEDs at baseline in the clinical trials is an artefact of the population that could be recruited and does not reflect the inclusion criteria in studies, or where clinical need lies in treatment practice. Patients with DS are highly drug refractory. As such, the standing population in clinical practice, from which trial patients were recruited, has been extensively treated. Recently diagnosed children with DS will have a high level of clinical need even with existing AEDs, and CBD will be a valuable treatment option in these patients.'

ERG interpretation: No references were provided to support the level of polypharmacy in DS. However, the ERG considered the company's response to be reasonable.

d. Please provide a histogram showing the number of prior treatments in each arm of the GWPCARE1 and GWPCARE2 trials.

Company response:

Figure 3.1: Histogram for the number of patients on prior AEDS (no longer taking) at baseline (GWPCARE1)

Figure 3.2: Histogram for the number of patients on prior AEDS (no longer taking) at baseline (GWPCARE2)

e. How was it established in the trials that patients had failed on their prior treatments and how does this relate to UK practice?

Company response: '*Patients were having seizures not controlled by their current AEDs. In GWPCARE1, patients were taking at least 1 AED. All medications or interventions for epilepsy were stable for 4 weeks prior to the trial and were to be maintained throughout the trial. Patients had 4 or more convulsive seizures during the first 28 days of the baseline period. In GWPCARE2, patients were taking 1 or more AEDs at a dose that had been stable for at least 4 weeks. Patients had at least 4 convulsive seizures during the first 28 days of the baseline period. All medications or interventions for epilepsy were stable for 4 weeks prior to screening. This reflects UK practice, where refractory epilepsy (as defined by the International League Against Epilepsy) is recognised as failure of adequate trial of two tolerated and appropriately chosen and used AED regimens (as monotherapies or in combination) to achieve sustained freedom from seizures.*'

ERG interpretation: The ERG agrees with the company's response.

f. The mean number of concurrent treatments in the trials was approximately three. How does this reflect UK clinical practice? Do the concurrent treatments used in the trials reflect UK practice?

Company response: '*This reflects UK clinical practice. See also A3c above. Despite the availability of a broad range of AEDs, non-pharmacological interventions and invasive surgery, seizure control in DS remains inadequate, with the majority of patients unresponsive to treatment or unable to tolerate current AEDs. As a result, physicians have used a variety of medical, surgical and dietary approaches in an attempt to control seizures, and polypharmacy on this scale is not uncommon*.'

ERG interpretation: The ERG notes that the company did not provide any references or statements from clinical experts in support of this response; this may be a point for discussion with clinical experts on the appraisal committee.

ERG question A12: How many UK centres and patients were included in GWPCARE1? How similar does the company consider the trials to be to patients seen in practice in England and Wales? Have you sought any clinical expert input on this issue?

Company response: 'There were 4 UK sites in GWPCARE1, of which 3 recruited, and none in GWPCARE2. Overall there were 16 UK patients in GWPCARE1.

It is expected that the patients in these studies will be very similar to those seen in practice in England and Wales.

GWPCARE1 included patients from the UK, the USA, France and Poland.

GWPCARE2 included patients from the USA, Spain, Poland, Australia, Israel and the Netherlands.

GWPCARE5 is an ongoing, open-label extension of GWPCARE1 (Dravet syndrome), GWPCARE2 (Dravet syndrome), GWPCARE3 (LGS) and GWPCARE4 (LGS).'

ERG interpretation: The ERG notes that the company did not provide any statements from clinical experts, in support of the above response. The applicability of the key trials to the UK population may be a point for discussion with clinical experts on the appraisal committee

We also asked the company to provide full results for all subgroup analyses conducted. The company's response and the results of these analyses are discussed in more detail in section 4 of this report.

3.2 Intervention

The intervention (cannabidiol (Epidyolex®) in addition to current clinical management) is in line with the scope. Orphan designation (EU/3/14/1339) was granted by the European Commission on 15 October 2014 for cannabidiol for the treatment of Dravet syndrome. Regulatory approval by the EMA is anticipated in April 2019.

Epidyolex is indicated for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients two years of age and older. It is described in the CS as '*a highly purified, plant-derived pharmaceutical formulation of cannabidiol, administered as an oral solution*.' [1]

The description of the technology being appraised (Table 2 of the CS) included the following statement about dosage: '*The recommended starting dose of cannabidiol (CBD) is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day). Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 20 mg/kg/day, should be made considering individual benefit and risk.*'[1] However, the majority of the clinical effectiveness evidence presented related to the maximum recommended dose (20 mg/kg/day).

ERG comment: The ERG asked a number of questions relating to the dose of CBD used in the key trials, GWPCARE1 and GWPCARE2, and how this related to the dose that would be expected to be used in UK clinical practice. The questions are given below with the company's responses and our interpretation.[12]

ERG question A1:

a. What proportion of patients do you anticipate will receive the 10 mg/kg /day dose and what proportion the 20 mg/kg/day dose in clinical practice?

Company response:

'*It is anticipated that all patients will start with the 10mg/kg/day dose*.

The latest version of the SmPC states the following: "The recommended starting dose of Epidyolex is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day). Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 20 mg/kg/day, should be made considering individual benefit and risk and with adherence to the full monitoring schedule."

As the dosage for CBD is patient-specific (i.e. based on patient weight and individual clinical response), an alternative mean dosage of CBD was tested in the scenario analysis. The maximum recommended dose of 20 mg/kg/day is most likely to be received only by a small proportion of patients who have the potential to achieve further seizure reductions and/or seizure-freedom. Therefore, the mean dose of CBD was estimated by assuming that patients who achieve ≥75% reduction in convulsive seizures receive 20 mg/kg/day, while patients experiencing <75% reduction in convulsive seizures receive 10 mg/kg/day. The proportion of responders with ≥75% and <75% reduction in convulsive seizures was obtained from the Phase 3 clinical trial, GWEP1424 (see Table 40 in Document B).'

b. How would patients be identified as being suitable for the 20 mg/kg/day dose? Do you anticipate that all patients will start with the lower dose? If so, what cut-off for inadequate response to the lower dose would be used and when would a response assessment to inform possible dose escalation be made?

Company response: *'It is anticipated that all patients will start with the lower maintenance dose. Increasing the dose in patients demonstrating good seizure reduction and tolerability to cannabidiol at 10mg/kg/day who the physician considers may gain additional seizure reduction by dose escalation will be at the physician's discretion. Patients not achieving good seizure reduction at 10mg/kg/day are unlikely to achieve efficacy by dose escalation.*

The decision to escalate would be at the clinician's discretion, in discussion with the patient and/or caregivers. Feedback suggests that specialist clinicians would be comfortable doing this, especially given their experience in managing existing treatments and the complex set of considerations when making dose adjustments. GW therefore considers the assumptions made to model the proportion of patients receiving 20mg/kg/day as reasonable (see answer to A1a).'

ERG interpretation: Given the above response, the ERG considers that only clinical effectiveness data for the 10 mg/kg dose are relevant to the whole population, specified in the decision problem. If only those patients who the physician considers may gain additional seizure reduction by dose escalation will receive the 20 mg/kg dose, and this has been defined as those experiencing ≥75% reduction in convulsive seizures on the 10 mg/kg dose, then data on the clinical effectiveness of the 20 mg/kg dose are only relevant for this specific subgroup; the CS did not provide subgroup data.

c. In the long term do you expect patients to continue taking CBD at the maintenance dose? In the ongoing long-term study (GWPCARE5) it is stated that '*Initially, patients were titrated to 20 mg/kg/day administered in two divided doses, which could then be decreased or increased to 30 mg/kg/day at the investigator's discretion*.'

Company response: '*Yes, in the long term, patients are expected to continue taking CBD at the maintenance dose. This is in line with the anticipated label from EMA. The OLE study protocol was written prior to the maintenance dose being established.'*

ERG interpretation: The ERG accepts the above response, but notes that this may limit the applicability of any long-term effectiveness data from the open-label extension study, GWPCARE5 to UK clinical practice. The interim report for GWPCARE5,[17] provided by the company in their clarification response, stated that, for [redacted] of participants with DS, the modal dose during the treatment period was [redacted] The overall mean modal dose for DS patients was [redacted] It is not possible to provide a more detailed breakdown of CBD doses received by patients during the open-label extension period, as the relevant tables were missing from the report provided. If, as suggested by the company, the maximum recommended dose of 20 mg/kg/day is most likely to be received only by a small proportion of patients who have responded well to the 10 mg/kg dose and are judged by clinicians to have the potential to achieve further seizure reductions and/or seizure freedom, the ERG is unclear what was the rationale for dose escalation in the context of an open-label extension study (GWPCARE5) when propensity for further response had presumably been established during the blinded phase of studies (GWPCARE1 and GWPCARE2).

ERG question A20: For GWPCARE2, please provide results of comparisons between the 20 mg and 10 mg CBD groups, for all outcomes where these are available.

Company response: '*No formal pre-specified test for significance between the CBD groups was included in the SAPs.*'

ERG interpretation: Equivalent effectiveness and safety cannot be assumed between the two doses. Section 4 of this report gives further detail on results according to dosage.

3.3 Comparators

The description of the comparators is in line with the scope (established clinical management without cannabidiol), which may include combinations of: sodium valproate, topiramate, clobazam, stiripentol, levetiracetam, ketogenic diet and vagus nerve stimulation. The comparator used in the key trials (GWPCARE1 and GWPCARE2) is current clinical management (CCM), which includes various combinations of different AEDs. Different combinations of AEDs were not considered as separate comparators.

The CS (Section B.2.7) states that '*no subgroup analyses were conducted*.' However, the CSRs for both key trials (GWPCARE1[14] and GWPCARE2[15]) reported a number of subgroup analyses, including for concurrent use of a number of individual AEDs . The results of these are included in this report.

ERG comment: It should be noted that the use of a 'mixed' CCM comparator assumes that the effectiveness of CBD does not vary with the combinations of AEDs to which it is added. The ERG questions the validity of this assumption.

In NICE's epilepsy guidance we note that there is some uncertainty on the most appropriate initial and add-on AEDs and that further research is recommended.[8] With this in mind, the ERG was concerned as to how well the trials in the CS might reflect the number and nature of treatments under the umbrella of clinical management in England and Wales. The ERG asked the company to clarify this. Furthermore, we wished to be clear that results in the two main trials reflected the impact of Epidyolex and were not reflective of the particular composition of clinical management. We asked the company to provide full results for all subgroup analyses conducted. The company's response and the results of these analyses are discussed in more detail in section 4 of this report.

3.4 Outcomes

The NICE final scope listed the following outcome measures:

- seizure frequency (overall and by seizure type)
- response rate (overall and by seizure type)
- seizure severity
- incidence of status epilepticus
- mortality
- adverse effects of treatment
- health-related quality of life

The CS focused primarily on convulsive seizures as these were the primary outcome in the two main trials. Data were available on overall frequency of seizures and there was some break down of seizure type in the full clinical study reports (CSRs). The company provided the rationale for differences in relation to seizure severity. '*A seizure severity proxy (duration of seizures) was measured through the caregiver surveys as an impression of seizure duration change rather than as a defined metric.*'[1] The surveys were the CGIC (Caregiver Global Impression of Change) and the CGICSD (Caregiver Global Impression of Change in Seizure Duration). The company also explained the rationale in relation to incidence of status epilepticus. '*The clinical trial patients were a highly refractory group of patients with status epilepticus as part of their disease. In the trials, the number of people with episodes of status epilepticus was reported, not the incidence*.' [1]

ERG comment: The outcomes presented in the CS did not completely match the outcomes identified in the NICE scope. However, this was due to the design of the two main trials. A potentially more important issue is that, although mortality was investigated, the two main trials were of 14 weeks' duration so could not provide long-term data on SUDEP and other deaths. The exact link between reduction in convulsive seizures and any associated reductions in mortality cannot be determined from the two main randomised trials.

The ERG asked a number of questions relating to the outcome measures used in the key trials, GWPCARE1 and GWPCARE2. The questions are given below with the company's responses and our interpretation.[12]

ERG question A9: Outcomes in the trials could be reported by patient or caregiver.

a. Was any guidance given as to when it was appropriate for the patient to respond or when it should be the caregiver or was this up to the individual patient/caregiver?

Company response: '*No specific guidance was given on when a patient should respond versus when a caregiver should complete reporting tools in the trials. This decision was left to the investigator and patient/caregiver to make together. In most cases, it was caregivers, reflecting the fact that patients with DS in the cannabidiol clinical trials were children and young adults with a broad spectrum of abilities, many of whom were unable to communicate effectively, and so would not be able to report outcomes.*'

b. What training were patients/caregivers given in recognition and recording of seizure type?

Company response: '*The separate document provided (QA9b. Collection of the Seizure Data (Primary Endpoint) on the IVRS) details the training given to the caregivers on recording seizure type and PROs.*'

ERG interpretation: The ERG is satisfied that outcomes were reported appropriately and that those reporting outcomes were suitably qualified to do so.

We also asked the company to provide full results for all outcomes assessed in GWPCARE1 and GWPCARE2, including listed outcomes that were not reported in the CS, incomplete data (e.g. results reported only as relative (%) change, missing baseline and end-point values), and provision of point estimates only (missing inter-quartile range (IQR), standard deviation (SD) or 95% confidence interval (CI)). The company provided a separate document with additional results and missing data.[18] Data from this document and, where necessary, taken directly from the relevant CSRs are included in section 4 of this report.

3.5 Other relevant factors

The company stated that '*The use of cannabidiol is unlikely to raise any equality issues*'. The CS noted that the indication is only for patients aged two years of age and older.

There is no Patient Access Scheme (PAS) application. The list price of cannabidiol is [redacted]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify evidence on the efficacy and safety of drug interventions in Dravet syndrome and Lennox-Gastaut syndrome (to inform a parallel appraisal). Section 4.1 critiques the methods of the review including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis. The systematic review also identified papers relevant to the cost effectiveness of this appraisal which will be discussed in section 5.

4.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical and cost effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[19] The submission was checked against the single technology appraisal (STA) template for company/sponsor submission of evidence.[20]

The company submission reported that a rigorous systematic review was carried out to identify relevant publications for the efficacy, safety and development of economic models for the use of cannabidiol in Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS).[1] The main submission presented one set of searches used to inform both the clinical and cost effectiveness content for both LGS and Dravet syndrome in Appendix D.[1] As the searching for the whole submission was conducted at once, the ERG's appraisal and comments will be presented here for both the clinical and cost effectiveness sections.

The single set of searches was reported in full in D1.1, and strategies were presented in Table 43.[1] The database searches were undertaken on 19 November 2018, and grey literature website searching was carried out between 19 November and 3 December 2018. Search strategies were reported in Table 42 of the CS for the following databases: Embase (ProQuest), PubMed, Heoro.com, and the Cochrane Library (Wiley). Additional searches were provided for ScHARRHUD, EuroQol Database, NHS EED (NHS Economic Evaluation Database), Database of Abstracts of Reviews of Effects (DARE) and HTA (Health Technology Assessment) databases via the Centre for Reviews and Dissemination's website. As part of the clarification process, additional searches were carried out on 6 and 11 February 2019, in order to correct errors and answer the ERG's clarification questions.[21] These strategies were not provided in the clarification response.[12]

All searches contained terms to identify the conditions of interest: Lennox-Gastaut syndrome, Dravet syndrome or alternative terminology for childhood epilepsies, however different terms were included in each strategy. No drug or intervention facets were included in the search, and study design filters were not applied. The searches were not restricted by date or limited by language of publication. A further trials search was presented for NIH Clinicaltrials.gov, and search terms were provided. The ERG noted the NIH trials register records were restricted to 'terminated', 'completed', 'suspended' or 'withdrawn' studies; with further limits to "Interventional studies (clinical trials)" and only those studies with results presented.

The CS documented browsing of the following conference proceedings, together with URLs and conference dates: American Epilepsy Society, International Epilepsy Congress, European Congress on Epileptology and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Additional supplementary web searches were carried out on specific organisational websites, such as NICE, All Wales Medicines Strategy Group (AWMSG) and Scottish Medicines Consortium (SMC).

The CS also reported asking the manufacturer for any additional publications, which yielded two further publications.

ERG comment:

- The search strategies that were reported were logically structured. Inclusion of one facet to search for the conditions of interest was appropriate and sensible, as was the decision not to apply any study design filters or restrictions.
- Each search reported in the CS contained different free-text terms, with little consistency between strategies. The ERG queried this variability during clarification, because comprehensive and methodical searches would be expected to include very similar free-text terms across all databases. Typically, only the database-specific indexing, command language and field tags change between resources. Although the response to clarification reported investigating these issues, corrected strategies were not provided for the ERG's appraisal. Therefore, the ERG was unable to assess how well these changes were made.
- Errors and inconsistencies in the original search strategies impaired the performance of the company's searching. The ERG queried these issues during clarification, however as the company did not provide corrected strategies in their clarification response, the ERG remains concerned about the quality of the company's searches. These errors and inconsistencies may have limited recall of potentially relevant references. The explanation given in the clarification response did not match the numbers retrieved when the ERG corrected the same strategies. Consequently, the ERG is unable to assess how well the searching was designed and conducted.
- The PubMed search presented in the CS contained incorrectly applied truncation within phrase searches e.g. "childhood epilep* encephalopath*". PubMed only permits truncation or phrase searching, the two operations do not work when combined in a single phrase search. The ERG corrected these errors prior to clarification, and re-ran the original and corrected searches to determine how many references were missed by the original strategy (search date 26 march 2019, see Appendix 1 for ERG searches). At the time of searching, the ERG's corrected version of the CS PubMed search retrieved 10,168 records, 6,069 of which were not retrieved by the company's original search. When ERG queried the truncation errors during clarification, the company responded that they found 19 new references after the truncation errors were corrected. As no corrected strategies were provided to the ERG, the ERG was unable to assess how effectively the corrections were made. It is still unclear how the company's corrected CS PubMed search varied so greatly when compared to the ERG version. As a consequence, the ERG remains concerned about the quality of the company's PubMed search.
- The Embase.com strategy in the CS did not include the phrase 'childhood epilepsy encephalopathy' or the abbreviation 'LGS'. The clarification response described incorporating these amendments and re-running the search, resulting in 600 additional records. The company did not provide a corrected search strategy in their clarification response, therefore the ERG was unable to assess how effectively the corrections were incorporated.
- The company's Cochrane Library strategy retrieved 207 records and contained basic phrase searching, without MeSH indexing. Prior to clarification, the ERG amended the CS search by including correct MeSH, truncation, phrase searching and added the abbreviation 'LGS' (see Appendix 1 for ERG searches). The amended ERG strategy retrieved 307 results. During clarification the ERG queried the lack of MeSH and free-text word variants. The company

responded that they had amended their Cochrane strategy to address these omissions, and no additional studies were retrieved. The ERG identified 100 references not picked up by the company's original search. As the company did not provide their corrected strategy, the ERG is unable to assess how well these omissions were addressed, and therefore remains concerned about the quality of the company's Cochrane Library search.

- The search of Heoro.com was considered adequate. The ERG attempted to re-run the search results on 26 March 2019, however significantly different results were retrieved. There appears to be an intermittent error with the Heoro.com resource itself, and the ERG was unable to fully investigate the Heoro.com strategy.

- The CRD databases, DARE, NHS EED and HTA, were searched using 'Lennox-Gastaut or Dravet' in the title only, and lacked relevant MeSH, truncation and other word variants. Prior to clarification, the ERG amended the CS search by including correct MeSH, truncation, phrase searching and added the abbreviations 'LGS' and 'SMEI' (see Appendix 1 for ERG searches). During clarification the ERG queried the lack of MeSH, abbreviations and free-text word variants. The company responded that they had amended their CRD strategy to address these omissions, and six additional studies were retrieved. The ERG search retrieved nine additional records, although as the company did not provide their corrected strategy, the ERG is unable to assess how well these omissions were addressed or why the ERG search retrieved more records. Therefore, the ERG remains concerned about the quality of the company's CRD Library search.

- The NIH Clinicaltrials.gov search reported in the CS did not include which fields were searched. In the clarification response, the company provided sufficient detail for the ERG to re-run their trials register search. The company's original search retrieved 30 results, whereas the ERG search resulted in 14 records. Although the company's search was conducted in November/December 2018 and the ERG re-ran the search in March 2019, it seems unlikely that trial progression would equate to such a difference in search results. The ERG is unable to account for this difference.

- The CS documented the conference proceeding searching and browsing, detailing URLs, years included and results per resource. The ERG considered the conference searching to be well documented.

4.1.2 Inclusion criteria

As stated above, the company conducted a systematic review to identify evidence on the efficacy and safety of drug interventions in Dravet syndrome and Lennox-Gastaut syndrome (to inform a parallel appraisal). The systematic review also identified papers relevant to the cost effectiveness of this appraisal which will be discussed in section 5. The eligibility criteria used to select studies for the review of clinical effectiveness is presented in Table 4.1. No specific exclusion criteria were reported.

Table 4.1: Eligibility criteria for the systematic review of clinical effectiveness

Inclusion Criteria	
Population	• Children and/ or adults with LGS or DS • Include mixed populations with other types of childhood epilepsy
Interventions	• Cannabidiol
Comparators	• Rufinamide, stiripentol: alone or in combination • Other antiepileptic drugs (valproate, topiramate, lamotrigine, clobazam, levetiracetam, felbamate, others); alone or in combination • Placebo/ usual care
Outcomes	• Seizure rate • Seizure severity • % seizure-free • % of participants achieving 50% reduction in seizure rate • % of participants achieving 75% reduction in seizure rate • Number of hospital or ICU admissions • Length of stay • Status epilepticus episodes • Mortality • Adverse events • Adherence to treatment/ study withdrawals
Study design	• Efficacy/safety: randomised controlled trials (RCTs); systematic literature reviews (SLRs) of RCTs for citation chasing
Publication date	• Full text publications: any • Conference abstracts: last 2 years (2016-18) • Most recent update of systematic reviews
Publication language	• Efficacy reviews: any
Source: Appendix D of the CS[1] AE = adverse event; CS = company submission; DS = Dravet syndrome; ICU = intensive care unit; LGS = Lennox-Gastaut syndrome; NICE = National Institute for Health and Clinical Excellence; QoL = quality of life; RCT = randomised controlled trial	

Briefly, the company searched for RCTs of cannabidiol compared to a range of treatments alone or in combination for a range of efficacy and safety outcomes in any language. The company further noted that '*Treatments are always given in combination, however we included RCTs that compare one drug with placebo, where all treatment arms also receive standard therapy. Details of concomitant medication were extracted*'.[1]

ERG comment:

- Two reviewers were involved in the selection of studies for the reviews which helps to minimise bias (confirmed in the response to letter of clarification question A5).[12]
- The ERG was unclear as to why conference abstracts were limited to the past two years and was unsure whether relevant data could have been missed.
- The ERG questioned whether ketogenic diet and vagus nerve stimulation were also valid comparators in the systematic review (as per the NICE scope).[16] The company confirmed that they were considered to be part of CCM of DS.[12]

- It is normally recommended to consider non-randomised evidence in relation to safety. This is particularly relevant as the main trials in the CS were of short duration (14 weeks) so longer term, rarer adverse events might not be identified. However, in response to clarification the company provided interim data on GWPCARE5, an ongoing open label study, designed to assess safety.
- The ERG was unclear on the exact number and nature of studies included in the systematic review. The PRISMA flow chart appeared to indicate that 24 studies were included for clinical effectiveness in the DS population. However there appeared to be eight in the table of included studies (Table 44 of the CS). The ERG also asked '*Table 43, question 9 (screening algorithm) indicates that randomised controlled trials (RCTs) which did not assess an included intervention (defined as CBD) would be excluded. Please explain why RCTs of other AEDs, which do not include a CBD arm and are not used in the submission, are in the list of included efficacy studies.*'[12] The company responded that GWPCARE 1, 2 and 5 were the only trials included for clinical effectiveness in the submission (reported in 10 publications). The remaining trials of treatments other than cannabidiol were included for transparency and completeness only.[12]
- The ERG checked the list of excluded studies. The company did not appear to have excluded relevant studies of cannabidiol.

4.1.3 Critique of data extraction

No information was provided on the number of reviewers who extracted data from included studies.

ERG comment: It is normally recommended that two reviewers are involved in data extraction for a systematic review to avoid bias and error.

4.1.4 Quality assessment

The company assessed the quality of the two main trials GWPCARE 1 and 2 and concluded that both trials were of high quality with a low risk of bias. The ongoing trial, GWPCARE5, was not quality assessed. The particular quality tool used was not referenced. Elements assessed were randomisation, allocation concealment, baseline comparability, researcher blinding, dropout imbalances, selective outcome reporting and use of intention to treat analysis.[1]

No information was provided on the number of reviewers who assessed the quality of included studies.

ERG comment: It is normally recommended that two reviewers are involved in the assessment of study quality to avoid bias and error. Results of the company's quality assessment and the ERG's assessment are presented in section 4.2.

4.1.5 Evidence synthesis

The company stated that no meta-analyses were conducted. Neither were there any indirect comparisons made comparing cannabidiol with other treatments. Both of these sections of the CS also included the following text:

'In the Phase 3 clinical trials of cannabidiol, the intervention was cannabidiol in addition to current clinical management and the comparator was established clinical management without cannabidiol (i.e. CCM + placebo).

For patients considered for treatment with Epidyolex®, it will be an add-on treatment for refractory seizures in people aged 2 years of age and older once two other appropriate AEDs, trialled to a maximally tolerated dose, have failed to achieve seizure freedom.

Therefore, the only viable comparator is established clinical management."[1]

ERG comment: The ERG agrees that, due to the variation in CCM in DS patients, it is unlikely that data would be available to support indirect treatment comparisons or mixed treatment comparisons of cannabidiol versus individual AEDs or specific combinations of AEDs. However, the ERG feels that the submission could have explored this option more fully. The ERG considers that an indirect comparison/network meta-analysis (NMA) may have been possible, based on the included trials (GWPCARE1 and GWPCARE2) and any RCTs where one of the listed comparator AEDs or non-pharmacological interventions was evaluated as an adjunct to CCM (comparator AED or non-pharmacological intervention + CCM versus CCM). It should also be noted that the use of a 'mixed' CCM comparator assumes that the effectiveness of CBD does not vary with the combinations of AEDs to which it is added. The ERG questions the validity of this assumption.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS identified two RCTs of cannabidiol (GWPCARE 1[14] and GWPCARE2[15]) and an ongoing open-label extension study[17] as relevant to the submission.

ERG comment: The ERG agrees that all relevant RCTs of cannabidiol were included in the submission. The company were asked to provide a protocol and all available results for the ongoing open-label extension study (GWPCARE5) in the CS.

4.2.1 Details of included cannabidiol studies

Both RCTs (GWPCARE1 and GWPCARE2) were conducted in patients aged two to 18 years with DS, whose seizures were incompletely controlled with previous AEDs and who had had at least four convulsive seizures per week in the past 28 days. The intervention was cannabidiol in addition to current clinical management (CCM) and the comparator was CCM without cannabidiol (i.e. CCM plus placebo). GWPCARE2 was a three-arm study, comparing two doses of cannabidiol (10 mg/kg/day and 20 mg/kg/day) in addition to CMM and CCM plus placebo, and GWPCARE1 compared cannabidiol (20 mg/kg/day) in addition to CCM and CCM plus placebo. Both trials had a dose escalation phase (14 days in GWPCARE1 and seven or 11 days in GWPCARE2) followed by a 12-week treatment period. Both trials were international in scope. GWPCARE1 included patients from the UK (four centres of which three recruited and 16 patients overall) but GWPCARE2 did not include patients from the UK.

A summary of study methodology, for GWPCARE1 and GWPCARE1, is provided in Table 4.2.

Table 4.2: Summary of study methodology for included trials

	GWPCARE1	GWPCARE2
Location	France, Poland, UK, USA	USA, Spain, Poland, Australia, Israel, Netherlands
Trial design	Multinational, randomised, double-blind, placebo-controlled trial.	Multinational, randomised, double-blind, placebo-controlled trial.
Eligibility criteria for participants	Aged 2 to 18 years with established diagnosis of DS, taking ≥1 antiepileptic drugs and had ≥4 convulsive seizures in previous 28 days.	Aged 2 to 18 years with established diagnosis of DS, taking ≥1 antiepileptic drugs and had ≥4 convulsive seizures in previous 28 days.
Settings and locations where data were collected	Patients or caregivers recorded number and type of seizures daily via interactive voice-response system; Laboratory assessments conducted after 2, 4, 8 and 14 weeks and end of taper period; Safety endpoints assessed at every visit.	Patients or caregivers recorded number and type of seizures daily via interactive voice-response system; Laboratory assessments conducted after 2, 4, 8 and 14 weeks and end of taper period; Safety endpoints assessed at every visit.
Trial drugs (number in each group)	Cannabidiol oral solution 100 mg/ml (n=61); dose escalated up to 20 mg/kg/day over 14 days then maintained for 12 weeks, followed by 10-day tapering before cessation or entry into open-label extension study. Matching placebo (n=59).	Cannabidiol oral solution 100 mg/ml; dose escalated up to 10 mg/kg/day (n=67) over 7 days or 20 mg/kg/day (n=67) over 11 days then maintained for 12 weeks, followed by 10-day tapering before cessation or entry into open-label extension study. Matching placebo (n=65).
Permitted and disallowed concomitant medication	Other anti-epileptic therapies allowed if stable for 4 weeks prior to screening and unchanged throughout the study.	Other anti-epileptic therapies allowed if stable for 4 weeks prior to screening and unchanged throughout the study.
Primary outcomes	Percentage change in convulsive seizure frequency from baseline/28 days.	Percentage change in convulsive seizure frequency from baseline/28 days.
Other outcomes used in the economic model or specified in the scope	• Caregiver Global Impression of Change; • Number with ≥25%, ≥50%, ≥75%, 100% reduction in convulsive seizures; • Reduction in total seizure frequency and seizure subtypes; • Seizure duration assessed by Caregiver Global Impression of Change in Seizure Duration; • Sleep disruption assessed with 0-10 numerical rating scale and Epworth Sleepiness Scale; • QOL using Quality of Life in Childhood Epilepsy scale; •Vineland Adaptive Behaviour Scale; •Hospitalisations due to epilepsy; •Emergence of new seizure types;	• Caregiver Global Impression of Change; • Number with ≥25%, ≥50%, ≥75%, 100% reduction in convulsive seizures; • Reduction in total seizure frequency and seizure subtypes; • Seizure duration assessed by Caregiver Global Impression of Change in Seizure Duration; • Sleep disruption assessed with 0-10 numerical rating scale and Epworth Sleepiness Scale; • QOL using Quality of Life in Childhood Epilepsy scale; • Vineland Adaptive Behaviour Scale; • Hospitalisations due to epilepsy; • Emergence of new seizure types;

	•Use of rescue medication; •Safety, including Columbia Suicide Severity Rating Scale; •Palatability.	• Use of rescue medication; • Safety, including Columbia Suicide Severity Rating Scale; • Palatability.
Pre-planned subgroups	None	None
Source: Table 5 of the CS[1] DS = Dravet syndrome; QOL = quality of life		

ERG comment: The ERG notes that the evidence for CBD is based on international RCTs investigating patient-relevant outcomes. However, neither trial specified that participants should have failed to achieve seizure freedom having trialled at least two other appropriate AEDs to a maximally tolerated dose (as indicated by the company's proposed care pathway shown in Figure 2.1 of this report). The company was asked to provide clarification on how many participants, in the included studies, did not meet this criterion. Information provided confirmed that participants with fewer than two prior (discontinued) AEDs made up 16% in GWPCARE1 and 15% in GWPCARE2.[12] The ERG considers that, with respect to prior AED treatments, the data of most, but not all, of the trial participants clearly reflect the placement of CBD in the care pathway, as described in the CS.[1] (see Section 2.2 of this report). It should be noted that the remaining participants may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled.

The main issue relating to applicability of the trials to UK practice is the age limit of 18 years. Although DS has its onset in childhood the expected licensed indication is for patients two years of age and older with no upper age limit. It is expected that patients will continue taking cannabidiol into adulthood. As stated in section 3.1, adult patients with DS are not represented in the clinical trials in the CS.

It should be noted that both of the key studies included in the CS (GWPCARE1 and GWPCARE2 had a double-blind, treatment maintenance phase of just 12 weeks, which may not be considered adequate, given that the primary outcome measure was change in 28-day convulsive seizure frequency. The ERG, therefore, considers that it is particularly important to establish whether any reductions in seizure frequency, observed in short-term trials of new AEDs such as CBD, are sustained in the longer-term. Evidence is lacking about the long-term effectiveness of CBD. Furthermore, the exact link between reduction in convulsive seizures and any associated reductions in mortality cannot be determined from the two main randomised trials. The interim report for the ongoing open-label extension study, GWPCARE5[17] focusses on safety data; the report does not list either SUDEP or overall mortality in the effectiveness outcomes to be assessed, but does include SUDEP in a table of serious TEAEs reported in >1 patient.

The included studies evaluated different doses of CBD. GWPCARE1 evaluated only 20 mg/kg/day and GWPCARE2 evaluated both 10 mg/kg/day and 20 mg/kg/day. The company were asked to provide clarification on the proportion of patients expected to receive each dose, whether all patients would be expected to start on the lower dose and how eligibility for the higher dose would be established, and whether patients are expected to continue on the maintenance dose in the long-term (see section 3.2 of this report). The company provided a detailed response, summarised by the statement: *'It is anticipated that all patients will start with the lower maintenance dose. Increasing the dose in patients demonstrating good seizure reduction and tolerability to cannabidiol at 10mg/kg/day who the physician considers may gain additional seizure reduction by dose escalation will be at the physician's discretion. Patients not achieving good seizure reduction at 10mg/kg/day are unlikely to achieve efficacy by dose*

escalation.' In the model (scenario analysis), patients achieving good seizure reduction at 10 mg/kg/day and hence receiving dose escalation to 20 mg/kg/day, were defined as those who achieve ≥75% reduction in convulsive seizures. The ERG, therefore, considers that only clinical effectiveness data for the 10 mg/kg/day dose are relevant to the whole population, specified in the decision problem. Under the dose strategy described by the company, data on the clinical effectiveness of the 20 mg/kg/day dose are only relevant for the subgroup of patients who achieve ≥75% reduction in convulsive seizures on the starting dose of 10 mg/kg/day; neither the CS nor the CSRs provided data for this subgroup. The ERG notes that randomised evidence on the effectiveness of the 10 mg/kg dose of CBD is, limited to data from [redacted] patients in the GWPCARE2 study.[1]

The CS stated that there were no pre-planned subgroups in either trial. However, the CSRs for both GWPCARE1[14] and GWPCARE2[15] described a number of potentially relevant subgroup analyses under the heading 'Statistical Methods Planned in the Protocol and Determination of Sample Size.' The company were asked to provide results for all subgroup analyses conducted.

Company response: 'The primary and key secondary endpoints were analysed in the following pre-specified subgroups for GWPCARE2. Very similar subgroups were analysed in GWPCARE1. The sources are shown in the table below.

- *Age group (2-5 years, 6-12 years and 13-18 years)*
- *Sex (Male, Female)*
- *Region (US, Rest of the World)*
- *Clobazam use (Yes, No)*
- *Valproate use (Yes, No)*
- *Stiripentol use (Yes, No)*
- *Clobazam and Stiripentol use (Yes, No)*
- *Levetiracetam use (Yes, No)*
- *Topiramate use (Yes, No)*
- *Baseline average convulsive seizure frequency per 28 days (≤ observed tertile 1, > observed tertile 1 to ≤ observed tertile 2, > observed tertile 2) The observed tertile values were rounded to the nearest 5*
- *Number of current AEDs (<3, ≥3)*
- *Number of prior AEDs (<8, ≥8).*

These outcomes were not included in the Evidence Submission as they are not relevant to clinical prescribing or the cost-utility analysis. They are standard demographic subgroup analyses that are done as part of any SAP. Furthermore, as an orphan indication, these subgroups have small population numbers with low statistical powering.

For the recommended 10 mg/kg/day dose, no clinically relevant trends were seen in these subgroup analyses; the point estimates were similar to that for the ITT population, and CIs between them heavily overlapped.'

The company provided references to the relevant CSRs for the results of these subgroup analyses; these results are described and discussed further in section 4.2.6 of this report.

4.2.2 Statistical analysis of the included cannabidiol studies

The primary outcome for both of the included trials was percentage change in convulsive seizure frequency from baseline to 28 days. A power calculation to ensure adequate sample size for the primary outcome was reported for both of the included trials. For GWPCARE1, a sample of 100 patients would provide 80% power to detect 32% difference in primary outcome with a standard deviation of 56% and a two-sided significance level of 5%. The company reported that 120 patients were randomised and included in the analysis set. For GWPCARE2 the company stated that '*for a Wilcoxon-Mann-Whitney test comparing 2 distributions with a 2-sided significance level of 0.05, a sample size of 62 per group (after pooling the placebo groups) was required to obtain a power of at least 80%. This used data from the GWCARE1 trial.*'[1] The company reported that the calculated sample size of 186 was exceeded and 198 patients were randomised and included in the analysis set in GWPCARE2.

The company reported that all patients in GWPCARE1 received their allocated treatment. The following deviations from protocol were reported for GWPCARE2. Two patients randomised to 10 mg/kg/day and two to placebo were given dosing schedules for 20 mg/kg/ day in error. One patient on 10 mg/kg/day was withdrawn as they were randomised in error and did not receive the treatment.

The company stated that in both trials analysis of the primary outcome was based on intention-to-treat (ITT) analysis. In GWPCARE2 this comprised all randomised patients who received at least one dose of cannabidiol or placebo and who had at least one post-treatment efficacy outcome recorded. In GWPCARE1 ITT analysis was defined as all patients in the safety dataset who had at least one post-treatment efficacy outcome recorded.

The primary outcome in both trials was originally planned to be the percentage change in convulsive seizure frequency from baseline over 28 days. This was compared between treatment groups using a Wilcoxon rank sum test and the median difference was estimated with the Hodges-Lehmann method (described as Holmes-Lehmann in the CS). However, this was changed in GWPCARE2 as part of a protocol amendment. The new analysis of the primary outcome used a negative binomial regression model as it was a better method for over-dispersed count data and accounts for varying lengths of patient follow-up.

The proportions of patients with at least a 25%, 50%, 75% and 100% reduction in seizures were compared between treatment groups using a Cochran-Mantel-Haenszel test. The CGIC score was compared between treatment groups using an ordinal logistic regression model.

ERG comment:

- The statistical analyses appeared to have been conducted appropriately. However, the ERG is concerned about the change of analysis method for the primary outcome in GWPCARE2.
- ITT analysis should be conducted on all patients randomised to a treatment whether or not that treatment was received. In GWPCARE1 the ITT analysis included all 120 randomised patients and in GWPCARE2 it included 198 of the 199 patients.

4.2.3 Trial participant characteristics

Table 4.3 shows the characteristics of the participants in GWPCARE1 and GWPCARE2.

Table 4.3: Baseline characteristics in GWPCARE1 and GWPCARE2

Baseline characteristics*	**GWPCARE1**		**GWPCARE2**		
	Cannabidiol 20 mg/kg/day + CCM	**Placebo + CCM**	**Cannabidiol 10 mg/kg/day + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**
Number in analysis	61	59	[redacted]	[redacted]	[redacted]
Age	Mean 9.7 SD 4.7y Median 9.1y Range 2.5 to 18y	Mean 9.8 SD 4.8y Median 9.2y Range 2.3 to 18.4y	[redacted]	[redacted]	[redacted]
Gender	35 male	27 male	[redacted]	[redacted]	[redacted]
Ethnicity	White: 44 Black/African American: 2 Asian: 1 Not Applicable: 11 Other: 3	White: 50 Black/African American: 2 Asian: 0 Not Applicable: 6 Other: 1	[redacted]	[redacted]	[redacted]
Location	USA: 35 France: 12 Poland: 6 United Kingdom: 8	USA: 37 France: 6 Poland: 8 United Kingdom: 8	[redacted]	[redacted]	[redacted]
Baseline seizure types	Convulsive (tonic, clonic, tonic-clonic or atonic), myoclonic, partial, absence seizures		[redacted]		

Baseline characteristics*	**GWPCARE1**		**GWPCARE2**		
Baseline seizure frequency	All seizures: median 24.0 per 28 days Convulsive seizures: median 12.4/28 days; range 3.9 to 1717	All seizures: median 41.5 per 28 days Convulsive seizures: median 14.9/28 days; range 3.7 to 718	[redacted]	[redacted]	[redacted]
Prior AED use	Mean 4.6 AEDs; SD 4.3	Mean 4.6 AEDs; SD 3.3	[redacted]	[redacted]	[redacted]
Concurrent AED use	Mean AEDs: 3.0; SD 1.0 Clobazam: 40 Valproate: 37 Stiripentol: 30 Levetiracetam: 16 Topiramate: 16 Ketogenic diet: 6 Vagus nerve stimulation: 6	Mean AEDs: 2.9; SD 1.0 Clobazam: 38 Valproate: 34 Stiripentol: 21 Levetiracetam: 17 Topiramate: 15 Ketogenic diet: 4 Vagus nerve stimulation: 9	[redacted]	[redacted]	[redacted]

Source: CS[1] and GWPCARE1 CSR[14]and GWPCARE2 CSR[15]
Footnote: *Missing data were taken from the full CSRs (including separate files containing Tables and Figures), which were provided by the company in their clarification response. Where there were discrepancies between the CS and the CSRs, data were taken from the CSRs.

CCM = current clinical management

GWPCARE1 had a total of 120 patients and GWPCARE2 198. The mean age across both trials was approximately nine. Female and male participants were represented equally in the trials. The overall percentage of women in GWPCARE1 was 48% and in GWPCARE2 was 53%. Both trials had predominantly participants who identified as white (GWPCARE1 78%, GWPCARE 2: 89%). Around half of the participants across the two trials were from the USA. Patients had used on average four or five prior AEDs although as mentioned in Section 3.1 there was a large range of prior treatments (0 to 26). The average number of concurrent treatments was three, although again the range was large.

ERG comment:

- The trials reflect a younger population with Dravet syndrome (mean age of nine and all participants under 18 as per the trials' inclusion criteria)
- The ERG notes that Black and Asian people appear to be underrepresented across the two trials.

The ERG asked a number of questions relating to the population defined in the decision problem[12] and the populations included in the key trials, GWPCARE1 and GWPCARE2. The following have been previously discussed in Section 3.1 so will only be briefly summarised here.

- The company was asked, given the numbers of prior AEDs used by participants, if the trials had more severe populations than might be expected in clinical practice? They stated that polypharmacy on this scale is not uncommon but did not provide any associated references. However, the ERG considered the company's response to be reasonable.
- The company was asked if the number of concurrent treatments in the trials reflected UK practice. They stated that it did but did not provide any accompanying support from clinical experts for this statement. This may benefit from discussion at committee.
- The company was asked how many UK centres and patients were involved in GWPCARE1 (GWPCARE2 did not have any UK patients). They stated that there were four UK sites in GWPCARE1, of which three recruited, and overall there were 16 UK patients in GWPCARE1. The company stated that there were too few UK patients in the trial to provide efficacy outcomes for UK patients specifically. This appears reasonable.
- The ERG asked the company if there was evidence to suggest an association between baseline seizure frequency and the patient's current clinical management. (ERG question A14). The company responded:

'In general, the data support the conclusion that existing prescribing is highly heterogeneous and patients are refractory to existing treatment modalities.

Due to the orphan nature of the disease, no formal pre-specified or post-hoc analysis to assess the association between baseline seizure frequency and CCM treatment was done.

Based on an informal analysis of the patient level data in GWPCARE1 and GWPCARE2 combined, there is a strong correlation between baseline seizure burden and number of concomitant AEDs, as is to be expected (see the figure below). A descriptive analysis of drug proportions amongst patients stratified by seizure frequency at baseline (also in the figure below) for the most commonly used pharmacological agents does not show any obvious trends.' [12]

The ERG is satisfied with this explanation.

4.2.4 Risk of bias assessment for included cannabidiol studies

The quality assessment of the key trials, reported in Appendix D of the CS, recorded judgements alone and did not include any supporting information. It was not clear how many reviewers were involved in the quality assessment process. The particular quality tool used was not referenced. Elements assessed were randomisation, allocation concealment, baseline comparability, researcher blinding, dropout imbalances, selective outcome reporting and use of intention to treat analysis.[1] The company's assessments of GWPCARE1 and GWPCARE2 are in Table 4.4.

Table 4.4: Quality assessment GWPCARE1

	GWPCARE1	GWPCARE2
Randomisation appropriate?	Yes	Yes
Treatment concealment adequate?	Unclear	Unclear
Baseline comparability adequate?	Unclear	Unclear
Researcher blinding adequate?	Yes	Yes
Dropout imbalances?	No	No
Outcome reporting selective?	No	No
Intention to treat?	Yes	Yes
Overall risk of bias?	Low	Low
Source: Table 46, Appendix D of the CS[1]		

ERG comment: Overall the trials were rated by the company as high quality and at low risk of bias. However, the ERG noted that trials would not normally receive a high rating when both treatment concealment and baseline comparability elements have been described as 'unclear'. The ERG re-assessed the two trials against the criteria above. Based on information in the CSRs, treatment concealment appeared to be adequate. Furthermore, the company appeared to have considered baseline comparability in their analyses. The quality assessment did not include an item on the adequacy of participant blinding; but based on information about the matched composition of the intervention and placebo, provided in the CSRs, the ERG considers that participant blinding was adequate. There was some imbalance in dropout (GWPCARE1 CBD 20 mg/kg/day arm: 9/61 [14.8%]; CCM arm: 3/59 [5.1%] and GWPCARE2 CBD 20 mg/kg/day arm: 6/67 [9.0%]; 10 mg/kg/day arm: 3/67 [4.5%]) and CCM arm: 0). However, analysis was conducted based on an intention-to-treat analysis including these patients.

4.2.5 Efficacy results

The efficacy results for GWPCARE1 and GWPCARE2 are shown in Table 4.5. This table includes results for outcomes reported in the CS, with additional data (e.g. baseline and endpoint values, interquartile range (IQR)) as provided in the company's clarification response.[12] and CSRs.[14, 15] Where results differed between sources, the company CSRs were used. The number of convulsive seizure-free days per 28-day period, a key outcome used in the cost effectiveness modelling but not listed in the company's definition of decision problem, is provided; again, results for this outcome were taken from the CSR tables provided in the company's clarification response.

Table 4.5: Efficacy results of GWPCARE1 and GWPCARE2

	GWPCARE1		GWPCARE2		
	Cannabidiol 20 mg/kg/day + CCM	**Placebo + CCM**	**Cannabidiol 10 mg/kg/day + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**
Number randomised	61	59	[redacted]	[redacted]	[redacted]
Study duration	14 weeks		[redacted]		
Primary outcome: Convulsive seizure frequency per 28 days					
Baseline convulsive seizure frequency	Median 12.4 (IQR 6.2 to 28.0	Median 14.9 (IQR 7.0 to 36.0)	[redacted]	[redacted]	[redacted]
Treatment period convulsive seizure frequency	Median 5.9 (IQR 3.2 to 17.3)	Median 14.1 (IQR 4.2 to 31.1)	[redacted]	[redacted]	[redacted]
% change in convulsive seizures during treatment	Median -38.9 (IQR -69.5 to – 4.8)	Median -13.3 (IQR -52.5 to 20.2)	[redacted]	[redacted]	[redacted]
Comparison to placebo	Median difference -22.8 (95% CI: -41.1 to -5.4); p = 0.012)	NA	[redacted]	[redacted]	[redacted]
Secondary outcomes					
Total seizure frequency per 28 days					
Baseline total seizure frequency	Median 24.0 (IQR 10.4 to 141.0)	Median 41.5 (IQR 12.0 to 367.0)	[redacted]	[redacted]	[redacted]

	GWPCARE1		GWPCARE2		
Treatment period total seizure frequency	Median 13.7 (IQR 4.8 to 137.2)	Median 31.1 (IQR 7.7 to 282.6)	[redacted]	[redacted]	[redacted]
% change in total seizures during treatment	Median -28.6 (IQR -70.4 to -4.0)	Median -9.0 (IQR -51.4 to 19.6)	[redacted]	[redacted]	[redacted]
Comparison to placebo	Difference 22.8 (95% CI: 5.4, 41.1)	NA	[redacted]	[redacted]	[redacted]
Response rate					
≥50% reduction in convulsive seizures	26 (42.6%)	16 (27.1%)	[redacted]	[redacted]	[redacted]
Comparison to placebo	OR 2.00 (95% CI: 0.93 to 4.30); p = 0.078	NA	[redacted]	[redacted]	[redacted]
75% reduction in convulsive seizures	14 (23.0%)	7 (11.9%)	[redacted]	[redacted]	[redacted]
Comparison to placebo	OR 2.21 (95% CI: 0.82 to 5.95); p = 0.112	NA	[redacted]	[redacted]	[redacted]
100% reduction in convulsive seizures during treatment period	3 (4.9%)	0 (0%)	[redacted]	[redacted]	[redacted]
Comparison to placebo	Difference 4.9% (95% CI: -0.5 to 10.3); p = 0.083	NA	[redacted]	[redacted]	[redacted]
Use of rescue medication	36 (59.0%)	41 (69.5%)	[redacted]	[redacted]	[redacted]
Global impression of change					
CGIC improvement in overall condition	37 (60.7%)	20 (33.9%)	[redacted]	[redacted]	[redacted]

	GWPCARE1		GWPCARE2		
Status epilepticus					
Convulsive status epilepticus at baseline	0	1 (1.7%)	[redacted]	[redacted]	[redacted]
Convulsive status epilepticus in treatment period	1 (1.6%)	0	[redacted]	[redacted]	[redacted]
Non-convulsive status epilepticus at baseline	2 (3.3%)	3 (5.1%)	[redacted]	[redacted]	[redacted]
Non-convulsive status epilepticus in treatment period	2 (3.3%)	2 (3.4%)	[redacted]	[redacted]	[redacted]
Quality of life					
Overall QOLCE score mean (SD) change from baseline to end of treatment	5.4 (14.60)	3.8 (9.93)	[redacted]	[redacted]	[redacted]
Comparison to placebo	Mean difference 1.5 (95% CI: -3.8 to 6.8); p = 0.577	NA	[redacted]	[redacted]	[redacted]
Convulsive seizure-free days per 28 days					
Baseline period	NR	NR	[redacted]	[redacted]	[redacted]
Treatment period	NR	NR	[redacted]	[redacted]	[redacted]
Change from baseline	NR	NR	[redacted]	[redacted]	[redacted]
Comparison to placebo	NR		[redacted]	[redacted]	[redacted]

Source: CS Tables 10 and 11[1]and CSRs[14, 15]

*[redacted]

CGIC = Caregiver Global Impression of Change; IQR = interquartile range; OR = odds ratio; QOLCE = Quality of Life in Childhood Epilepsy

ERG comment: The ERG notes that only GWPCARE2 provides effectiveness data for the recommended dose of CBD, 10 mg/kg/day, which is specified as the starting dose for all patients in the company's response to clarification.[12] Patients in GWPCARE2, who received 10 mg/kg/day CBD in addition to CCM, achieved better seizure frequency outcomes than those who received CCM + Placebo. For convulsive seizures the company changed the primary outcome analysis method to use negative binomial regression which gave a rate ratio of [redacted] A sensitivity analysis using a Wilcoxon rank sum test and the Hodges-Lehmann estimate of the median difference (the original analysis plan) [redacted] A higher proportion of patients in the 10 mg/kg/day CBD group achieved at least a 50% reduction in convulsive seizures, during the treatment period, than in the placebo group ([redacted]). [redacted] patients in the CBD group of GWPCARE2 and [redacted] in the placebo group achieved freedom from convulsive seizures for the whole 14-week treatment period.

Patients in the 10 mg/kg/day CBD group of GWPCARE2 experienced fewer seizures overall, during the 14-week treatment period, than those in the placebo group ([redacted]).

The ERG does not consider the clinical effectiveness evidence for the 20 mg/kg/day dose of CBD to be directly relevant to this submission. Since the company have stated in their clarification response,[12] that only those patients who the physician considers may gain additional seizure reduction by dose escalation will receive the 20 mg/kg/day dose, and this has been defined as those experiencing ≥75% reduction in convulsive seizures on the 10 mg/kg dose, then data on the clinical effectiveness of the 20 mg/kg/day dose are only relevant for this specific subgroup. Neither the CS nor the CSRs provided data on the effectiveness of 20 mg/kg/day CBD in the subgroup of patients who had responded adequately to the 10 mg/kg/day dose.

The company were asked to provide the results of comparisons between the 20 mg/kg/day and 10 mg/kg/day groups in GWPCARE2, for all outcomes where these were available. The company stated, in their clarification response,[12] that: '*No formal pre-specified test for significance between the CBD groups was included in the SAPs.*' The ERG notes that the CS.[1] Section B.2.6, includes the statement that: '*A higher proportion of patients in the 20 mg CBD group achieved at least a 75% reduction in convulsive seizures (25%) compared with the 10 mg group (11%) and the placebo group (3%).*' The ERG therefore questions the validity of the criteria for dose escalation, described above.

The CS did not include any data on the long-term effectiveness (>14 weeks) of CBD + CCM compared to placebo + CCM. The CS included some interim results from an ongoing open-label extension study (GWPCARE5), see section 4.2.9 of this report. However, the ERG does not consider these results to be directly applicable to this submission, since for [redacted] of participants with DS, the modal dose during the treatment period was >[redacted] The overall mean modal dose for DS patients was [redacted]). The overview of trial design, given in the interim report for this study,[17]states that: [redacted]

[redacted]

We asked the company to comment on the relatively large placebo response observed across the trials included in the CS. The company provided a detailed, referenced response summarised by the following points:

- Large placebo effects are well documented in epilepsy clinical trials. Although no study has formally assessed placebo effects across DS studies, they have been consistently observed in LGS studies.
- A comparison of the size of the placebo effect in GWPCARE1 and GWPCARE2 relative to those seen in other studies in DS is not possible, as there is too much heterogeneity in study design between trials. Nonetheless, numerical comparisons have been published for LGS trials. The primary endpoint (median percent change in convulsive seizure frequency from baseline) in GWPCARE3 (which studied a CBD dose of 10 mg/kg/day in patients with LGS) showed a placebo effect that was at the upper end of, but still in line with, those seen with other agents.
- Even with this placebo effect, a robust treatment effect on the primary and all secondary endpoints was achieved at a CBD dose of 10 mg/kg/day. Assessed across the totality of the clinical development plan, this treatment effect was consistently observed across two studies at a dose of 10 mg/kg/day and four studies at a dose of 20 mg/kg/day. It was further maintained in the open-label extension study.
- The hypothesised sources of placebo effects cited in the literature are either an artefact of the clinical trial environment, or a short-term psychological response to "something new" in patients/caregivers with a high level of clinical need. These effects are unlikely to apply and persist in clinical practice, especially given the highly drug-resistant nature of DS patients.

The ERG agrees with that the placebo effects observed in CBD trials are at the upper end of, but still broadly in line with, those seen with other agents.

4.2.6 Subgroup analysis for included cannabidiol studies

The CS (Section B.2.7) stated that '*no subgroup analyses were conducted*.' However, the CSRs for both key trials (GWPCARE1[14] and GWPCARE2[15]) reported a number of subgroup analyses. The company was asked for further details of the subgroup analyses. They indicated that the primary and key secondary endpoints were analysed for GWPCARE2 and very similar groups for GWPCARE1: Age group (2-5 years, 6-12 years and 13-18 years), Sex (Male, Female), Region (US, Rest of the World), Clobazam use (Yes, No), Valproate use (Yes, No), Stiripentol use (Yes, No), Clobazam and Stiripentol use (Yes, No), Levetiracetam use (Yes, No), Topiramate use (Yes, No), Baseline average convulsive seizure frequency per 28 days (≤ observed tertile 1, > observed tertile 1 to ≤ observed tertile 2, > observed tertile 2), Number of current AEDs (<3, ≥3) and Number of prior AEDs (<8, ≥8). The company further stated that '*These outcomes were not included in the Evidence Submission as they are not relevant to clinical prescribing or the cost-utility analysis. They are standard demographic subgroup analyses that are done as part of any SAP. Furthermore, as an orphan indication, these subgroups have small population numbers with low statistical powering. For the recommended 10 mg/kg/day dose, no clinically relevant trends were seen in these subgroup analyses; the point estimates were similar to that for the ITT population, and CIs between them heavily overlapped.*'[12] Results of the subgroup analysis are presented in Figure 4.1 for the primary endpoint of GWPCARE2 only as this trial compared the proposed dose of CBD (10 mg/kg/day) to placebo.

Figure 4.1:Subgroup analysis of the primary endpoint (10 mg/k/day CBD vs. placebo): negative binomial regression effect modification analysis of convulsive seizure count during baseline and treatment periods (ITT analysis set)

[redacted]

The ERG agrees with the company that the very small numbers of patients in some subgroups mean that the results of these analyses cannot be considered reliable. However, we do not agree that these analyses are '*standard demographic subgroup analyses that are done as part of any statistical analysis plan*' and are '*not relevant to clinical prescribing or the cost-utility analysis.*' The subgroup analyses relating to current and prior AED use and to baseline seizure frequency are specific to this clinical topic area.

[redacted]

4.2.7 Health-related quality of life data for included cannabidiol studies

The CS clinical effectiveness results section did not include any results for health-related quality of life outcomes.[1] Overall results for the Quality of Life in Childhood Epilepsy (QOLCE) score were provided in the company's clarification response and these are reproduced in Table 4.5 of this report.

The innovation section of the CS (Section B.2.12) stated that: '*It is also important to consider that, for some patients with DS, their quality of life may be impaired as much by the side-effects of current treatments and polypharmacy as by the seizures themselves. For those patients who respond to CBD, there may be an opportunity to reduce their concomitant drug burden over time. This may be achieved either through a reduction in dose or through complete elimination of concomitant AEDs, thereby potentially reducing the overall drug-related adverse event burden in these patients.*'[1]

ERG comment: The ERG notes that none of the included trials provided data on reduction or complete elimination of concomitant AEDs. In GWPCARE1 and GWPCARE2, all medications or interventions for epilepsy were required to be stable for four weeks prior to screening and patients had to be willing to maintain a stable regimen throughout the study.

4.2.8 Safety results

This section considers the information about adverse events provided in the CS. A more detailed breakdown of AEs and serious adverse events (SAEs) was provided by the company in their clarification response, along with interim results from the open-label extension study, GWPCARE5.[17] These results are summarised in Table 4.6. Table 4.7 provides details of those individual, treatment-related adverse events which occurred in at least 3% of patients, in any of the included studies. These data appear to indicate a pattern of gastrointestinal and 'tiredness'-related AEs in patients taking CBD, as well as a detrimental effect on markers of liver function. With respect to markers of liver function, the CS[1] reported '*Raised liver aminotransferases were reported with CBD and were seen more often with the higher dose of CBD (20 mg/kg/day), when the patient had elevated transaminases at baseline, or when CBD was taken with concomitant valproate or clobazam. Cases of raised liver transaminases resolved either spontaneously (without dose reduction or interruption of CBD treatment during the studies) or with dose adjustments of CBD or concomitant AEDs'* The rates of individual, treatment-related AEs were generally higher in the 20 mg/kg/day CBD groups than in the 10 mg/kg/day CBD group.

The company's clarification response[12] included the following additional detail on SAEs for the two main included studies:

GWPCARE1

'In total, 10 patients (8.3%) developed at least 1 (all-causalities) TEAE that led to discontinuation and withdrawal from the study: 9 patients in the CBD group (14.8%) (although 1 patient was reported as 'Withdrawn by the Investigator') and 1 patient in the placebo group (1.7%).

Treatment-related TEAEs leading to discontinuation of IMP were reported in 8 CBD patients (13.1%). No treatment-related TEAEs leading to discontinuation of IMP were reported in the placebo group.

Five patients reported at least 1 TEAE leading to withdrawal that was also considered a serious TEAE.

The majority of TEAEs leading to discontinuation were considered treatment-related (25/28 events [89.3%]). The only exceptions were 1 event of moderate convulsion (reported as a serious TEAE) in a CBD patient, 1 event of severe liver function test abnormal in a placebo patient, and 1 event of mild pyrexia in a CBD patient (NB. the latter patient also experienced decreased appetite and fatigue [both moderate] concurrently that were considered treatment-related and were also reported as the reason for withdrawal).

The most common treatment-related TEAE leading to discontinuation was somnolence, which was reported in 5 CBD patients (8.2%). For 4 of these patients, the event was reported as severe and of these, 2 were also considered serious. The remaining patient experienced moderate somnolence. For each patient, the event resolved following cessation of IMP and withdrawal from the trial.

Collectively, 4 CBD patients had liver-related TEAEs that led to withdrawal (PTs: AST increased, GGT [reported term: GGT 115 U/L], transaminases increased, and liver function test abnormal); all events were moderate or severe, considered treatment-related, and most resolved (4/5 events; 80%). Treatment-related decreased appetite leading to discontinuation was reported in 3 CBD patients (4.9%). For 2 of these patients, the event was moderate and for 1 patient it was severe and considered serious. For each patient, the event resolved following cessation of CBD and withdrawal from the trial.

Treatment-related fatigue, AST increased, convulsion, and hypotonia leading to discontinuation of IMP were each reported in 2 CBD patients and led to those patients withdrawing from the trial. One patient

experienced moderate fatigue and severe AST increased concurrently (along with severe GGT and severe platelet count), all of which led to withdrawal, were considered serious TEAEs, and resolved following cessation of CBD. Another patient experienced convulsion and hypotonia concurrently (along with somnolence and aggression), all of which were severe in intensity and resolved following cessation of CBD.

All other TEAEs leading to discontinuation were reported in a single patient only. Only 1 TEAE leading to discontinuation was ongoing following withdrawal of the patient from the trial. This CBD patient experienced moderate transaminases increased; the event was not considered a serious TEAE and the patient experienced no other TEAEs leading to withdrawal.'

GWPCARE2

'[redacted]'

GWPCARE5

No narrative detail was provided for GWPCARE5. The interim report for GWPCARE5[17] included the following information about SAEs for the overall study population (LGS and Dravet syndrome combined):

[redacted]

As can be seen from Table 4.6, the numbers of withdrawals due to adverse events occurring in DS patients during the open-label extension study were not reported. The interim report [redacted][17] [redacted][17] [redacted] The relevant tables, detailing numbers of withdrawals and reasons for withdrawal, were missing from the interim report provided by the company in the clarification response.[12]

ERG comment: The ERG is concerned that the apparently high rate of withdrawals from GWPCARE5, which were not attributable to adverse events, together with the dose escalation in some patients (up to a maximum of 30 mg/kg), may indicate a loss of efficacy over time. No evidence has been provided to support the long-term efficacy (beyond 14 weeks) of the recommended CBD dose (10 mg/kg). [redacted]

The RCTs included in the CS were too small and of too short duration to provide a full picture of the adverse event profile of CBD and the open-label extension study, GWPCARE5 does not provide data about the recommended CBD dose (10 mg/kg/day).

The safety results for GWPCARE1, GWPCARE2 and GWPCARE5 are shown in Tables 4.7 to 4.8. This Table includes results for outcomes reported in the CS, with additional data taken from the company's clarification response and CSRs.

Table 4.6: Safety results of GWPCARE1, GWPCARE2 and GWPCARE5

	GWPCARE1		GWPCARE2			GWPCARE5
	Cannabidiol 20 mg/kg/day + CCM	**Placebo + CCM**	**Cannabidiol 10 mg/kg/day + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol (variable dose) DS patients**
Number in safety analysis set*	61	59	[redacted]	[redacted]	[redacted]	[redacted]
No (%) with adverse events	57 (93.4%)	44 (74.6%)	[redacted]	[redacted]	[redacted]	[redacted]
No (%) with serious adverse events	10 (16.4%)	3 (5.1%)	[redacted]	[redacted]	[redacted]	[redacted]
No (%) withdrawals due to adverse events	9 (14.8%)	1 (1.7%)	[redacted]	[redacted]	[redacted]	[redacted]
No (%) Treatment-related adverse events	43 (70.5%)	16 (27.1%)	[redacted]	[redacted]	[redacted]	[redacted]
No (%) Treatment-related serious adverse events	5 (8.2%)	0	[redacted]	[redacted]	[redacted]	[redacted]
No (%) withdrawals due to TRAEs	8 (13.1%)	0	[redacted]	[redacted]	[redacted]	[redacted]
No (%) of deaths	0	0	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS [1], Clarification response[12] and CSRs[14, 15, 17]

* All randomised patients who took at least one dose of study medication were included and analysed according to the treatment received; **not considered to be treatment-related

CCM = current clinical management; TRAE = treatment-related adverse event

Table 4.7: Treatment-related adverse events occurring in ≥3% of patients in any study GWPCARE1, GWPCARE2 or GWPCARE5

	GWPCARE1		GWPCARE2			GWPCARE5
	Cannabidiol 20 mg/kg/day + CCM	**Placebo + CCM**	**Cannabidiol 10 mg/kg/day + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol (variable dose) DS patients**
No in safety analysis set*	61	59	[redacted]	[redacted]	[redacted]	[redacted]
No of patients (%) with						
Abdominal pain	2 (3.3%)	1 (1.7%)	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	13 (21.3%)	2 (3.4%)	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	10 (16.4%)	1 (1.7%)	[redacted]	[redacted]	[redacted]	[redacted]
Gait disturbance	3 (4.9%)	0	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
GGT increased	4 (6.6%)	0	[redacted]	[redacted]	[redacted]	[redacted]
LFT abnormal	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Transaminases increased	4 (6.6%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Toxicity to various agents	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	3 (4.9%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	13 (21.3%)	3 (5.1%)	[redacted]	[redacted]	[redacted]	[redacted]
Increased appetite	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Ataxia	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Balance disorder	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Convulsion	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]

	GWPCARE1		GWPCARE2			GWPCARE5
	Cannabidiol 20 mg/kg/day + CCM	**Placebo + CCM**	**Cannabidiol 10 mg/kg/day + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol (variable dose) DS patients**
Hypotonia	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Lethargy	7 (11.5%)	2 (3.4%)	[redacted]	[redacted]	[redacted]	[redacted]
Poor quality sleep	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Sedation	1 (1.6%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Psychomotor disorder	1 (1.6%)	2 (3.4%)	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal behaviour	1 (1.6%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Irritability	4 (6.6%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	19 (31.1%)	4 (6.8%)	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS [1], Clarification response[12] and CSRs[14, 15, 17]
* All randomised patients who took at least one dose of study medication were included and analysed according to the treatment received
CCM = current clinical management

4.2.9 Supporting efficacy evidence from the ongoing GWPCARE5

GWPCARE5 is an ongoing, open-label extension of GWPCARE1 and GWPCARE2 and also of GWPCARE3 and GWPCARE4 (Lennox-Gastaut syndrome). It aims to investigate the safety of cannabidiol in children and adults with inadequately controlled DS or LGS who had previously participated in one of the previous trials. The trial is estimated by the company to complete in June 2019. As yet the trial has published only interim findings in abstract format.

The primary outcome is incidence of adverse events and other measures of safety with patients being followed up for a maximum of three years. These data have been included in the previous section on adverse events. Efficacy outcomes are also being assessed through comparison with baseline values in the randomised study in which the patient participated.

The interim efficacy results were based on 14% of the 278 participants who had completed the study after a median of 50 weeks (range 1 to 99 weeks). There was a median 44% to 57% reduction in convulsive seizures from a baseline of 12 per 28 days and a median 49% to 67% reduction in total seizures from a baseline frequency of 32 per 28 days with cannabidiol. Fifty-two percent of the 278 patients were still undergoing treatment, and 34% had withdrawn from the study.[1]

ERG comment: The ERG does not consider this open-label extension study to be directly applicable to this submission, since it does not include follow-up data from patients continuing on an uninterrupted maintenance dose of 10 mg/kg/day. The overview of trial design, given in the interim report for this study,[22] states that:

[redacted]

4.2.10 Ongoing trials

Apart from GWPCARE5, the company did not list any other relevant ongoing trials.

ERG comment: The company were further asked '*Are there any other ongoing studies that would provide relevant information for this submission (such as longer-term follow-up data relating to changes in mortality including sudden unexpected death in epilepsy (SUDEP))? If so, when will data become available for these studies*?'[12] The company stated that there were not.

There is a lack of long-term data on the effects of CBD on Dravet syndrome. The main randomised trials, as previously stated, are of 14 weeks' duration so cannot provide long-term data on SUDEP and other deaths. The exact link between reduction in convulsive seizures and any associated reductions in mortality cannot be determined from the two randomised trials.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

4.5 Conclusions of the clinical effectiveness section

The CS included a systematic review of the evidence for CBD for DS. From this review the company identified and presented evidence from two RCTs (GWPCARE1 and GWPCARE2) and an open-label extension study (GWPCARE5). Both RCTs (GWPCARE1 and GWPCARE2) were conducted in patients aged two to 18 years with DS, whose seizures were incompletely controlled with previous AEDs and who had had at least four convulsive seizures per week in the past 28 days. Although the decision problem did not specify any age restriction and the expected licenced indication for Epidyolex® is for patients two years of age and older, neither of the key trials used in the submission (GWPCARE1 and GWPCARE2) included adult patients (over the age of 18 years). Therefore, adults with DS are not represented in the CS.

The company expects to place CBD as an add on treatment for refractory seizures in people aged two years or older once two other appropriate AEDs trialled to a maximum dose have failed to achieve seizure freedom. However, across the two trials approximately 16% of patients had received no or one previous (discontinued) AEDs. It should be noted that these patients may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled.

One of the RCTs had 16 UK patients, the other had none. This is most relevant when considering the nature of background current clinical management, which is the comparator in the trials. Current clinical management is considered to be a 'basket' of choices of AED and although the company conducted a number of subgroup analyses based on the presence or absence of various AEDs, they assumed that there were no treatment interaction effects. The ERG questions this assumption.

A major limitation of the evidence is the small size of the data set relating to the 10 mg/kg/day cannabidiol dose to be used in practice. Just 66 patients in GWPCARE2 and none in GWPCARE1 received the 10 mg/kg/dose. In the open-label extension study, GWPCARE5, the average dose was [redacted] making this study less relevant to the decision problem.

A further limitation is the short-term nature of the RCTs (14 weeks). There is a lack of long-term efficacy and safety data particularly based on the 10 mg/kg/day dose. Any observations of reduction in seizures in the short-term trials, particularly convulsive seizures, may not be sustained in the long-term and the effects on outcomes relating to mortality (especially SUDEP) are unknown.

Patients in GWPCARE2, who received 10 mg/kg/day CBD in addition to CCM, experienced fewer convulsive seizures and fewer seizures overall, during the 14-week treatment period, than those in the placebo group. Alongside this, safety data appear to indicate a pattern of gastrointestinal and 'tiredness'-related AEs in patients taking CBD, as well as a detrimental effect on markers of liver function. The ERG is concerned that the apparently high rate of withdrawals from GWPCARE5, which were not attributable to adverse events, together with the dose escalation in some patients (up to a maximum of 30 mg/kg/day), may indicate a loss of efficacy over time. No evidence has been provided to support the long-term efficacy (beyond 14 weeks) of the recommended CBD dose (10 mg/kg/day).

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Searches performed for cost effectiveness section

The company submission reported that a rigorous systematic review was carried out to identify relevant publications for the efficacy, safety and development of economic models for the use of cannabidiol in Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS).[1] The main submission presented one set of searches used to inform both the clinical and cost effectiveness content for both LGS and DS in Appendix D.[1] As the searching for the whole submission was conducted at once, the ERG's appraisal and comments are presented in section 4.1.1 of this report.

5.1.2 Inclusion/exclusion criteria used in the study selection

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 5.1.

Table 5.1: Eligibility criteria for the systematic literature reviews

PICOS	Inclusion criteria	Exclusion criteria
Patient population	• Any age • Any gender • Any race • Has DS/SMEI • Or a caregiver of a patient with DS (only applicable to utility and cost searches)	No data reported on relevant population
Intervention	• Any intervention included in the efficacy review • Placebo (only applicable to utility search) • Best supportive care (only applicable to utility and costs searches) • No intervention (only applicable to utility and costs searches)	No data reported on relevant intervention
Comparator	• Any of the included interventions • Placebo (only applicable to cost effectiveness studies search) • Best supportive care (only applicable to cost effectiveness studies search) • No comparator (only applicable to utility and costs searches)	No data reported on relevant comparator

PICOS	Inclusion criteria	Exclusion criteria
Outcomes(s) 1 (Published economic evaluations)	• Cost per life-year saved • Cost per QALY gained • Costs saved	No data reported on a relevant outcome
Outcomes(s) 2 (Utility studies)	• Utility values • Other quality of life measures using an established questionnaire	No data reported on a relevant outcome; qualitative study reporting views
Outcomes(s) 3 (Cost/resource use studies)	• Direct costs • Indirect and informal costs • Resource use	No data reported on a relevant outcome
Study design 1 (Cost effectiveness analysis studies)	• Cost-benefit analyses • Cost-effectiveness analyses • Cost-utility analyses • Budget Impact models • Cost minimisation models • Other economic models • Systematic reviews were used for citation chasing only • Studies only available as conference abstracts were included if they reported sufficient relevant data to inform model development or parameterisation	Other study design
Study design 2 (Utility studies)	• Randomised controlled trials • Observational studies • Systematic reviews were used for citation chasing only • Studies only available as conference abstracts were included if they reported sufficient relevant data to allow analysis	Other study design
Study design 3 (Cost/resource use studies)	• Randomised controlled trials	Other study design

PICOS	Inclusion criteria	Exclusion criteria
	• Observational studies • Database studies • Systematic reviews were used for citation chasing only • Studies only available as conference abstracts were included if they reported sufficient relevant data to inform model development or parameterisation	
Source: Appendix G, I and H of the CS [1].		

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies.

5.1.3 Included/excluded studies in the cost effectiveness review

In total, five unique economic modelling publications met the pre-defined eligibility criteria, including four analyses of HTA submissions of stiripentol[23-26] and an economic evaluation reporting a cost utility Markov model of stiripentol for the treatment of patients with DS who have been unresponsive to concomitant treatment with clobazam and valproate, for the Canadian jurisdiction.[27] No cost effectiveness studies appraising CBD were identified from the search.

The search yielded six utility studies that were relevant to the reference case of patients with DS who were either receiving a drug therapy of interest or were reporting on quality of life (QoL) regardless of treatments.[5, 25, 27-30] However, none of the studies estimated utilities for health states defined by number of convulsive seizures and convulsive seizure-free days, two main parameters in the economic model.

The search for studies reporting cost and resource use identified nine publication that were relevant for the UK.[5, 23, 24, 28, 31-35] However, none of these studies reported costs or resource use for health states defined by number of convulsive seizures and convulsive seizure-free days.

ERG comment: The rationales for excluding CE studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.2: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Cohort state transition model		B.3.2
States and events	• convulsive seizure free, • ≤8 convulsive seizures, • >8 - ≤25 convulsive seizures, • >25 convulsive seizures, • death	Absolute instead of relative reductions were preferred to define health states as they more accurately captures costs and quality of life.	B.3.2
Comparators	Current clinical management	Market research in the UK	B.3.3
Population	People with DS who are aged 2 years or older, whose seizures are inadequately controlled by current clinical management.	Consistent with the therapeutic indication proposed to the European Medicines Agency.	B.3.2
Treatment effectiveness	Treatment effectiveness was estimated based on the frequency of convulsive seizures, number of days without convulsive seizures and discontinuation rates.	The pivotal clinical trials (GWPCARE1 and GWPCARE2) and the open label extension study (GWPCARE5).	B.3.3
Adverse events	Adverse events were based on a pooled analysis considering both the DS and LGS pivotal clinical trials.	GWPCARE1, GWPCARE2, GWPCARE3 and GWPCARE4.	B.3.3
Health related QoL	Utilities were estimated using patient vignettes that were based on the health states included in the cost utility model.	No relevant utility values were identified by the systematic literature review.	B.3.4
Resource utilisation and costs	The cost categories included in the model were treatment costs, health state costs and mortality costs.	Resource utilisation and unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF), Personal Social Services Research Unit (PSSRU), Prescription cost analysis, published research and expert opinion.	B.3.5
Discount rates	Discount of 3.5% for utilities and costs.	As per NICE reference case.	Table 15
Subgroups	No subgroups were explored		B.3.9
Sensitivity analysis	Both DSA and PSA were performed as well as scenario analyses.		B.3.8

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Yes	
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Partly	Different (combinations of) AEDs were not considered as separate comparators.
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	No	Time horizon was restricted to 15 years.
Synthesis of evidence in outcomes	Systematic review (SLR)	Yes	
Measure of health effects	Quality adjusted life years (QALYs)	Yes	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	No	The patient vignette instrument that was used is not considered a standardised and validated instrument by the ERG.
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	No	VAS scores estimated using patient vignettes were used.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic modelling	Partly	Not all parameters have been included in

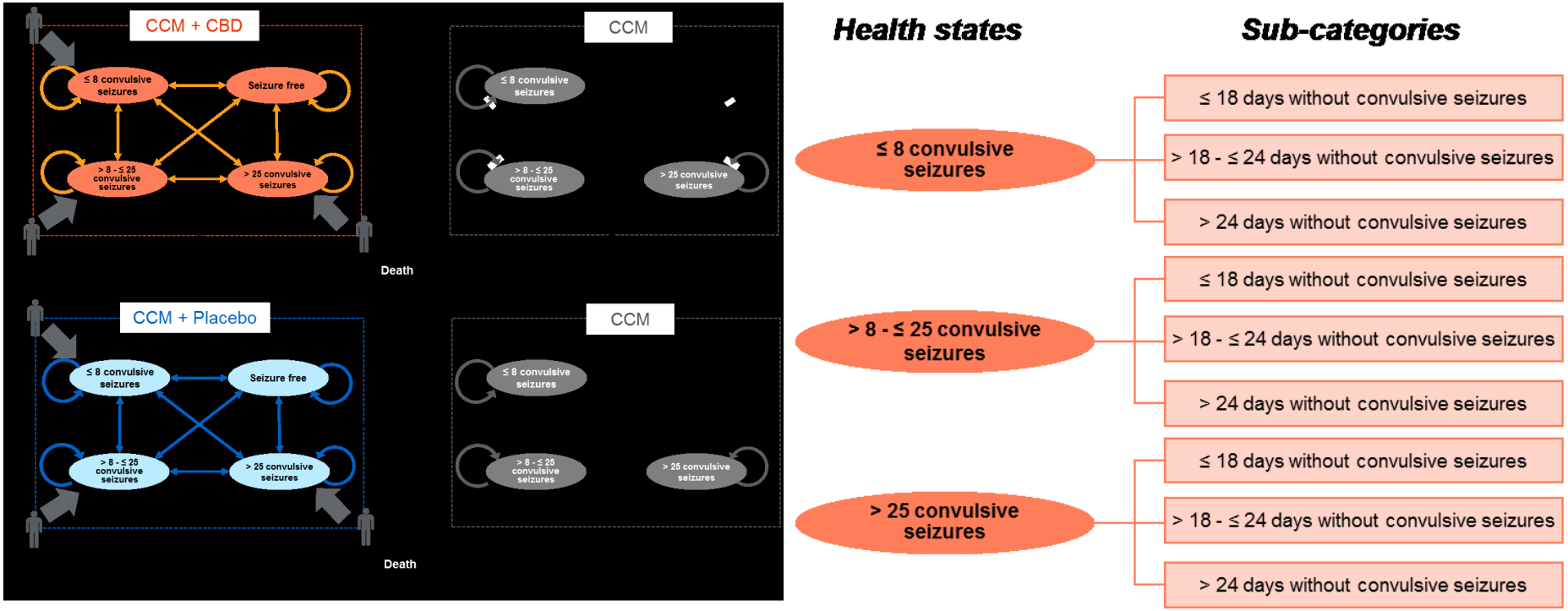
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
			the probabilistic analyses.
NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review			

5.2.2 Model structure

The company developed a cohort state transition model using Microsoft Excel®. The model consisted of five health states, i.e. convulsive seizure free, ≤8 convulsive seizures per 28 days, >8 - ≤25 convulsive seizures per 28 days, >25 convulsive seizures per 28 days, and death (Figure 5.1). Convulsive seizures were defined in the clinical study reports of GWPCARE1 and GWPCARE2 as tonic-clonic, tonic, clonic or atonic seizures.[14, 15] As improvements in patients' quality of life were assumed by the company to relate to the total number of convulsive seizures and number of convulsive seizure-free days, each of the convulsive seizure frequency health states was categorised into three sub-categories based on the number of convulsive seizure-free days experienced in the corresponding health state, i.e. ≤ 18 convulsive seizure-free days, > 18 - ≤ 24 convulsive seizure-free days, and > 24 convulsive seizure-free days (Figure 5.1). Patients receiving CCM plus CBD could transit between the four convulsive seizure frequency health states for the first nine cycles (i.e. 27 months), after which patients stayed in the same health state for the remaining duration of the analysis. Patients receiving CCM without CBD could transit between the convulsive seizure frequency health states during the first cycle only and returned to their baseline convulsive seizure frequency state afterwards (i.e. after three months). The transition probabilities for the first cycle were derived from the GWPCARE1 and GWPCARE2 trials. For the first nine cycles, time-dependent transition probabilities for CBD were estimated using the open-label extension study, GWPCARE5. Patients entered the model via one of the three health states with convulsive seizures (i.e. ≤ 8, > 8 - ≤ 25, > 25 convulsive seizures per month). At each cycle, patients receiving CBD plus CCM either continued to receive CBD, discontinued CBD or died. When patients discontinued CBD treatment, they returned to their baseline convulsive seizure frequency and remained in this state until the end of the time horizon. Patients receiving CCM without CBD could not discontinue treatment.

The model cycle length was three months, no half-cycle correction was used.

Figure 5.1: Model structure: convulsive seizure frequency health states and corresponding heath state sub-categories



Abbreviations. CBD: cannabidiol; CCM: current clinical management.
*Revert to baseline convulsive seizure frequency rates

Source: Based on Figure 3 and 4 of the CS [1]

ERG comment: The main concerns of the ERG relate to: a) not incorporating non-convulsive seizures in the model structure; b) the assumption that patients receiving CCM transfer back to their baseline convulsive seizure frequency after the first cycle; c) no half-cycle correction was used.

a) The health states defined in the model solely focus on convulsive seizures and convulsive seizure free days. Our concerns relate to the fact that patients with DS who have a reduction in convulsive seizures or who have become convulsive seizure-free, are still likely to suffer from non-convulsive seizures. For example, the health state convulsive seizure-free might include patients who are not free from non-convulsive seizures. When patients are still suffering from non-convulsive seizures, they are at risk of SUDEP and non-SUDEP. In response to clarification question B1a[12] the company clarified that in the GWPCARE studies non-convulsive seizures were an explanatory endpoint only. Nevertheless, it should be noted that overall seizure frequency is listed as a secondary outcome in the GWPCARE studies. Additionally, the company clarified that CBD showed an improvement in non-convulsive seizures. Furthermore, the company provided an overview of the number of non-convulsive seizures across the convulsive seizure frequency-defined health states and clarified that within the treatment period the median number of non-convulsive seizures reduces substantially across convulsive-seizure-based health states. In response to clarification question B1b[12] the company incorporated epilepsy-related SUDEP and non-SUDEP probabilities for the convulsive-seizure free health state that are >0.
b) In the model, patients receiving CCM transfer back to their baseline seizure frequency after the first cycle. In the CS and in response to clarification question B2,[12] the company clarified that this was done as a placebo effect was observed in both the GWPCARE1 and GWPCARE2 studies and argued it was not reasonable to assume that these effects would be sustained in clinical practice. The ERG does not agree with this approach as this effect may also be present in the CBD group (and hence is part of the demonstrated effects) and these patients do not transfer back to their baseline seizure frequency after the first cycle. Removing the presumed placebo effect for CCM while not removing it for CBD would likely result in an overestimated treatment effect for CBD (similar to that which might be expected with pre-post comparisons). Unfortunately, due to the complexity and the lack of transparency of the model, the ERG was not able to explore a scenario in which patients in the CCM group stay in their respective health state after the first cycle instead of transferring back to their baseline health state. The ERG considers that this assumption is most likely to bias the economic model in favour of CBD. The company further argued that patients discontinuing CBD treatment are transferred back to their baseline seizure frequency. However, as the number of days without convulsive seizures (and corresponding utility values) seems to be treatment-dependent favouring CBD, this is not seen as a conservative approach. This last comment is further elaborated upon in sections 5.2.6 and 5.2.8 (and considered in ERG analyses).
c) In response to clarification question B3b,[12] the company clarified that given the cycle length of three months, it was deemed not useful to apply a half-cycle correction. The ERG believes this to be a reasonable assumption which is likely to have minor implications to the results of the model.

5.2.3 Population

In line with its anticipated marketing authorisation, CBD was considered for the treatment of patients with DS who are aged two years or older and in whom the condition is inadequately controlled by the

established current clinical management (CCM) in the UK.[1] This is in line with the final scope issued by NICE. [16]

Baseline demographic characteristics such as mean age, weight and disease severity (i.e. frequency of convulsive seizures and the number of days without convulsive seizures) were obtained from GWPCARE1 and GWPCARE2, and were assumed to be the same for the entire cohort of patients entering the model, i.e. assumed to be treatment independent (Table 5.4).

Table 5.4: Key baseline patient characteristics as applied in the CS base-case model based on patient-level data of phase three GWPCARE1 and GWPCARE2 studies

	<12 years		**≥12 years**	
Demographic characteristics at baseline	[redacted]	[redacted]	[redacted]	[redacted]
% of patients	[redacted]	[redacted]	[redacted]	[redacted]
Mean age	[redacted]	[redacted]	[redacted]	[redacted]
Mean weight	[redacted]	[redacted]	[redacted]	[redacted]
Frequency of convulsive seizures at baseline				
≤ 8 convulsive seizures per 28 days	[redacted]		[redacted]	
> 8 - ≤ 25 convulsive seizures per 28 days	[redacted]		[redacted]	
> 25 convulsive seizures per 28 days	[redacted]		[redacted]	
Number of days without convulsive seizures (per 28 days) at baseline				
≤ 8 convulsive seizures per 28 days				
≤ 18 days	[redacted]		[redacted]	
> 18 - ≤ 24 days	[redacted]		[redacted]	
> 24 days	[redacted]		[redacted]	
> 8 - ≤ 25 convulsive seizures per 28 days				
≤ 18 days	[redacted]		[redacted]	
> 18 - ≤ 24 days	[redacted]		[redacted]	
> 24 days	[redacted]		[redacted]	
> 25 convulsive seizures per 28 days				
≤ 18 days	[redacted]		[redacted]	
> 18 - ≤ 24 days	[redacted]		[redacted]	
> 24 days	[redacted]		[redacted]	
Source: Based on Table 15 of the CS[1]				

ERG comment: The main concern of the ERG relates to the extent to which the population of the trial is representative for the target population of the model. The anticipated marketing authorisation for CBD focuses on the treatment of refractory seizures which are inadequately controlled by established clinical management. As indicated by the response of the company to clarification question A3b,[12] a small proportion (16% in GWPCARE1 and 15% in GWPCARE2) of the patients included in GWPCARE1 and GWPCARE2 do not match this definition (i.e. <2 prior, discontinued AEDs). It is unclear to what extent these patients have influenced the effectiveness parameters included in the model.

However, it should be noted that these patients may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled. Moreover, due to the limited number of patients aged 18-55 years in GWPCARE1 and GWPCARE2, it is unclear to what extent results of these trials hold true for the adult population.

5.2.4 Interventions and comparators

In the proposed licensed indication (currently awaiting marketing authorisation in the UK) for DS, CBD oral solution is recommended to be administered by means of a starting dose of 2.5 mg/kg twice daily (5 mg/kg/day) increased to a maintenance dose of 10 mg/kg/day [1]. In the CS, the base-case analysis utilises the maintenance dose of 10 mg/kg/day as the company assumes that the majority of patients will receive this dose in clinical practice.

In the GWPCARE2 trial, [14] efficacy of CBD was examined in two different dosages, i.e. CBD 10 mg/kg/day in addition to CCM, and CBD 20 mg/kg/day in addition to current clinical management. In the GWPCARE1 trial, [33] efficacy of CBD was examined based on a dosage of CBD 20 mg/kg/day in addition to CCM. In the open-label extension study (GWPCARE5), mean modal dose during treatment was [redacted]. [17]

For both trials, CCM consisted of (combinations of) clobazam, valproate, stiripentol, levetiracetam, topiramate, ketogenic diet, and vagus nerve stimulation. In the final scope issued by NICE, established clinical management without CBD includes combinations of sodium valproate, topiramate, clobazam, stiripentol, levetiracetam, ketogenic diet, and vagus nerve stimulation.

In the economic model, CCM was established as the following concomitant therapies: valproic acid, clobazam, stiripentol, topiramate and levetiracetam. The company assumed that, although the ketogenic diet and vagus nerve stimulation are issued in the final scope by NICE and clinical guideline 137 as second/third-line treatments alongside AEDs for DS, [8, 16] they were not recommended for all patients due to issues concerning adherence, adverse effects and long term complications such as bone fractures, kidney stones, decreased growth (ketogenic diet) and low efficacy (vagus nerve stimulation). As a result, they were explicitly not incorporated as CCM in the economic model.

ERG comment: The main concerns of the ERG relate to: a) the use of GWPCARE1 and the open label study GWPCARE5 to derive input parameters for the model as the prescribed dose in both studies is higher than the CBD 10 mg/kg/day in the base-case and the anticipated license; b) the combination of all AEDs as CCM.

a) In response to clarification question B7a, [12] the company stated that it is not clinically meaningful to compare patients on 10 mg/kg/day and 20 mg/kg/day doses of CBD. Furthermore, the company stated that the SmPC defines 10 mg/kg/day as the maintenance dose in clinical practice, with a small proportion of patients benefiting from escalation up to 20 mg/kg/day. However, both GWPCARE1 and GWPCARE5 focused on substantially higher dosages of CBD (20 mg/kg/day or more). The company stated (question B12a) that GWPCARE1 was only used to model scenarios in which a minority of patients is escalated to 20 mg/kg/day. In addition, in the CS base-case, transition probabilities for cycles 2-9 in the model were derived from the overall population in GWPCARE5. The company justifies this by stating '*the transition probabilities derived from GWPCARE5 are considered to be a good approximation for those that would have been observed on 10 or 20 mg/kg/day, and are not intended in the model to represent outcomes on doses above 20mg/kg/day.*'[12]

However, the company also stated (response to clarification question B7) '*that a minority of patients may achieve seizure-freedom on the higher dose*', seemingly suggesting that there is a difference in treatment effectiveness between CBD 10 mg/kg/day and CBD 20 mg/kg/day. Hence, it is questionable whether the GWPCARE5 evidence can be used for the maintenance dose of 10 mg/kg/day. To reflect the evidence from GWPCARE5, the ERG has explored the impact of a higher maintenance dose after the first cycle, by examining the results of a scenario in which the maintenance dose was increased to 20 mg/kg/day in accordance with results of the GWPCARE5 study in which [redacted] the mean modal dose was [redacted].[17]

b) Contrary to (the ERG's interpretation of) the final scope issued by NICE, different (combinations of) AEDs were not considered as separate comparators. This implies that the (cost) effectiveness of CBD is assumed to not vary with the combination to which it is added. However, the Clinical Study Reports (CSRs) for the key trials (GWPCARE1 and GWPCARE2) indicate that the company has also conducted a number of subgroup analyses that show an effect on the primary outcome of the presence of a specific AED or number of AEDs in the CCM combination. In response to clarification question B9a,[12] the company stated that given the orphan nature of the condition and the heterogeneous nature of the patients, it is not clinically or statistically meaningful to compare the intervention to individual or specific combinations of AEDs. Consequently, it is unclear to the ERG what the impact is of assuming that the (cost) effectiveness of CBD does not vary with different AED combination.

5.2.5 Perspective, time horizon and discounting

The analysis takes an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits, with a 15-year time horizon.

ERG comment: The main concerns of the ERG relate to the time horizon of the model (15 years). It seems unlikely that all differences in costs and effects are captured in this time frame. For instance, patients with DS are at risk of higher mortality depending on their seizure frequency. In response to clarification question B3,[12] the company clarified that given the lack of long-term data a 15-year time horizon was considered appropriate to provide insight into future costs and benefits. This is inconsistent with the NICE guide to the methods of technology appraisal indicating that a lifetime time horizon is required when alternative technologies lead to differences in survival or benefits that persist for the remainder of a person's life. Given the survival differences in (non-) SUDEP, a lifetime time horizon would have been appropriate. Therefore, the ERG extended the time horizon to 20 years (the maximum allowed in the submitted economic model)

5.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness are the pivotal clinical trials (GWPCARE1 and GWPCARE2) and the open label extension study (GWPCARE5). It should be noted that GWPCARE1 is not used in the base-case analyses, only in the scenario analyses that used CBD 20 mg/kg/day. These studies are used to obtain evidence for the frequency of convulsive seizures, number of days without convulsive seizures, discontinuation rates and adverse events for both CCM plus CBD and CCM. GWPCARE2 was mainly used to inform treatment effectiveness during cycle one, while GWPCARE5 (in combination with assumptions) was used for subsequent cycles. Moreover, treatment effectiveness was estimated separately for patient subgroups <12 years and ≥12 years.

Transition probabilities between convulsive seizure frequency health states

During the first cycle, transition probabilities between convulsive seizure frequency health states (see section 5.2.2 for more details) were based on GWPCARE2 for both CCM plus CBD and CCM. For CCM plus CBD cycles two to nine were informed using the open label extension study (GWPCARE5). After cycle nine, patients receiving CCM plus CBD were assumed to remain in their current convulsive seizure frequency health states. Once CBD was discontinued, patients were assumed to revert back to their baseline convulsive seizure frequency health state.

First cycle for CCM plus CBD and CCM

Transition probabilities between convulsive seizure frequency health states (based on GWPCARE2) are reported in Table 5.5 below for both CCM plus CBD and CCM.

Table 5.5: Transition probabilities between convulsive seizure frequency health states (first cycle)[a]

		<12 years				≥12 years			
		Seizure	≤8 seizures	8-25 seizures	>25 seizures	Seizure	≤8 seizures	8-25 seizures	>25 seizures
CCM plus CBD 10 mg mg/kg/day	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCM	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]The transition probabilities for CBD 20 mg/kg/day plus CCM (not used in the company base-case) are presented in CS Table 17.

Cycles two to nine for CCM plus CBD

Transition probabilities between convulsive seizure frequency health states (based on the GWPCARE5 trial) are reported in Table 5.6 below for CCM plus CBD.

Table 5.6: Transition probabilities between convulsive seizure frequency health states for CCM plus CBD 10 mg/kg/day (cycles two to nine)a

		<12 years				≥12 years			
		Seizure	≤8 seizures	8-25 seizures	>25 seizures	Seizure	≤8 seizures	8-25 seizures	>25 seizures
Cycle 2	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		<12 years				≥12 years			
		Seizure	≤8 seizures	8-25 seizures	>25 seizures	Seizure	≤8 seizures	8-25 seizures	>25 seizures
Cycle 7	Seizure free	[redacted]							
	≤8 seizures								
	8-25 seizures								
	>25 seizures								
Cycle 8	Seizure free	[redacted]							
	≤8 seizures								
	8-25 seizures								
	>25 seizures								
Cycle 9	Seizure free	[redacted]							
	≤8 seizures								
	8-25 seizures								
	>25 seizures								

[a]The transition probabilities for CBD 20 mg/kg/day plus CCM (not used in the company base-case), are identical as those presented for CBD 10 mg/kg/day plus CCM in this Table (see also CS Table 17).

After cycle nine for CCM plus CBD

After cycle nine, patients receiving CCM plus CBD were assumed to remain in their convulsive seizure frequency health states until CBD treatment discontinuation or death.

CBD treatment discontinuation

CBD discontinuation probabilities were dependent on the convulsive seizure frequency health state and were only applied for CCM plus CBD. Treatment discontinuation probabilities for cycle one were based on GWPCARE2, while GWPCARE5 was used for subsequent cycles (Table 5.7). The CBD discontinuation probabilities estimated for subsequent cycles were assumed to remain constant over time for the remaining duration of the time horizon.

Table 5.7: CBD 10 mg/kg/day treatment discontinuation probabilities per health state[a]

	<12 years		≥12 years	
	Cycle 1	Subsequent cycles	Cycle 1	Subsequent cycles
Seizure free	[redacted]	[redacted]	[redacted]	[redacted]
≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]
8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]
>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]

[a]The discontinuation probabilities for CBD 20 mg/kg/day plus CCM (not used in the company base-case) are presented in CS Table 19.

Number of days without convulsive seizures

As described in section 5.2.2, the convulsive seizure frequency health states were subdivided into three groups based on the number of convulsive seizure-free days per 28 days (categories: ≤18 days, >18 - ≤24 days, >24 days, see Table 5.8). This subdivision was incorporated to reflect the impact of number of convulsive seizure-free days on HRQOL and was assumed to be dependent on the treatment received, as well as the convulsive seizure frequency health states.

Table 5.8: Number of days without convulsive seizures per health state [a]

		<12 years			≥12 years		
		≤18 days	>18 - ≤24 days	>24 days	≤18 days	>18 - ≤24 days	>24 days
CCM plus CBD 10 mg/kg/day	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCM	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]The probabilities for CBD 20 mg/kg/day plus CCM (not used in the company base-case) are presented in CS Table 18.

Mortality

Patients in the convulsive seizure-free health state were assumed to experience all-cause age-dependent mortality probabilities derived from the national life tables for England.[36] Disease-specific mortality

was incorporated for the other convulsive seizure frequency health states (Table 5.9). DS mortality in terms of SUDEP and non-SUDEP deaths, was retrieved from published literature.[37]

The Dravet-specific SUDEP rate of 9.32/1000-person-years, reported by Cooper et al. (2016),[37] was converted to a 0.23% mortality probability per cycle (i.e. per three months). This mortality probability was assumed for the >8 - ≤25 convulsive seizure frequency health state. To calculate mortality probabilities for the other convulsive seizure frequency health states, risk ratios of [redacted] and [redacted] were assumed for the ≤8 and >25 convulsive seizure frequency health states respectively (relative to the >8 - ≤25 convulsive seizure frequency health state; no evidence was provided for these risk ratios).

To obtain the non-SUDEP mortality probabilities, the Dravet-specific mortality rate (15.84/1000-person-years) was subtracted from the Dravet-specific SUDEP rate (9.32/1000-person-years).[37] Similarly for SUDEP mortality, this mortality rate (6.52/1000-person-years) was converted to a mortality probability per cycle (i.e. 0.16% per three months) and assumed for the >8 - ≤25 convulsive seizure frequency health state. Subsequently, risk ratios of [redacted] and [redacted] were assumed for the ≤8 and >25 convulsive seizure frequency health states respectively (relative to the >8 - ≤25 convulsive seizure frequency health state; no evidence provided for these risk ratios).

Table 5.9: Disease-specific mortality probabilities

	SUDEP	Non-SUDEP
Seizure free	[redacted]	[redacted]
≤8 seizures	[redacted]	[redacted]
8-25 seizures	[redacted]	[redacted]
>25 seizures	[redacted]	[redacted]

ERG comment: The main concerns of the ERG relate to: a) using evidence based on CBD 20 mg/kg/day as a proxy for CBD 10 mg/kg/day for month 3 to month 27 (cycles two to nine) for convulsive seizure frequency and CBD discontinuation; b) assuming constant CBD treatment effectiveness after month 27 (i.e. CBD patients were assumed to remain in the same health state until CBD discontinuation or death while assuming constant CBD discontinuation); c) lack of face validity of the treatment discontinuation probabilities (treatment discontinuation does not always increase with higher convulsive seizure frequencies and is 0% for some health states); d) the number of days without convulsive seizures is assumed to be dependent on both treatment allocation and health state; e) the lack of appropriate explanation and justification regarding the calculation of epilepsy-related mortality rates and; f) using DS evidence that is mainly based on patients aged <18 years for adults.

a) For convulsive seizure frequency and CBD discontinuation, only the first model cycle (month 0 to month 3) was informed by evidence based on CBD 10 mg/kg/day. For month 3 to month 27, the company used evidence from GWPCARE5. In this OLE study, the median (IQR) CBD dose was 21 (15-25) mg/kg/day at 12 weeks and 25 (21-25) mg/kg/d at 96 weeks[38] (mean modal dose during the treatment period for the DS and LGS populations was [redacted] respectively[17]). Hence, the company assumed that evidence from CBD 20 mg/kg/day or higher could be used for CBD 10 mg/kg/day. The company justified this assumption (clarification responses B7 and B12) by stating that there is a lack of a broad dose response on efficacy endpoints between the two doses in GWPCARE2 and GWPCARE3 for DS and LGS respectively. However, no supporting evidence was provided by the company. Moreover, the company stated (response to clarification question B7) 'that a minority of

patients may achieve seizure-freedom on the higher dose', seemingly suggesting that there is a difference in treatment effectiveness between CBD 10 mg/kg/day and CBD 20 mg/kg/day. The company also states (in response to clarification question A15) that 'no formal pre-specified test for significance between the CBD groups was included in the SAPs.' Consequently, the ERG considers the extrapolation beyond month 3 to be potentially biased (as indirect evidence is used). As the company did not explore the impact of this assumption (as requested in clarification question B12c), the ERG performed a scenario analysis.

b) After month 27, CBD evidence is lacking and the company assumed constant treatment effectiveness by assuming that CBD patients remain in the same health state until CBD discontinuation or death while assuming a constant CBD discontinuation probability. The ERG considers this to be uncertain and requested the company (clarification question B4b) to perform a scenario analysis assuming waning of treatment effect over time. Unfortunately, the company did not explore this scenario. Consequently, the ERG performed a scenario analysis to examine the potential impact of this assumption. Additionally, it should be noted that these clinical effectiveness data from GWPCARE5 were only introduced in the cost effectiveness sections of the CS (these were not discussed in the interim CSR nor the clinical effectiveness section of the CS) and thus could not be fully assessed by the ERG.

c) The CBD discontinuation probabilities reported in the original CS as well as those reported in the revised assessment accompanying the company's clarification response seemed to lack face validity. Potentially due to the relatively small sample size, CBD discontinuation does not always increase with higher convulsive seizure frequencies and CBD discontinuation probabilities reported in the original CS also contained 0% probabilities, which the company acknowledged is unlikely to be fully representative of a real-world setting. Given the apparent lack of face validity; the ERG used alternative CBD discontinuation probabilities in its base-case. These alternative CBD discontinuation probabilities were informed by Table 2 of the revised assessment of the company. Except the CBD discontinuation probabilities for the 8-25 convulsive seizures and >25 seizures convulsive seizures health states (for <12 years) reported in Table 2 of the revised assessment, these were averaged (given the reported probabilities do not always increase with higher convulsive seizure frequencies as would be expected). Moreover, the long-term CBD discontinuation probabilities (i.e. beyond cycle 9) reported in Table 2 of the revised assessment were not used by the ERG given these probabilities were not appropriately supported by evidence (see Table 5.10 for the CBD discontinuation probabilities used in the ERG base-case). Moreover, using long-term CBD discontinuation probabilities that are different than for cycles 2-9 is not appropriately supported by evidence, nor was it requested by the ERG.

Table 5.10: CBD 10 mg/kg/day treatment discontinuation probabilities used by the ERG

	<12 years		≥12 years	
	Cycle 1	Subsequent cycles	Cycle 1	Subsequent cycles[a]
Seizure free	[redacted]	[redacted]	[redacted]	[redacted]
≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]
45-110 seizures	[redacted]	[redacted]	[redacted]	[redacted]
> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]

d) The company assumed that the number of days without convulsive seizures is dependent on both treatment allocation and health state. The company justified this in response to clarification question B15 by stating that CBD impacts both the frequency of convulsive seizures and the number of convulsive seizure-free days per month and that treatment-independent number of convulsive seizure-free days would thus contradict evidence from the pivotal trials. Nevertheless, it would have been informative to explore the impact of this assumption on the results (requested in clarification question B15). Moreover, the number of convulsive seizure-free days per month is only considered as an exploratory outcome in the pivotal trials and is not discussed in the clinical effectiveness sections of the CS. Finally, including treatment dependent number of days without convulsive seizures might overestimate the treatment effect of CBD and is thus adjusted in ERG analyses (see section 5.2.8 for more detail).
e) The lack of justification for the risk ratios used to calculate epilepsy-related mortality probabilities is considered problematic by the ERG. The only justification provided the CS was 'The calculated risk ratios ensured that the annual SUDEP rate for the >25 seizure frequency category was 1.3%; i.e. consistent with the upper limit of published SUDEP death rates'. The ERG considers this justification to be insufficient. Firstly it is unclear why the upper limit of published SUDEP mortality probability is considered applicable to the >25 convulsive seizure frequency health state particularly given this health state is only based on convulsive seizures and does not (directly) capture non-convulsive seizures. Secondly, no evidence has been provided to support the relationship (e.g. type and magnitude) between convulsive seizure frequency and (non-)SUDEP mortality for the population of interest. Thirdly, no justification was provided for the risk ratio of 1.6.

   Given this lack of evidence for the chosen risk ratios, the ERG assumed equal (non-)SUDEP mortality for the convulsive seizure frequency health states as derived from Cooper et al[37] while assuming the risk ratio of 0.42 (=1.4/3.3[39]) for the convulsive seizure-free health state. This resulted in three monthly SUDEP and non-SUDEP probabilities of 0.23% and 0.16% respectively[37] for the convulsive seizure frequency health states while this was 0.10% and 0.07% respectively for the convulsive seizure-free health state. Nevertheless, these (non-)SUDEP probabilities for the convulsive seizure-free health state are potentially underestimated given the seizure-free definition in Trinka et al[39] (used to obtain the risk ratio of 0.42) is presumably not restricted to convulsive seizures only, potentially inducing bias in favour of CBD (given more patients are seizure free after CBD).
f) It is questionable whether the DS evidence can be extrapolated to patients aged over 18 years given the large majority of patients ([redacted] based on GWPCARE1 and GWPCARE2) is aged under 18 (with the remainder only 18 and a few months). The potential impact of this issue on the cost effectiveness is unclear to the ERG.

5.2.7 Adverse events

Adverse events were based on a pooled analysis considering both the DS and LGS phase III trials (GWPCARE1, GWPCARE2, GWPCARE3 and GWPCARE4). The adverse event probabilities were assumed to remain constant for the duration of the time horizon (see CS Table 21).

ERG comment: The main concerns of the ERG relate to: a) the selection of adverse events for the model (based on different thresholds for CBD and CCM); b) combining LGS and DS evidence to obtain

adverse event probabilities and; c) assumptions regarding the occurrence of adverse events in the revised assessment.

a) The company used different thresholds to select the most frequently occurring treatment-emergent adverse events of special interest for CBD and CCM (either events reported in ≥3% or ≥1% of patients respectively). In response to clarification question B17 the company clarified that this selection of adverse events is a priori defined in the statistical analysis plan and is unrelated to observed incidences in the clinical trials. Given the clarification provided by the company, the ERG believes this approach is reasonable.
b) It is unclear to the ERG why the company combined data from both LGS and DS to obtain adverse event probabilities and thus implicitly assumed that the safety profile is identical for both diseases. Moreover, it is unclear to the ERG whether the adverse event probabilities are only based on CBD 10 mg/kg/day evidence (or also based on CBD 20 mg/kg/day). However, the ERG does not believe this is a major issue given that the impact of adverse events in the economic model is minimal (see also response to clarification question B17b).
c) In the revised assessment, the company assumed that adverse events could only occur until cycle 9. In the original CS base-case, adverse events could occur during the entire CBD treatment. This adjustment was not requested by the ERG and no clinical evidence was provided to support this assumption. However, the ERG does not consider this to be particularly problematic given the minimal impact adverse events are expected to have on the estimated cost effectiveness.

5.2.8 Health-related quality of life

Utility values were estimated for every sub-category (i.e. ≤ 18 convulsive seizure-free days, > 18 - ≤ 24 convulsive seizure-free days, and > 24 convulsive seizure-free days; see Figure 5.1) within the four convulsive seizure health states: convulsive seizure free, ≤8 convulsive seizures, >8 - ≤25 convulsive seizures, and >25 convulsive seizures.

Utilities were estimated using patient vignettes that were based on the health states included in the model. In total, 23 vignettes were developed. Patients and/or caregivers of patients with DS or other forms of epilepsy were asked to complete a quality of life questionnaire and to score patient vignettes using a visual analogue scale (VAS). In total, there were 28 respondents; 20 caregivers and eight patients [1]. The average VAS scores obtained in the survey were converted to values between 0 and 1 for the base-case analysis by using the following formula: $U_{HSi} = VAS_{HSi}/100$. In addition, in the sensitivity analyses, the VAS scores were converted using conversions based on time trade-off and standard gamble methods by using formulas taken from Torrance et al.[40] A summary of the utility values used in the base-case model is provided in Table 5.11.

As mentioned in section 5.2.2, patients receiving CCM only revert to baseline convulsive seizure frequency after the first cycle and patients receiving CBD revert to their baseline convulsive seizure frequency after discontinuation of treatment. However, given that the sub-categories of convulsive seizure-free days differ per health state between CBD and CCM, it is important to note that the corresponding baseline utilities also potentially differ between CBD and CCM. The resulting baseline utilities per health state are displayed in Table 5.12.

Health-related quality of life data identified in the review

According to the CS, the SLR identified six studies that were relevant to the NICE reference case of patients with DS who were either receiving a drug therapy of interest or were reporting on quality of

life regardless of treatments. However, none of the studies were used by the company as they stated that the studies did not estimate utilities for health states defined by number of convulsive seizures and convulsive seizure-free days.

Table 5.11: Health state utility values

State	Sub-category	Utility value	Reference	Justification
No convulsive seizures	≤ 18 convulsive seizure-free days	Not estimated	CS[1]	No convulsive seizures
	>18-≤24 convulsive seizure-free days	Not estimated	CS[1]	No convulsive seizures
	> 24 convulsive seizure free days	[redacted]	Vignette study by company	No utilities available in literature
≤8 convulsive seizures	≤ 18 convulsive seizure-free days	Not estimated	CS[1]	No convulsive seizures
	>18-≤24 convulsive seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	> 24 convulsive seizure free days	[redacted]	Vignette study by company	No utilities available in literature
>8 - ≤25 convulsive seizures	≤ 18 convulsive seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	>18-≤24 convulsive seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	> 24 convulsive seizure free days	[redacted]	Vignette study by company	No utilities available in literature
>25 convulsive seizures	≤ 18 convulsive seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	>18-≤24 convulsive seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	> 24 convulsive seizure free days	[redacted]	Vignette study by company	No utilities available in literature
Source: Based on Table 32 of the CS				

Table 5.12: Health state utility values per treatment

Health state	Utilities for CBD10	Utilities for CBD20[a]	Utilities for CCM
No convulsive seizures	[redacted]	[redacted]	[redacted]

≤8 convulsive seizures	[redacted]	[redacted]	[redacted]
>8 - ≤25 convulsive seizures	[redacted]	[redacted]	[redacted]
>25 convulsive seizures	[redacted]	[redacted]	[redacted]
Source: Based on Table 32 of the CS [a]Only used in a scenario analysis			

Adverse event related disutility values

The company did not incorporate disutilities for any of the adverse events used in the model. The company justified this by claiming that adverse events are unlikely to have a significant impact on the ICERs.

ERG comment: The main concerns of the ERG relate to: a) the methodology used to elicit utility values; b) the inclusion of caregivers QALYs; c) the lack of disutilities for adverse events and; d) the difference in utilities between CBD and CCM.

a) Utility estimates were based on patient vignettes that only presented information on convulsive seizure frequency and convulsive seizure-free days. This approach is condition-oriented and does not appropriately capture other aspects known to influence quality of life and generally incorporated into utility estimates (e.g. mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression) or leaves these aspects to the conceptualization of the respondents. In response to clarification question B19a,[12] the company clarified that for methodological purposes, the vignette study could not formally measure the impact on utilities beyond condition-related factors. The company further argues that "*this is still clinically meaningful, and the use of a "live" population partially overcomes this limitation*". However, it is unclear to what extent the population may be considered to have experience with DS as this was not specifically part of the inclusion criteria ("[redacted]"). Neither the vignette study nor the use of patients to value health states are in line with the NICE reference case, which specifically states that the valuation of health-related quality of life measured in patients (or by their carers) should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method. [41] The use of vignettes and a "live" population is also suggested to be suboptimal in scientific literature compared to multi-attribute utility instruments and public preferences. [42-44] As an alternative, the ERG suggested exploring a scenario in which utilities were based on the Quality of Life in Childhood Epilepsy (QOLCE) instrument which was used in the GWPCARE2 study. In response to this clarification question (B18f [12]), the company clarified that QvOLCE scores were not used to estimate utilities for the base-case for the following reasons: 1) The response rate was low in the trials (~<50%); 2) lack of an appropriate mapping algorithm to convert the QOLCE scores to EQ-5D values; and 3) it was not possible to estimate the QOLCE scores based on both seizure frequency and seizure-free days. The ERG agrees that the low response rate and the lack of an appropriate mapping algorithm are indeed important arguments which makes it hard to obtain valid estimates, but according to the ERG the QOLCE results could have been used to check face validity of the vignette study.
b) In the revised base-case, the company included QALY decrements for caregivers and incorporated these as gains in the total QALY estimates for both CBD and CCM. The decrements per health state are presented in Table 5.13. However, this is not in accordance with the NICE reference case, which

states '*the measurement of changes in health-related quality of life should be reported directly from patients and the utility of these changes should be based on public preferences using a choice-based method*'. Hence, the addition of caregivers QALYs was discarded in the ERG base-case analysis. In addition, the methods of deriving utility estimates for caregivers is questionable given that caregivers were only asked to evaluate three vignette tasks in total, likely not providing the required granularity. Caregivers' vignettes were constructed in the same way as the patients' vignettes but only included only one vignette for every health state. The influence of caregivers' QALYs was examined by the ERG in a scenario analysis.

Table 5.13: Summary of mean caregiver VAS score utility decrements

Health state		Mean decrements (standard error)
No seizures	No seizure	[redacted]
≤8 convulsive seizures	≤18 seizure-free days	[redacted]
	>18-≤24 seizure-free days	[redacted]
	>24 seizure free days	[redacted]
>8 - ≤25 convulsive seizures	≤18 seizure-free days	[redacted]
	>18-≤24 seizure-free days	[redacted]
	>24 seizure free days	[redacted]
>25 convulsive seizures	≤18 seizure-free days	[redacted]
	>18-≤24 seizure-free days	[redacted]
	>24 seizure free days	[redacted]
Source: Based on Table 5 of the revised economic assessment [45]		

c) In the model, the occurrence of adverse events is not accompanied by loss in QALYs. In response to this clarification question (B21[12]), the company argued that 'on this basis, the contribution to disutilities from AEs associated with CBD is likely to be small relative to those from worsening health states. Furthermore, AEs on CBD are happening against a background of those from the drugs in the CCM basket, which may "dilute" their incremental impact'. Not including the impact of adverse events on HRQOL is unlikely to be conservative (given the occurrence of adverse events). However, it was not feasible for the ERG to implement disutilities in the model.

d) As reported in Table 5.8, the number of days without convulsive seizures is treatment-dependent, resulting in treatment-dependent health state utility values (Table 5.12). It should be noted that (as mentioned in 5.2.6), the number of convulsive seizure-free days per month is only considered as an exploratory outcome in the pivotal trials and is not discussed in the clinical effectiveness sections of the CS. Moreover, it is unlcear to the ERG how convulsive seizure-free days are incorporated in the model after CBD discontinuation (i.e. whether the treatment benefits in terms of hight health state utilities are maintained or not). If the treatment benefits are maintained after CBD discontinuation, this might have introduced an upwards bias to the QALY gains for the CBD group. Given the above, the ERG assumed that the number of days without convulsive seizures is treatment independent, averaging these across the treatments at baseline.

5.2.9 Resources and costs

The cost categories included in the model were costs associated with treatment (drug acquisition costs included concomitant therapies and costs associated with treatment-related AEs), health state costs and mortality costs.

Unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and clinical opinion.

Resource use and costs data identified in the review

According to the CS, the SLR identified nine studies[5, 23, 24, 28, 31-35] reporting UK relevant resource use and cost information. None of these were considered to be appropriate for the CEA model, given that costs and resource use for health states in these studies were not defined by the number of convulsive seizures and convulsive seizure-free days.

Treatment costs

The list price of CBD is [redacted]. Costs for AEDs were obtained from the NHS Electronic Drug Tariff 2018[46] and the costs per mg were estimated using a weighted average based on prescribing proportions obtained from the Prescription Cost analysis published by the NHS business services authority[47] (Table 5.14). Treatment administration costs were not considered in the submission, as all included drugs were administered orally. No dose escalation period was assumed in the model. Furthermore, the company stated that monitoring requirements were similar for CBD and CCM, and therefore resource use and costs associated with routine patient monitoring were not incorporated into the cost effectiveness model. AEDs costs were based on the CCM basket that was determined based on market research (Table 16 of the CS). The company referred to this market research as "data on file" and no details were provided. In addition, the company's base-case assumed that a proportion of patients (based on Laux et al.[38]) had a 33% reduction (based on clinical opinion) in the dose of concomitant AEDs (Table 27 of the CS[1]).

As the treatment dosages for CBD and some other AEDs are weight-based, the trial populations were split into four age groups (2-5 years, 6-11 years, 12-17 years and 18-55 years), in order to ensure more precise estimation of the treatment dosages (Table 5.4). The company further amalgamated these groups into two groups for the cost effectiveness analysis to improve statistical power: <12 years and ≥12 years.

Table 5.14: Treatment acquisition costs

Treatment	Average dose (mg/kg/day)		Average cost per mg (£)	Costs per kg per cycle (3 months)		Reference drug dose
	<12 years	≥12 years		<12 years	≥12 years	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clobazam*	0.65	0.45	0.0559	3.32	2.30	Auden McKenzie, 2008[48]
Stiripentol	30.00	50.00	0.0180	49.31	82.18	Biocodex, 2017ref[49]
Valproic acid*	27.50	25.00	0.0002	0.50	0.46	Sanofi, 2006[50]
Topiramate	7.00	5.45	0.0044	2.81	2.19	Janssen-Cilag 2010[51]
Levetiracetam*	40.00	36.36	0.0002	0.73	0.66	UCB Pharma 2015[52]
Source: based on Table 27 and Table 29 of the CS [1].						

*For CBD, a dose reduction of 33% was assumed for this drug (based on clinical opinion).

Health state costs

Health state specific costs and resource use estimates for physician visits, hospitalisations and institutionalisation were obtained from UK clinical experts (Table 5.15). The company stated that these experts indicated that older patients were more likely to be institutionalised, and therefore the probability of being institutionalised and the associated costs were only applied to patients aged 18 years and older. Furthermore, the company did not apply the risk and costs of being institutionalised to patients in the convulsive seizure-free group, based on the suggestion from the literature [53-55] that there is a likely association between decline in cognitive functioning and the symptomatic level of epileptic activity in early age.

Table 5.15: Health state related costs

Resource use		Number of annual visits[1]		Costs per visit		Reference unit prices
		<12 years	≥12 years	<12 years	≥12 years	
Nurse visit	Seizure-Free	2	2	£44	£44	PSSRU 2017[56]
	≤ 8	4	2			
	>8 - ≤ 25	8	4.8			
	> 25	12	12			
Paediatric Epileptologist (<12 years) / Neurologist (≥12 years) Visit	Seizure-Free	1	0.5	£366	£167	NHS Reference Costs 2016-17[57]
	≤ 8	2	0.5			
	>8 - ≤ 25	4	0.5			
	> 25	6	3			
Paediatrician Visit	Seizure-Free	2	0	£196	£0	PSSRU 2017[56]
	≤ 8	4	0			
	>8 - ≤ 25	8	0			
	> 25	12	0			
Emergency department	Seizure-Free	0	0	£237	£237	NHS Reference Costs 2016-17[57]
	≤ 8	6	3			
	>8 - ≤ 25	12	6			
	> 25	24	12			
Phone Call Follow-up	Seizure-Free	0	0	£258	£107	NHS Reference Costs 2016-17[57]
	≤ 8	2	1			
	>8 - ≤ 25	6	2.5			
	> 25	12	6			
Dentist	Seizure-Free	2	2	£127	£127	PSSRU 2017[56]
	≤ 8	2	2			

Resource use		Number of annual visits[1]		Costs per visit		Reference unit prices
		<12 years	≥12 years	<12 years	≥12 years	
	>8 - ≤ 25	2	2			
	> 25	2	2			
Hospitalisation	Seizure-Free	0	0	£597 in general ward £1,583 in ICU	£460 in general ward £1,299 in ICU	NHS Reference Costs 2016-17[57]
	≤ 8	3	1.5			
	>8 - ≤ 25	6	3			
	> 25	12	6			
Institutionalisation[2]	Seizure-Free	0%	0%	£0	£1,337	PSSRU 2017[56]
	≤ 8	0%	10%			
	>8 - ≤ 25	0%	10%			
	> 25	0%	10%			
Cost of Rescue Medication by intake	Seizure-Free	0	0	£34	£34	BNF 2018[58]
	≤ 8	12	6			
	>8 - ≤ 25	24	12			
	> 25	48	24			

Source: Based on Table 29 and Table 30 of the CS
[1]Based on clinical opinion.
[2]The probability and costs of being institutionalised were only applied to patients aged 18 years and older.

Mortality costs

The company stated that due to a lack of evidence on costs associated with death due to DS, costs and resource use associated with SUDEP (£0) and non-SUDEP (£237 for one visit to the emergency department, and £1,583 and £1,299 per day in an intensive care unit for <12 years and ≥12 years respectively) were based on clinical opinion. Costs associated with emergency department visits and intensive care unit were obtained from the NHS reference cost schedule 2016-2017.[57]

Adverse event related costs

Commonly identified treatment emergent adverse events were included in the analysis as one visit to a specialised nurse (£44 per visit, PSSRU 2017[56]), based on clinical experts who indicated that these events were unlikely to be resource intensive.

ERG comment: The concerns of the ERG relate to: a) the dose escalation period in the model is not in line with the escalation period used in the pivotal trials; b) The percentage of patients who are institutionalised in the model in the seizure-free group; c) the costs of ketogenic diet and vagus nerve stimulation are not incorporated into the model; d) the assumption that, in the base-case, CBD leads to a dose reduction of 33% for some AEDs; e) resource use for the seizure-free health state; f) not considering costs associated with routine patient monitoring; g) the justification for the average weight by age group used to calculate treatment costs and; h) mean weight for patients aged 18-55 years.

a) Contrary to the pivotal trials, in which an escalation period (or treatment period) of two weeks is used (i.e., 5 mg/kg/day to start, titrated up to the target dose over two weeks), no escalation period was assumed in the model. Although this may slightly over-estimate the treatment costs (e.g. for the first week in the cycle), the ERG expects no large implications from the simplification.
b) In the initial CS, a zero percentage of the patients in the convulsive seizure-free group was subjected to institutionalisation due to cognitive decline. However, cognitive functioning of these patients could still decline as a result of other aspects of DS, including non-convulsive seizures. Hence, in response to clarification question B22a,[12] the company has included a 2% risk of institutionalisation for patients in the convulsive seizure-free health state. It remains unclear, however, to what extent the patients' risk of institutionalisation is associated with convulsive seizure-freedom and whether this risk is indeed lower compared to the other health states. In accordance with the revised base-case submitted by the company, the ERG used a 2% institutionalisation risk for patients aged above 18 years in the convulsive seizure-free category.
c) In response to clarification question B10, [12] the company stated that the effects of the ketogenic diet and vagus nerve stimulation are included in the effectiveness estimates from the pivotal trials (as some patients received these treatments as part of the CCM). However, although this is a reasonable assumption, however, costs of both the ketogenic diet and the vagus nerve stimulator are not included in the model. This most likely resulted in an underestimation of the CCM costs, which likely favours CBD (as patients with CBD are estimated to live longer and hence the CCM treatment duration is likely longer for CBD).
d) It is stated that patients in both the intervention and comparator group receive the same clinical management, but for some AED, a dose reduction of 33% is applied for CBD plus CCM. In response to clarification question B25a, [12] the company stated that [redacted]. However, this is not consistent with the evidence presented by the company.[1] The poster by Laux et al. indicated that some patients have an increased AED dose, [38, 59] and it is unclear from the evidence what percentage of dose reduction/increase was observed in the patients in whom a dose adjustment was observed. Hence, it is questionable whether it is correct to assume a 33% reduction in a selection of AEDs. The ERG incorporated a 0% dose reduction in their revised base-case.
e) Health state resource utilisation, based on expert opinion, is assumed to be considerably lower for the seizure-free health state. The ERG has explored the impact of this assumption in a scenario in which resource use for the seizure-free group is equal to half of the units reported for the second-best health state for every cost category.
f) The company stated that monitoring requirements were similar for CBD and CCM, and therefore resource use and costs associated with routine patient monitoring were not incorporated into the cost effectiveness model. However, given the survival differences that are estimated to favour CBD in the model, the total routine patient monitoring costs would probably be higher for CBD (given these patients are estimated to live longer) despite monitoring requirements were similar for CBD and CCM. Nevertheless, the ERG does not expect this issue to have a substantial impact on the results.
g) In response to clarification question B5d, [12] the company clarified that it was not possible to definitively conclude whether the mean weights at baseline in the clinical trials (used to calculate treatment costs) were representative of those for the DS population in the UK. No data were identified in the literature and there were too few UK patients in the GWPCARE1 and GWPCARE2 trials (16 overall) to use only this subgroup in the model. In the revised base-case of the model,

however, the company replaced the mean weights across age groups at baseline by the median weights across age groups at baseline, which is likely to be an underestimation of the mean weights. In response to clarification question B5b, [12] the company clarified that this was done to account for the asymmetric weight distribution (likely due to outliers) and that this addresses the face-validity issue in the prior assumptions. According to the ERG this assumption is not reasonable as the weights are used to determine mean dosages over time, and hence, outliers are part of this mean dosage. Hence, the ERG discarded the use of median weights proposed by the company and included mean weights.

h) The mean weights for the age category "18-55 years" in the original submission were deemed implausible as this category was based on a small number of patients (1.89%) and lacked face validity
([redacted]).
Hence, for the category aged 18-55 years, the mean weight in the ERG base-case was based on the LGS submission.

5.2.10 Cost effectiveness results

[redacted]

Table 5.16: Company's base-case results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM	[redacted]	[redacted]	--	--	--
CCM + CBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the base-case results in the economic model
CBD = cannabidiol; CCM = current clinical practice; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year;

ERG comment: The main concerns of the ERG relate to: a) the calculation of QALYs does not match the time horizon; b) relevant results are not presented; c) the additional assumptions in the revised submission and economic model of the company.

a) In the initial base-case submitted by the company the total QALYs for both treatments exceeded the time horizon of the model. Hence these results should be interpreted with extreme caution (see also section 5.2.12). In response to clarification question B30,[12] the company did not elaborate on the origin of this error but provided a revised base-case.
b) Total life years and the duration that patients are in the various health states over time were not presented. This information would help to perform face validity checks on, e.g. the estimated QALYs.
c) The company provided a revision of the original submission and economic model accompanying the clarification letter. [21] It was however, unclear what exactly was changed and why certain input

parameters/assumptions changed (the company made various changes that were not requested by the ERG). The company's revised submission is presented below (Table 5.17). Given the changes to the input parameters and assumptions of the economic model (some of which were not requested by the ERG) as well as some persistent validity issues (see section 5.2.12), the ERG believes these revised results submitted by the company should be interpreted with extreme caution as well. Therefore, the ERG used the revised model submitted by the company (with some of the validity issues resolved), while setting all input parameters as described in the original CS, as a starting point for the ERG analyses.

Table 5.17: Company's revised base-case results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM	£195,786	3.10	--	--	--
CCM + CBD	£227,309	4.01	£31,522	0.91	£34,789

Source: Based on the base-case results in the economic model
CBD = cannabidiol; CCM = current clinical practice; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year;

5.2.11 Sensitivity analyses

The company performed and presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) in order to show the uncertainty surrounding the initial CS base-case results.

[redacted]

The company conducted DSAs by varying key model parameters between upper and lower values based on the literature, clinical opinion or a specified range (e.g. +/- 10%). Transition probabilities were not included in the DSA. The initial ICER was most sensitive to discount rates for costs and outcomes and the average dose in subsequent cycles. The ICER exceeded the WTP threshold of £30,000 (Figure 5.2) in these three DSA analyses.

Table 5.18: The company's initial probabilistic base-case results (500 iterations)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM + CBD	[redacted]	[redacted]	--	--	--
CCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the revised PSA results in the economic model.
ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; SoC =standard of care

[redacted]

Scenario analyses

The company conducted several scenario analyses. The initial results showed ICERs ranging between [redacted] and [redacted] per QALY gained. The three most influential scenarios that increased the ICER were varying the CBD dosage ([redacted]), including patients aged between 12 and 55 years only [redacted]), and using algorithm 1 (SG 3) to model utilities [redacted]) The three most influential scenarios that decreased the ICER were including patients aged between two and 11 years only ([redacted]), using algorithm 2 (SG 8) to model utilities [redacted]), and assuming the same long-term discontinuation rate for all convulsive seizure groups ([redacted]).

ERG comment: The main concerns of the ERG relate to: a) the company did not provide all requested scenario analyses; b) not all parameters have been included in the PSA; c) the use of bootstrapping to obtain distributions for transition probabilities in the PSA and; d) the additional assumptions in the revised submission and economic model of the company.

a) The ERG requested the following additional scenario analyses: 1) a scenario analysis using the GWPCARE1 trial only (clarification question B12c); 2) a scenario analysis using the average treatment discontinuation probability across the health states (clarification question B14f); 3) a scenario analysis using equal number of days without seizures across treatment allocation (clarification question B15b); 4) a scenario analysis in which utilities are based on the QOLCE instrument from the phase 3 trials (clarification question B19g); and 5) a scenario assuming a 0% dose reduction of concomitant AEDs (clarification question B25b). Based on these requests the company only added a scenario assuming 0% dose reduction in the revised submission and the company adjusted the discontinuation rates in their revised base-case (though they did not apply the requested discontinuation rates). This hampered the review of the ERG.
b) Based on CS Table 36 some parameters (e.g. non-SUDEP costs) were not included in the PSA. In response to clarification question B28d, [21] the company clarified that the parameters that had a minor impact on the results were not included in the PSA. No further changes were made to the PSA in terms of included parameters. Hence, the ERG believes that the PSA still does not include all relevant parameters (e.g. excluding discontinuation probabilities up to cycle 9, which are potentially influential).
c) Transition probabilities were included in the PSA using a bootstrapping method. However, bootstrapping is not the recommended approach to incorporate interdependent transition probabilities (see for instance Briggs et al.[60]). In response to clarification question B28, [21] the company clarified that the bootstrapping method was preferred to the Dirichlet distribution as the transition probabilities are not only interdependent, but also time dependent. Furthermore, it was argued that the company would have used Dirichlet if only one set of transition probabilities was used. Although the ERG does not necessarily agree with this approach, it is reasonable to assume that this does not have major implications for the results of the model.
d) In response to the clarification letter, [21] the company provided a revision of the original submission and economic model. It was however, unclear what exactly was changed and why certain input parameters/assumptions changed (the company made various changes that were not requested by the ERG). The company's revised sensitivity and scenario analyses are presented below. Given the changes to the input parameters and assumptions of the economic model (that were not requested by the ERG), as well as some persistent validity issues (see section 5.2.12), the ERG believes these revised analyses submitted by the company should be interpreted with extreme caution as well. Consistently, the ERG used the revised model submitted by the company, while setting the

adjusting the input parameters as described in the original CS, as a starting point for the ERG analyses.

Revised sensitivity analyses submitted by the company

The company performed and presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) in order to show the uncertainty surrounding the base-case results.

Compared with the revised deterministic results, the PSA showed slightly lower incremental QALYs and lower incremental costs, which resulted in an increased ICER (£36,046) (Table 5.19). The cost effectiveness acceptability curve in the revised model showed that CCM plus CBD approximately had a [redacted] probability of being cost effective at a willingness to pay (WTP) threshold of [redacted]

The company conducted DSAs by varying key model parameters between upper and lower values based on the literature, clinical opinion or a specified range (e.g. +/- 10%). Transition probabilities were not included in the DSA. The ICER was most sensitive the average dose in all cycles subsequent cycles and the costs of emergency department visits. The ICER exceeded the WTP threshold of £30,000 (Figure 5.3) in these three DSA analyses.

Table 5.19: The company's revised probabilistic base-case results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM + CBD	£226,681	3.98	--	--	--
CCM	£195,578	3.09	£31,103	0.89	£36,046

Source: Based on the revised PSA results in the economic model.
ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; SoC =standard of care

[redacted]

Revised scenario analyses submitted by the company

The company conducted several scenario analyses. The results showed ICERs ranging between [redacted] and [redacted] per QALY gained. The three most influential scenarios that increased the ICER were including patients aged between 12 and 55 years only [redacted]), varying the CBD dosage ([redacted]), and no variation across seizure categories for the number of hospital admissions ([redacted]. The three most influential scenarios that decreased the ICER were all patients 2-5 years at model entry ([redacted], varying the ICU/general ward ratio to 90% in ICU and 10% in general ward ([redacted], and including patients aged between 2 and 11 years only ([redacted]).

5.2.12 Model validation and face validity check

Face validity

The model structure, inputs regarding CCM in the UK and key assumptions regarding health care resource use and long-term efficacy were validated by UK clinical experts.

Internal validity

The model was quality-checked by the economists who developed the economic model and a senior economist not involved in the model development reviewed the model for coding errors and inconsistencies. A further validation and quality assessment of the model was also conducted by an external consultancy. This review included a check of the model structure (e.g. formulae, VBA coding, cell references and functionality), of cost inputs against the Drug Tariff and NHS Tariff, and of the validity of distributions used in the sensitivity analyses. Pressure tests were conducted, in some cases using extreme values, in order to test the accuracy and validity of the model's results.

Cross validity

No cross validation was reported.

External validity

Clinical outcomes of the economic model, in terms of proportion of convulsive seizure-free patients (at year 1) and 10-year CCM mortality, were compared against evidence (see CS Appendix J).

ERG comment: The main concerns of the ERG relate to the a) revised assessment submitted by the company; b) internal validity and; c) transparency of the model.

a) After the clarification phase (with delay), the company submitted their clarification responses, a revised assessment and a revised economic model. Besides attempting to resolve validity issues (see clarification question B30), this revised assessment also included adjustment to the structure (duration of adverse events) and input parameters of the economic model. Most of these additional adjustments were not requested by the ERG (e.g. structural adjustments regarding duration of adverse events and adjusting long-term CBD discontinuation probabilities) nor were all adjustments clearly described. Consequently, it is unclear to the ERG what the original CS base-case results would be if the validity issues were resolved. Therefore, the ERG used the revised model submitted by the company, while setting the input parameters to the values as described in the original CS, as a starting point for the ERG analyses.
b) Although the company reported an extensive quality/internal validity check (as summarised above), the model initially submitted by the company had clear internal validity issues given that the estimated QALYs exceeded the model time horizon. This issue was highlighted in clarification question B30. In the clarification phase, the company submitted a model that had QALYs that did not exceed the time horizon, however the company did not highlight the exact changes in the model (code), making it more difficult for the ERG to examine the changes made in response to clarification question B30. Particularly given the updated economic model submitted during the clarification phase included multiple adjustments (which were mostly not requested by the ERG).
c) Additionally, the ERG regarded the VBA coded model to lack transparency, although the company helpfully provided detailed information regarding model implementation in response to clarification question B26, the ERG still believes that an economic model that is not programmed mostly in VBA would be more transparent. Particularly given the relatively simple model structure, an economic model not programmed mostly in VBA would have been preferred. This would allow more extensive validation and implementation of adjustments/analyses by the ERG within the available timeframe.

To internally validate the revised economic model (submitted by the company during the clarification phase), the ERG did the following

- rebuilt the state transition trace in order to recalculate QALYs and costs of CBD. The ERG was able to reproduce the state transition trace and QALY calculation for CBD 10 mg/kg/day to a fair level of accuracy (estimated CBD discounted QALYs, without carer QALYs, [redacted] versus [redacted]). For the costs this was true to a lesser extent (estimated CBD discounted total costs [redacted] versus [redacted]). The difference between the ERG calculations and the company's updated model that was most prominent was the disease management (or health state) costs (estimated CBD discounted management costs [redacted] versus [redacted]) and treatment costs (estimated CBD discounted treatment costs [redacted] versus [redacted]).
- changed the clinical effectiveness input parameters for CBD 10 mg/kg/day to the clinical effectiveness input parameters for CCM. The expected result would be a QALY difference of 0.000. Conversely, the produced results indicated a QALY gain for CBD 10 mg/kg/day of 0.36 (excluding carer QALYs). Even if it is, in addition to the above, assumed that all patients remain in their baseline seizure frequency health state (by setting the diagonal of the transition matrices for cycle 1 on the "# SEIZURES" worksheet to 100%) a QALY gain for CBD 10 mg/kg/day of 0.10 is produced (excluding carer QALYs). This suggests that there are fundamental problems with the economic model (i.e. VBA code) that induce a QALY gain for CBD 10 mg/kg/day. Consequently, the cost effectiveness results, calculated using the economic model submitted by the company, lack credibility. Due to the complexity and limited transparency of the model, the ERG was unable to resolve these validation issues within the available timeframe.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Table 5.20 summarises the main issues highlighted by the ERG in section 5.2, indicates the expected direction of bias introduced by these issues and whether these are examined in any analyses/incorporated in the ERG base-case.

Table 5.20: Main ERG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Model structure (section 5.2.2)			
Ignorance of non-convulsive seizures in the model	+/-	-	-
Assumption that patients in the CCM group transfer back to their baseline seizure frequency after the first cycle	+	-	-
Population, interventions and comparators, perspective and time horizon (sections 5.2.3-5.2.5)			
Extent to which the population of the trial is representative for the target population of the model	+/-	-	-
Weight for patients aged 18 years or older	+	ERG base-case	
The combination of all AEDs as CCM	+/-	-	-
No lifetime time horizon	+/-	Scenario	Scenario
Treatment effectiveness and extrapolation (section 5.2.6)			
Using evidence based on CBD 20 mg/kg/day as a proxy for CBD 10 mg/kg/day for month 3 to month 27	+/-	Scenario	-
Assuming constant treatment effectiveness after month 27	+	Scenario	-
Face validity of the treatment discontinuation probabilities	+/-	ERG base-case	-
Treatment dependent number of days without seizures	+	ERG base-case	-
Lack of appropriate justification regarding the calculation of epilepsy-related mortality rates	+	ERG base-case	-
Health-related quality of life (section 5.2.8)			
The methodology used to elicit utility values	+/-	-	-
Lack of disutilities for adverse events	+	-	-
Resources and costs (section 5.2.9)			

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
The dose escalation period in the model is not in line with the escalation period used in the pivotal trials	-	-	-
The percentage of patients who are institutionalised in the model in the seizure-free group	+	ERG base-case	Scenario
Resource use in the seizure-free group	+	Scenario	-
The costs of ketogenic diet and vagus nerve stimulation are not incorporated into the model	+	-	-
It is assumed that CBD leads to a dose reduction of 33% for some AEDs	+	ERG base-case	Scenario
Not considering costs associated with routine patient monitoring	+	-	-
Cost effectiveness analyses (sections 5.2.10 and 5.2.11)			
Relevant results are not presented	+/-	-	-
Methods used for probabilistic analyses	+/-	-	-
Validation (section 5.2.12)			
Fundamental validity problems with the economic model severely hampering. the credibility of the cost effectiveness results calculated using the economic model submitted by the company	+	-	-
Footnotes: [a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator. ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; ICER = incremental cost effectiveness ratio; MJ = matters of judgement;			

Based on all considerations discussed in section 5.2 (summarised in Table 5.20), the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[61]). The ERG's has major concerns with both the original CS base-case as well as the revised CS base-case (see 5.2). Therefore, as mentioned above, the ERG used the revised model submitted by the company, while setting the input parameters to the values as described in the original CS, as a starting point for the ERG analyses.

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Fixing errors

1. Revised economic model (section 5.2.12).

   The ERG used the revised economic model submitted (by the company) during the clarification phase (using the input parameters as described in the original CS). A word of caution is that this model still has important validity concerns, such as an induced QALY gain for CBD 10 mg/kg/day and the ERG was unable to reproduce costs for CBD 10 mg/kg/day.

Fixing violations

2. Time horizon (section 5.2.5).

   The ERG extended the time horizon to 20 years (maximum time horizon allowed in the submitted model)

Matters of judgment

3. Adjusted weight for adults (section 5.2.3)
   The ERG adjusted the weight for adults (assuming the LGS for patients aged ≥18).
4. Adjusted mortality probabilities (section 5.2.6).
   The ERG adjusted the health state dependent SUDEP and non-SUDEP mortality probabilities.
5. Adjusted discontinuation probabilities (section 5.2.6).
   The ERG adjusted the CBD discontinuation probabilities (see Table 5.10) to improve face validity of this input parameter.
6. Treatment independent number of days without seizures (sections 5.2.6 and 5.2.8).
   The ERG assumed number of days without seizures to be treatment independent to prevent overestimating the utility difference between treatments.
7. Institutionalisation risk in the seizure-free category (section 5.2.9).
   The ERG used a 2% institutionalisation risk in the seizure-free health state for patients aged above 18 years.
8. AED dose reduction for CBD (section 5.2.9).
   The ERG adopted a 0% AED dose reduction for CBD (consistent with CCM)
9. No treatment effect after 27 months (section 5.2.6).

   The ERG assumed that all patients revert to their baseline seizure frequency health state after 27 months (9 cycles) due to lack of evidence regarding long-term effectiveness.

Table 6.1 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the (deterministic) ERG base-case. The 'fixing error' adjustments were combined and the other ERG analyses were performed also incorporating these 'fixing error' adjustments given the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

5.3.1 ERG base-case results

The ERG base-case consisted of an ICER range reflecting the uncertainty surrounding the extrapolation of treatment effectiveness. The probabilistic ERG base-case (Table 6.2) indicated that the ICER, for CBD compared with CCM, would range between £76,013 per QALY gained (assuming a constant treatment effect after 27 months) and £477,476 per QALY gained (assuming no treatment effect after 27 months). For these two assumptions, the probabilities of CBD being cost effective were [redacted] respectively, at a willingness to pay threshold of £20,000 per QALY gained while these probabilities were [redacted] respectively, at a willingness to pay threshold of £30,000 per QALY gained (Figures 5.4 and 5.5). It should however be reiterated that some of the abovementioned potential biases (see for instance the model structure and validity sections) could not be explored by the ERG. Consequently, the ICERs reported might be an underestimation of the true ICERs.

Figure 5.2: Cost effectiveness acceptability curve: ERG base-case assuming a constant treatment effect after 27 months

[redacted]

Figure 5.3: Cost effectiveness acceptability curve: ERG base-case assuming no constant treatment effect after 27 months

[redacted]

5.3.2 Additional exploratory analyses performed based on the ERG base-case

Additional sensitivity analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. These were all performed using the ERG base-case (assuming constant treatment effectiveness).

Exploratory analyses using the ERG base-case:

1. Scenario assuming an increased CBD dose of 20 mg/kg/day after cycle 1 (in accordance with the evidence from GWPCARE5).
2. Scenario including caregivers QALYs.
3. Scenario assuming disease management resource use for the seizure-free health state to be equal to half of the units reported for the second-best seizure frequency health state.
4. Scenario using only CBD 10 mg/kg/day evidence (i.e. patients will remain in their respective health state after the first cycle until discontinuation / death).

The results of the probabilistic exploratory scenario analyses are presented in Table 6.3. These analyses indicate that assuming an increased CBD dose of 20 mg/kg/day after cycle 1 for the cost calculations

(in accordance with the evidence from GWPCARE5) might have a substantial impact on the estimated cost effectiveness.

5.3.3 Subgroup analyses performed based on the ERG base-case

No subgroup analyses were described in section B.3.9 of the CS.

5.4 Conclusions of the cost effectiveness section

Errors and inconsistencies in the original search strategies impaired the performance of the company's searching. As the company did not provide corrected strategies in their clarification response, the ERG remains concerned about the quality of the company's searches, which may have limited recall of potentially relevant references. The explanations given in the clarification response did not match up to the numbers retrieved when the ERG corrected the same strategies. Consequently, the ERG is unable to assess how well the searching was designed and conducted.

The company developed a de novo economic model. The model structure proposed by the company, however, does not fully capture (the natural progression of) DS. The model structure was focussed on convulsive seizures and did not explicitly capture non-convulsive seizures. Also, assuming that patients treated with CCM revert to their baseline health states after three months (with no possibility to become seizure-free) and remain in this state for the remainder of the time horizon is considered restrictive and potentially biases the cost-effectiveness in favour of CBD. Moreover, the extent to which the trial population (which includes a small proportion of patients that does not match the anticipated marketing authorisation) is representative to the UK setting, is unclear to the ERG. Additionally, the ERG considers that the economic model and base-case analyses described in the CS only partly meets the NICE reference case. Deviations from the NICE reference case included the restricted time horizon of 15 years and the method used to estimate utilities.

Key uncertainties in this cost effectiveness assessment are, according to the ERG, the extrapolation of treatment effectiveness, the estimated health state utility values and the model validity. Firstly, extrapolation of CBD 20 mg/kg/day evidence to CBD 10 mg/kg/day. The CBD effectiveness evidence used beyond three months is based on GWPCARE5, using CBD 20 mg/kg/day as maintenance dose (mean modal dose during treatment was [redacted]). It is debatable whether this evidence is representative for a CBD maintenance dose of 10 mg/kg/day. Secondly, the extrapolation after 27 months is uncertain due to the lack of evidence beyond this time period. After 27 months the company assumed a constant treatment effectiveness, i.e. assuming that CBD patients remain in the same health state until CBD discontinuation or death while assuming a constant CBD discontinuation probability. Thirdly, it is questionable whether the evidence can be extrapolated to patients aged 18 year above given the large majority of patients ([redacted] based on GWPCARE1 and GWPCARE2) is aged below 18 year. This uncertainty related to extrapolation is, in part, reflected in the ERG base-case ICER range. Another source of uncertainty were the estimated health state utility values. The ERG considered the methodology to be not in line the NICE reference case. Finally, the model validity (as well as transparency) can be regarded as a major limitation of the current assessment. Despite the company attempted to resolve validity issues during the clarification phase, the ERG also considered the model validity of the revised model to be problematic. According to the ERG, there are fundamental problems with the economic model that potentially induce a QALY gain for CBD 10 mg/kg/day. Consequently, the cost effectiveness results, calculated using the economic model submitted by the company, lack credibility. Due to the complexity and limited transparency of the model, the ERG was unable to satisfactory resolve these validation issues within the available timeframe.

In the company base-case (probabilistic), the ICER of CBD compared with CCM was estimated to be [redacted] per QALY gained. However, this ICER was based on technically implausible QALY estimates and is, according to the ERG, not informative / seriously flawed. Similarly, the revised base-case ICER submitted by the company (£36,046) should be interpreted with extreme caution given the validity issues and adjustments (model structure and input) made by the company. The ERG has incorporated various adjustments to the CS base-case (using the revised economic model with input parameters from the original CS as starting point). The ERG base-case consisted of an ICER range, reflecting the uncertainty surrounding the long-term extrapolation of treatment effectiveness. The ERG base-case (probabilistic) indicated that the probabilistic ICER, for CBD compared with CCM, would range between £76,013 per QALY gained and £477,476 per QALY per QALY gained. However, it should be reiterated that some of the abovementioned potential biases (model structure, validity) could not be explored by the ERG. Consequently, the ICERs reported are likely to be underestimations of the true ICERs.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Analyses undertaken by the ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. It should be noted that the ERG used the revised model submitted by the company (with some of the validity issues resolved), while setting all input parameters as described in the original CS, as a starting point for the ERG analyses (fixing errors analysis). The changes to the input parameters and assumptions of the revised economic model (some of which were not requested by the ERG) are discussed in Chapter 5. Table 6.1 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The probabilistic CS and ERG base-cases are presented in Table 6.2. These are all conditional on the ERG base-case. Finally, Table 6.3 provides the results of the exploratory scenario analyses (described in Section 5.3.2), all conditional on the ERG base-case assuming a constant treatment effect after 27 months. The submitted model file contains technical details on the analyses performed by the ERG.

Table 6.1: Deterministic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) vs BSC
Company base-case (original CS)					
CCM	£190,322	18.585			
CCM + CBD	£300,687	21.819	£110,364	3.234	£34,126
Fixing errors (company's revised model, setting the input parameters as in the original CS)					
CCM	£191,458	4.585			
CCM + CBD	£302,148	5.501	£110,689	0.916	£120,838
Fixing errors + time horizon of 20 year					
CCM	£229,820	5.509			
CCM + CBD	£367,006	6.654	£137,186	1.145	£119,785
Fixing errors + adjusted weight for adults					
CCM	£199,915	4.585			
CCM + CBD	£327,882	5.501	£127,966	0.916	£139,698
Fixing errors + adjusted mortality probabilities					
CCM	£192,052	4.525			
CCM + CBD	£299,326	5.375	£107,274	0.850	£126,275
Fixing errors + adjusted discontinuation probabilities					
CCM	£191,458	4.585			
CCM + CBD	£239,437	5.239	£47,979	0.654	£73,379
Fixing errors + treatment independent number of days without seizures					
CCM	£191,458	4.585			
CCM + CBD	£302,148	5.478	£110,689	0.892	£124,037
Fixing errors + institutionalisation risk in the seizure-free category					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) vs BSC
CCM	£191,458	4.585			
CCM + CBD	£302,913	5.501	£111,455	0.916	£121,673
Fixing errors + AED dose reduction for CBD					
CCM	£191,458	4.585			
CCM + CBD	£302,917	5.501	£111,459	0.916	£121,677
ERG base-case (assuming a constant treatment effect after 27 months)					
CCM	£243,272	5.414			
CCM + CBD	£299,780	6.126	£56,508	0.712	£79,401
ERG base-case (assuming no treatment effect after 27 months)					
CCM	£243,272	5.414			
CCM + CBD	£301,873	5.533	£58,601	0.119	£493,726

Table 6.2: Probabilistic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) vs BSC
Company base-case (original CS)					
CCM	£190,208	18.625			
CCM + CBD	£300,984	21.772	£110,776	3.147	£37,422
ERG base-case (assuming constant treatment effect after 27 months)					
CCM	£244,040	5.416			
CCM + CBD	£297,062	6.114	£53,023	0.698	£76,013
ERG base-case (assuming no treatment effect after 27 months)					
CCM	£243,325	5.425			
CCM + CBD	£297,789	5.539	£54,464	0.114	£477,476

Table 6.3: Probabilistic scenario analyses (conditional on ERG base-case assuming a constant treatment effect after 27 months)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) vs BSC
ERG base-case (assuming constant treatment effect after 27 months)					
CCM	£244,040	5.416			
CCM + CBD	£297,062	6.114	£53,023	0.698	£76,013
ERG base-case (assuming constant treatment effect after 27 months) + increase treatment dose of CBD to 20 mg/kg/day after the 1st cycle					
CCM	£243,651	5.411			
CCM + CBD	£364,835	6.108	£121,184	0.697	£173,781
ERG base-case (assuming constant treatment effect after 27 months) + include caregivers QALY					
CCM	£243,497	3.608			

CCM + CBD	£296,125	4.625	£52,629	1.017	£51,734
ERG base-case (assuming constant treatment effect after 27 months) + resource use for the seizure-free group assumed equal to half of the units reported for the second-best health state					
CCM	£244,039	5.412			
CCM + CBD	£298,769	6.100	£54,730	0.687	£79,617
ERG base-case (assuming constant treatment effect after 27 months) + only use evidence based on the 10 mg/kg/day CBD dose					
CCM	£243,436	5.409			
CCM + CBD	£296,520	6.094	£53,084	0.684	£77,574

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Appendix 1: ERG version of CS searches including corrections

PubMed search

The ERG noted that the following search terms failed to work properly, due to incorrectly applied truncation within the phrase search:

"Dravet* syndrome"

"childhood epilep* encephalopath*"

The ERG re-ran the company's search (#1), as well as running a corrected version of the company's search (#4). The company's original search including errors was removed from the corrected search results using the Boolean operator 'NOT' (#5), which resulted in 6069 references missed by the company's search.

ERG's PubMed (NLM) search testing the company's strategy with and without errors

Search	Add to builder	Query	Items found
#5	Add	Search **(#4 NOT #1)**	6069
#4	Add	Search **(#2 OR #3)**	10168
#3	Add	Search **("Lennox Gastaut Syndrome"[Mesh] OR ("Epilepsies, Myoclonic"[Mesh] AND (child* or infan*)) OR "Dravet syndrome" OR "Lennox Gastaut" OR "childhood epilepsy encephalopathies" OR "severe myoclonic epilepsy" OR SMEI OR LGS)**	10111
#2	Add	Search **("Lennox Gastaut Syndrome"[Mesh] OR ("Epilepsies, Myoclonic"[Mesh] AND (child* or infan*)) OR "Dravets syndrome" OR "Lennox Gastaut" OR "childhood epilepsy encephalopathy" OR "severe myoclonic epilepsy" OR SMEI OR LGS)**	9889
#1	Add	Search **("Lennox Gastaut Syndrome"[Mesh] OR ("Epilepsies, Myoclonic"[Mesh] AND (child* or infan*)) OR "Dravet* syndrome" OR "Lennox Gastaut" OR "childhood epilep* encephalopath*" OR "severe myoclonic epilepsy" OR SMEI)**	4164

PubMed (NLM): up to 2019/03/26

Cochrane Library search

The company's Cochrane Library search contained very basic phrase searching without inclusion of MeSH Indexing. The ERG amended the CS search by including correct MeSH, truncation, phrase searching and added the abbreviation 'LGS'. The ERG's corrected Cochrane Library search retrieved 307 results, whereas the company's reported strategy retrieved only 207.

Cochrane Library: up to 2018/01/24
Searched 24.1.19

ID	Search	Hits
#1	MeSH descriptor: [Epilepsies, Myoclonic] explode all trees	51
#2	MeSH descriptor: [Lennox Gastaut Syndrome] explode all trees	24
#3	#1 and (child* or infan*)	47
#4	#3 or #2	74
#5	"Dravet syndrome" OR "Lennox Gastaut" OR "Dravets syndrome"	237
#6	"childhood epilepsy encephalopathy" OR "severe myoclonic epilepsy" OR SMEI	36
#7	LGS	129
#8	**#4 or #5 or #6 or #7**	**307***

* with Cochrane Library publication date from Jan 1890 to Dec 2018
The original company submission search of the Cochrane Library retrieved 207 references.

CRD search: NHS EED, DARE & HTA databases

The company's search of the CRD databases was restricted to 'Lennox-Gastaut or Dravet' in the title only. The ERG amended the CS search by including correct MeSH, truncation, phrase searching and added the abbreviations 'LGS' and 'SMEI'. The ERG's corrected CRD search retrieved, 17 results, whereas the company's reported strategy retrieved only 9.

DARE, HTA & NHS EED (CRD): up to 2018/03/31
Searched 26.3.19

Line	Search	Hits
1	MeSH DESCRIPTOR Lennox Gastaut Syndrome EXPLODE ALL TREES	1
2	MeSH DESCRIPTOR Epilepsies, Myoclonic EXPLODE ALL TREES	4
3	#1 OR #2	5
4	(child* or infan*)	10960
5	#3 AND #4	5
6	(Dravet* syndrome) OR (Lennox Gastaut) OR (childhood epilep* encephalopath*)	13
7	((severe myoclonic epilepsy) OR (SMEI) OR LGS)	8
8	#5 OR #6 OR #7	17

The original company submission search of the CRD databases retrieved 9 results.

Issue 1 Revised economic assessment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Applies to the whole ERG report. The company noted errors in the economic model, notified NICE on 1st February 2019 and rectified this with an updated economic assessment (as per NICE instructions). The ERG has continued to refer to the original model/outputs in its report. The key changes in the revised economic assessment were made to correct the original errors. The changes were clearly highlighted in the Revised Economic Assessment document. The company did NOT conduct the updated economic assessment in response to the clarification letter, but did incorporate some of the ERG's requests for scenarios etc into the revised economic assessment.	Because of the errors identified in the original model, all the outputs from the original submission (including e.g. QALYs, costs, ICERS, Tornado diagram, cost-effectiveness acceptability curve, scenarios) should be replaced by the revised values from the updated economic assessment. The revised model has undergone QC/validation by the original modelling team and two independent third party reviewers.	The original economic model contained errors. These were notified to NICE in February 2019 (prior to the clarification letter).	Not a factual inaccuracy. The ERG report was based on the original CS and the updated economic assessment was considered in the appropriate sections. This includes the errors that were corrected by the company (see for instance the "Fixing errors" adjustment).

Issue 2 Orphan indication

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Applies to the whole ERG report. It is not made clear in the report that	It should be made clear that: DS is an orphan indication (possibly even	DS is an orphan indication. This has not been noted clearly by the ERG	Not a factual inaccuracy. Section 3.2 of the ERG report

DS is an orphan indication and cannabidiol has Orphan designation.	ultra-orphan). Orphan designation (EU/3/14/1339) was granted by the European Commission on 15 October 2014 for cannabidiol for the treatment of DS.	in the report.	includes the following text: “The intervention (cannabidiol (Epidyolex®) in addition to current clinical management) is in line with the scope. Orphan designation (EU/3/14/1339) was granted by the European Commission on 15 October 2014 for cannabidiol for the treatment of Dravet syndrome.” Orphan designation is mentioned at several other points in the ERG report.

Issue 3 Outputs of original economic assessment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 13, 15, 87 and 88. The ERG cites outputs from the original economic model/assessment.	Because of the errors identified in the original model, all the outputs from the original submission (including e.g. QALYs, costs, ICERs, Tornado diagram, cost-effectiveness acceptability curve, scenarios) are erroneous and should be replaced by the revised values from the updated economic assessment (as agreed with NICE). The revised model has undergone QC/validation by the original modelling team and two independent third party reviewers.	The original economic model contained errors. These were notified to NICE in February 2019 and corrected in the revised economic assessment.	Not a factual inaccuracy. See response to issue 1.

Issue 4 'Third line' treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 11 and 24. The ERG states that the treatment pathway proposed by the company places CBD as a 'third line treatment'.	It should be noted that CBD is not placed as a 'third line treatment'. As shown in the proposed treatment pathway, it is part of a 'basket' of potential subsequent adjunctive therapies that come after first line and first adjunctive therapy. The anticipated label indication is "for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older." The above place in therapy is in line with the ILAE definition of refractory epilepsy: recognised as failure of adequate trial of two tolerated and appropriately chosen and used AED regimens (as monotherapies or in combination) to achieve sustained freedom from seizures.	CBD is part of a 'basket' of potential subsequent adjunctive therapies that come after first line and first adjunctive therapy.	Not a factual inaccuracy. The text of the company submission (section B.1.3, pg 24) states that: "For patients with DS considered for treatment with CBD, it will be an add-on treatment for refractory seizures in people aged 2 years of age and older once two other appropriate AEDs, trialled to a maximally tolerated dose, have failed to achieve seizure freedom (see Figure 2)." and this text is quoted in section 2.2 of the ERG report. The proposed treatment pathway (Figure 2.1 in the ERG report) was taken from the company submission (Figure2), as indicated in the footnote.

Issue 5 Mixed CCM comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 11, 21, 29, 37 and 52. The ERG questions the validity of the use of a 'mixed' CCM comparator.	The company considers that it is valid to use a 'mixed' CCM comparator, as agreed with NICE at the scoping meeting and the decision problem meeting. Across the Phase 3 trial programme for CBD, no observable trend in primary or key secondary outcomes was seen on the treatment effect of CBD versus placebo in patients taking different concomitant AEDs.	The CCM comparator is valid and was agreed with NICE at both the scoping meeting and at the decision problem meeting.	Not a factual inaccuracy. This is a matter of opinion and the ERG's opinion remains as expressed in our report.

Issue 6 'Detrimental' effect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 12, 52 and 59 and 64. The ERG notes that safety data appears to suggest that CBD has a 'detrimental' effect on markers of liver function.	Removal of the word 'detrimental'. If necessary, the words 'a detrimental effect' should be replaced with 'a transient effect'. As noted in the company's submission: raised liver aminotransferases were reported with CBD and were seen more often with the higher dose of CBD (20 mg/kg/day), when the patient had elevated transaminases at baseline, or when CBD was taken with concomitant valproate or clobazam. Cases of raised liver transaminases resolved either spontaneously (without dose reduction or interruption of CBD treatment during the studies) or with dose adjustments of CBD or concomitant AEDs. Liver function is commonly	The safety data do not suggest a 'detrimental' effect on markers of liver function.	Not a factual inaccuracy. The text used in the ERG report is in relation to reported instances of changes to liver function markers; the proposed change is a wording preference only.

	monitored for other AEDs.		

Issue 7 Small size of data set

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12. The ERG refers to the 'small size of the data set'.	The company considers that it should be noted that this is an orphan indication. The patient numbers in the CBD Phase 3 trial programme are significant for an orphan disease.	For an orphan disease, the patient numbers in the CBD clinical trials should not be classed as 'small'.	Not a factual inaccuracy. The text referred to actually states: "In addition, a major limitation of the evidence is the small size of the data set relating to the 10 mg cannabidiol dose to be used in practice. Just [redacted] patients in GWPCARE 2 and none in GWPCARE1 received the 10 mg/kg/day dose (this trial compared 20 mg/kg/day CBD to placebo)." The comment relates to the fact that most of the trial data are for a dose which is higher than the recommended dose used in the submission, rather than to the small size of the trials.

Issue 8 15-year time horizon

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 14, 23, 64, 70, 98.	The 15-year time horizon should not be	This is not a deviation. The NICE	Not a factual inaccuracy. See

The ERG refers to the 15-year time horizon used in the economic model as a deviation from the NICE reference case	referred to as a deviation from the NICE reference case. The company considers that the 15-year time horizon for estimating clinical and cost effectiveness is sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	reference case stipulates that 'the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared'. In the most recent examples of HTA submissions for a new drug for the treatment of DS - stiripentol - submissions to UK HTA bodies (SMC/AWMSG) used a 15-year time horizon. This was accepted.	explanation in section 5.2.5 of the ERG report.

Issue 9 SmPC and care pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19. In relation to the company's response to the ERG's clarification question ('does the placement of CBD in the care pathway reflect a narrower use than the expected licence?'; company answer 'No'), the ERG noted that 'This response appears to be inconsistent with the therapeutic indications stated in the submitted summary of product characteristics (SmPC), which does not include any limitation based on prior trials of other	It should be noted that the company's response was not inconsistent with the SmPC. The word 'adjunctive' in the label indication means that there will have been trial of other AEDs. The company also notes that, later in the ERG report (page 19): "The ERG considers that, with respect to prior AED treatments, the trial populations are consistent with the placement of CBD in the care pathway, as described in the CS".	The proposed position of CBD in the care pathway is consistent with the SmPC indication.	Not a factual inaccuracy. See response to issue 4. The text of the company submission (section B.1.3, pg 24) states that: "For patients with DS considered for treatment with CBD, it will be an add-on treatment for refractory seizures in people aged 2 years of age and older once two other appropriate AEDs, trialled to a maximally tolerated dose, have failed to achieve seizure freedom (see Figure

AEDs'.			2)." whereas the SmPC does not specify a number of prior AEDs failed.

Issue 10 Adult patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, 12, 21, 24, 39, 59. The ERG noted that 'The two main trials in the submission excluded adult (> 18) patients. There are therefore no clinical data relevant to adult patients.'	It should be noted that Dravet syndrome is an early childhood onset epilepsy syndrome. As the ERG noted in its report, the 'stages' of the syndrome may include: a febrile or diagnostic stage in the first year; a worsening stage between one and five years with frequent seizures, behavioural deterioration and neurologic signs; a stabilisation stage after five years, where convulsive seizures may decrease in some patients. Thus, the majority of patients with DS requiring treatment for uncontrolled convulsive seizures are likely to be identified and diagnosed in childhood. These children currently have a high mortality risk: those reaching adulthood are likely to be those whose seizures are better controlled. The clinical trial population in the CBD DS studies was a refractory population experiencing convulsive seizures at baseline, reflecting the above.	Although the Phase 3 CBD trials did not include patients >18 years, it would not be unreasonable to assume that any benefits obtained from CBD in patients with DS <18 years would persist into adulthood for some patients.	Not a factual inaccuracy, no change needed.

Issue 11 Sub-group analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 50. The ERG considered that there were some potentially relevant sub-groups in studies GWPCARE1 and GWPCARE2.	It should be noted that these sub-groups are not relevant to clinical prescribing or the cost-utility analysis. As indicated in the company's clarification response, these were standard demographic subgroup analyses that are done as part of any statistical analysis plan. Furthermore, as an orphan indication, these subgroups have small population numbers with low statistical powering. Across the Phase 3 trial programme for CBD, no observable trend in primary or key secondary outcomes was seen on the treatment effect of CBD versus placebo in the different demographic subgroups above.	The sub-groups are not relevant to clinical prescribing or the cost-utility analysis.	Not a factual inaccuracy. This is a matter of opinion and the ERG's opinion remains as expressed in our report. As noted in our report, the subgroup analyses included subgroups based on concurrent AED use and baseline drop seizure frequency, which cannot reasonably be described as 'standard demographic subgroup analyses that are done as part of any statistical analysis plan.'

Issue 12 Withdrawals from GWPCARE5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54. It was stated that 'the ERG is concerned that the apparently high rate of withdrawals from GWPCARE5, which were not attributable to adverse events… may indicate a loss of efficacy over time'	It should be noted that it is not possible from these data to speculate that withdrawals indicate a loss of efficacy over time. The withdrawal rate for patients with DS in GWPCARE5 is [redacted]. Conversely, this is a retention rate of [redacted] Patients withdraw from long-term studies for many reasons, not just adverse events or a lack	It is not possible or factually correct to state that the rates of withdrawal from GWPCARE5 may indicate a loss of efficacy over time.	Not a factual inaccuracy. The ERG report does not state that these withdrawals were caused by a loss of efficacy, but only raises this as a possible area of concern.

	of efficacy (e.g. logistical reasons, change of life circumstances, family-related issues, change of physician etc). For patients with DS in the GWPCARE5 study, [redacted] have withdrawn to date. Of these: [redacted] withdrew due to AEs; [redacted] were withdrawn by the parent/guardian; [redacted] were withdrawn by the investigator; the remainder were protocol violations/lost to follow-up. Thus, it is not possible from these data to speculate that withdrawals indicate a loss of efficacy over time.		

Issue 13 Trial population being representative of target population in model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9, 11, 20, 24, 39, 59, 68 and 69. The ERG states that 16% of patients in GWPCARE1 and 15% of patients in GWPCARE2 did not meet the definition of inadequately controlled – these percentages being patients who had discontinued fewer than two prior AEDs	It should be noted that the 16%/15% figures are incorrect. Even if a patient had discontinued <2 AEDs, that patient could still be taking his/her current AEDs (one or more), and still having seizures, thus meeting the definition of inadequately controlled. Current AEDs are not always discontinued even when the seizures are not controlled.	The ERG has not considered that patients entering the CBD trials could be inadequately controlled even while taking their *current* AED(s). These current AEDs could be in addition to the prior AEDs that the patient had already discontinued.	Explanatory text has been added, at all relevant points, to address this issue, e.g.: “It should be noted that these patients may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled.”

Issue 14 Change in analysis method for GWPCARE2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 41. The ERG was concerned about the change of analysis method for the primary outcome in GWPCARE2.	It should be noted that a negative binomial regression (NBR) was introduced as the primary analysis method as part of a protocol amendment for the GWPCARE2 study implemented prior to database lock. This methodology has been discussed with the EMA.	A NBR was introduced as the primary analysis method as part of a protocol amendment for the GWPCARE2 study implemented prior to database lock. The rationale for this amendment was that the NBR would provide a superior modelling approach for over-dispersed seizure count data than the non-parametric Wilcoxon rank-sum test, as it allows estimates of effect size that can incorporate age as a stratification variable and time, treatment arm and treatment arm-by-time interaction as effect-modifying co-variables. An analysis of previous epilepsy trials in DS and LGS indicated that modelling of seizure counts implemented within the framework of general linear models, using the negative binomial response distribution, might provide a more optimal fit to the data. Moreover, an NBR model accounts for the number of days over which each patient is evaluated, and so adjusts for variable periods of patient follow-up in the analysis. This methodology has been discussed with the EMA.	Expression of opinion, not a factual inaccuracy.

Issue 15 Adult population reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 17 and 24. The reference cited for the ERG's statement 'Around 80% of people with Dravet syndrome can survive into adulthood' is incorrect. The source is the US Dravet Syndrome Foundation, not Dravet Syndrome UK. It also originates from a US patient organisation, not from a peer-reviewed journal. With limited details on the survey, it is not possible to assess the quality of the reference or the data.	The reference source should be corrected. It should be noted that the reference is not from a peer-reviewed journal. It is from a US patient organisation. In addition, it should be noted that no details are provided as to the survey design, so it is not possible to assess the quality of the reference or the data.	Incorrect source of reference. The source is the US Dravet Syndrome Foundation, not Dravet Syndrome UK.	The reference has now been corrected and the source labelled as a survey.

Issue 16 Incorrect data reported: confidence interval

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 46 Table 4.5. Incorrect reporting of Confidence Interval for % change in convulsive seizures during treatment in GWPCARE2, 10mg/kg/day arm. GWPCARE2 results for % change in convulsive seizures during	Change 37.9 to -37.9	Incorrect data reported by the ERG.	This error has been corrected.

treatment. 10 mg/kg column states: "Median -48.7 (95% CI -57.6 to 37.9)". It should read "-37.9".			

Issue 17 Median

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 46 Table 4.5. GWPCARE2 results for % change in convulsive seizures during treatment, Placebo, 10mg/kg/day and 20mg/kg/day arms states results as “Median”	Remove the word “Median” from each of the cells	Presenting the results of a negative binomial regression analysis, not a Wilcoxon rank sum test.	This error has been corrected.

Issue 18 Incorrect data reported: response rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 47 Table 4.5. Incorrect reporting of patient number for response rate for 75% reduction in convulsive seizure in GWPCARE1, placebo arm. Response rate for 75% reduction in convulsive seizure, GWPCARE1, placebo column. Patient number is given as 6 (Cell reads "6 (11.9%)"). Actual number should be 7 (11.9% is correct).	Change 6 to 7	Incorrect data reported by the ERG.	This error has been corrected.

Issue 19 Model structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 67. The ERG states that it is concerned that the model does not incorporate the impact of non-convulsive seizures. The health states defined in the model focus on convulsive seizures and convulsive seizure-free days.	This structural feature of the model should not be stated as a concern. As outlined in the company's response to B1a of the ERG Clarification Questions, the focus on convulsive seizures reflects the primary endpoint in the clinical trials and the main source of morbidity and mortality in DS. The company does not consider this approach to have a biasing effect on the cost-effectiveness outcomes for CBD. It is more likely to **under**-estimate the utility gain with CBD since the number of **non**-convulsive seizures decreases substantially on average with convulsive seizure frequency health state (see response to B1a).	1) The model should reflect the primary endpoint in the clinical trials (reduction in convulsive seizure frequency). 2) Convulsive seizures are recognised to drive the morbidity and mortality in DS. 3) Non-convulsive (and thus total seizures - which were a key secondary endpoint in the trials) reduce substantially in frequency with convulsive seizure health states. As such, it is reasonable to assume that there is unmodelled upside in utility gain with CBD from reductions these seizure types.	Not a factual inaccuracy. See explanation in chapter 5 (e.g. sections 5.2.2, 5.2.6, 5.2.8 and 5.2.9) of the ERG report.

Issue 20 Placebo effect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14 and 67. The ERG is concerned that patients receiving CCM transfer back to their baseline seizure frequency after the first cycle (i.e. the 'placebo effect' observed with CCM during the 3 months in the clinical trials is not continued in	It should be noted that, based on clinician feedback, the company does not feel it is reasonable to assume that the placebo effect observed in the clinical trials should be continued for CCM for the duration of the model, as it would not be present in real-world clinical practice.	Feedback from clinicians indicated that the 'placebo effect' on CCM would not be relevant in a real-world clinical setting. Thus, in the model, it was assumed that patients on CCM would return to their baseline health state after	Not a factual inaccuracy. See explanation in section 5.2.2 of the ERG report.

the model).		cycle 1.	

Issue 21 Use of data from GWPCARE1 and GWPCARE5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 12, 13, 29, 39, 49, 54, 58, 59, 69 and 70. The ERG has concerns about the use of data from the GWPCARE1 and GWPCARE5 studies to derive input parameters for transition probabilities in the model, as the CBD dose in both studies was higher than the 10 mg/kg/day in the base-case.	It should be noted that: 1) Data from the 20 mg/kg/day arms of the GWPCARE1 and GWPCARE2 studies were NOT used to model clinical effectiveness for patients on 10 mg/kg/day in the model. The model does not use data from the GWPCARE1 study to model outcomes in patients on 10 mg/kg/day. It uses data from this study (and from the 20 mg/kg/day arm of the GWPCARE2 study) to model outcomes only in patients assigned to doses above 10 mg/kg/day (who are then assumed to be on 20 mg/kg/day) in cycle 1. In the company's base-case there are no such patients, so these data are not applied. In the company's Revised Economic Assessment, a scenario was run in which a proportion of patients ([redacted]) were on a dose >10 mg/kg/day (assumed to be 20 mg/kg/day). The rationale for this proportion is explained in the company's response to B7b of the ERG Clarification Questions. 2) In the anticipated label, the recommended maintenance dose will be 10 mg/kg/day, but patients will be permitted to escalate up to 20 mg/kg/day. The expectation is that only a minority of patients will do so (individuals who show a good response on the recommended maintenance dose). Thus, the main dose used in clinical practice will be 10 mg/kg/day. For this reason, the company has assumed 10 mg/kg/day as the dose in its base-case. 3) The company considers that the GWPCARE5 open-label extension data are the best data available to model transition probabilities beyond 3 months (up to 27 months). For this reason, these data have been used in preference to long-term	The company considers that the current model structure - using GWPCARE5 data where appropriate - uses the best data available at the current time.	Not a factual inaccuracy. See explanation in section 5.2.6 of the ERG report.

	extrapolation of the GWPCARE1 and GWPCARE2 data. The totality of the evidence in the GWPCARE studies does not support a clear dose response above 10 mg/kg/day. 4) It is not clinically meaningful to assign all patients to a maintenance dose of 20 mg/kg/day after cycle 1, as in the scenario analysis conducted by the ERG (Table 6.3, page 101). Very few patients in clinical practice will be maintained on this dose or one above 10 mg/kg/day. The company considers that the current model structure - using GWPCARE5 data to model long-term clinical effectiveness in all patients - is the most clinically plausible.		

Issue 22 Sub-group analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 71 (see also Issue 11 above). The ERG felt that it was unclear what the impact was of assuming that the effectiveness of CBD does not vary with different AED combinations. The ERG cited pre-specified sub-population analyses, which include patients on specific AEDs or combinations of AEDs in the CCM mix (page 51 of the ERG report). The company does not believe that this is unclear.	It should be noted that the pre-specified subgroup analyses on the GWPCARE1 and GWPCARE2 studies do not support the conclusion that the efficacy of CBD (and thus, by extension, its cost effectiveness) is greater in patients on any given concomitant AED or AED combination versus the ITT population, in which patients were on a heterogeneous mix of existing AEDs (and is thus representative of the CCM mix in clinical practice).	The subgroup analyses were exploratory. In none of the outcomes did any subgroup based on concomitant AEDs have 95% confidence intervals on risk ratios versus placebo that did not overlap with the ITT population. The results do not support a preferential treatment effect for CBD versus CCM alone in patients on any given concomitant AED or AED combination. This restriction is not anticipated in the label.	Not a factual inaccuracy.

Issue 23 Treatment effectiveness extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 14, 75, 100 and 101. The ERG expressed concern that the model assumes constant efficacy after month 27 on CBD. The ERG performed a scenario analysis assuming that patients on CBD return to their baseline health state after month 27, and made this an alternative version of its base case. The company strongly disagrees with the methodological validity of this assumption. The company recognises that efficacy (as with any chronic therapy) may wane over time. However, this is better modelled using long-term discontinuation rates rather than by using an arbitrary cut-off in the treatment effect of the drug.	It should be noted that the long-term discontinuation rate assumptions used in the revised model are supported by evidence and rationale. The company strongly disagrees with the ERG's alternative base-case in Table 6.1 p100 (in which CBD patients arbitrarily go back to their baseline health state after 27 months) and requests that it is removed or, as a minimum, changed to a scenario analysis. In its Revised Economic Assessment, the company implemented long-term discontinuation rates for the two health states with the highest seizure frequency to model treatment 'stopping' in non-responders. It further applied a discontinuation rate as observed in a real-world data set from a CBD Early Access Program to the health state with the lowest seizure frequency. These evidence-based discontinuation rates specifically account for waning of effectiveness; this has been lost in the ERG's base-case and replaced with an arbitrary assumption.	It is methodologically more appropriate to model the long-term waning of clinical effectiveness through discontinuation assumptions than via an arbitrary decline or cut-off in treatment effect.	Not a factual inaccuracy.

Issue 24 Seizure-free days

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 14, 75, 77, 100 and 101. The ERG expressed concern about the assumption that the number of days without convulsive seizures (a health sub-state in each cycle) is assumed to be dependent on both treatment allocation and health state (based on seizure frequency). The ERG considered that this may over-estimate the treatment effect of CBD.	The company requests that the ERG's base-case (Table 6.1 p100) should reinstate this assumption, or alternatively consider its removal only in a scenario analysis. The company wishes to emphasise (as it did in its response to B15a/b in the ERG's Clarification Questions) that CBD demonstrated a treatment effect on both the frequency of convulsive seizures and the number of days without convulsive seizures. The reduction in convulsive seizure frequency was observed in the primary and key secondary endpoints. The seizure-free day outcome was a tertiary endpoint. The actual transition probabilities and probability assignments were derived from analyses of the patient-level data from GWPCARE1 and GWPCARE2. It is therefore reasonable that the assignment probabilities between convulsive seizure-free health sub-states in each model cycle are dependent on both seizure-frequency health state (the transition probabilities for which also vary by treatment) and treatment assignment.	CBD has a treatment effect on both the frequency of convulsive seizures and the number of days without convulsive seizures, which was observed in the ITT population and in the patient-level data analyses used to derive the transition probabilities and probability assignments for the model.	Not a factual inaccuracy. See explanation in sections 5.2.6 and 5.2.8 of the ERG report.

Issue 25 Risk ratios for mortality

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 76 and 77. The ERG considered that there was a lack of appropriate justification for the risk ratios used to calculate epilepsy-related mortality rates (SUDEP and non-SUDEP).	It should be noted that there is an evidence-based rationale for the risk ratios and mortality rates due to SUDEP per health state (as per p65 of the Evidence Submission and p8 of the Revised Economic Assessment). Although these are assumptions, the risk ratios for SUDEP mortality have a rationale that is based on evidence. In the absence of evidence in the literature, the company also considered it a reasonable assumption to consider that the risk ratios for non-SUDEP causes were the same as the evidence-based assumptions for SUDEP.	The company's assumptions on mortality rates per health state are derived from an evidence-based rationale, as explained on p65 of the Evidence Submission and p8 of the Revised Economic Assessment.	Not a factual inaccuracy. See explanation in section 5.2.6 of the ERG report.

Issue 26 Utilities/vignette study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 14 and 80. The ERG expressed concerns about the means by which utilities were elicited for health states as follows: 1) The ERG considered that the vignettes methodology is condition-orientated, does not value health states through public preference, and is in contravention of the NICE	It should be noted that: 1) The company considers that the vignette methodology represents a reasonable and sincere effort to generate utility estimates in the absence of published alternatives for a very rare condition. 2) In the vignette study conducted, 57% ([redacted] out of [redacted]) of respondents were either individuals with DS or severe refractory epilepsy, or caregivers of patients with DS or severe	In orphan conditions, where there is a dearth of utilities evidence in the literature, it is not uncommon to rely on methods outside of the reference case. A number of NICE HST Appraisals have used a vignette methodology in "live" populations. In this case, the company has studied valuations directly in patients/caregivers, rather than treating physicians as a proxy	Not a factual inaccuracy. See explanation in section 5.2.8 of the ERG report.

Reference Case 2) The ERG felt that it was 'unclear' to what extent the respondents may be considered to have experience with DS as this was not specifically part of the inclusion criteria "DS or any epilepsy condition". (Note: this information was included in the company's submission). The ERG report does not consider the methodological challenges/limitations of generating utility estimates in an orphan disease, as outlined in the company's response to question B19 in the ERG clarification questions. The company notes that other technologies being assessed in NICE appraisals have deviated from the reference case due to similar challenges.	refractory epilepsy. 3) The rationale for the use of the vignette methodology (due to the challenges presented in recruitment by the orphan status of the condition) was clearly presented in the company's submission; there is also a precedent for using these methodologies in other NICE appraisals for technologies with similar challenges. The rationale for using the EQ5D VAS instead of the EQ5D questionnaire stemmed from the same limitations.	(as was the case in some of these precedents). The challenges and limitations associated with the vignette study were clearly highlighted in the company's submission. The use of the EQ5D VAS (instead of the EQ5D questionnaire) within the vignette study stemmed from the same limitations. Using EQ5D would have increased 5-fold the number of questions asked, making it almost impossible to test enough vignette health states. Despite these limitations, the company considers that the vignette methodology represents a reasonable and sincere effort to generate utility estimates in the absence of published alternatives for a very rare condition.	

Issue 27 Caregiver disutilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, 80 and 81. The ERG considered that including QALY decrements for caregivers in the total QALY estimates for both CBD and CCM was not in accordance with the NICE reference case. The addition of caregiver disutilities was discarded in the ERG base-case analysis.	Caregiver disutilities should be included in the base-case. The Company recognises the NICE Reference Case. However, NICE clarified in its "Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)" (https://www.nice.org.uk/guidance/gid-ta10274/documents/scope-consultation-comments-and-responses) for this appraisal that "Care giver related quality could be considered under health-related quality of life or could be captured within the innovation section". There is also precedent from seven NICE appraisals under the HST pathway where caregiver QoL has been considered in utility modelling, or the NICE committee has encouraged its use. In other conditions such as Alzheimer's disease, it has been acknowledged that the disease of the patient affects the HRQOL of their carer(s). This has been included in cost-effectiveness models accepted by NICE (see, for example, TA217). DS is a rare (orphan/ultra-orphan) and potentially life-threatening condition which places a very significant burden on the parents, siblings and other caregivers who care for the patient with DS. As such, there is a clear case for including caregiver disutilities in the economic assessment.	The inclusion of caregiver disutilities is relevant in this case. Patients with DS are often entirely dependent on others for their care, and the HRQoL of the carer(s) can be severely impacted.	Not a factual inaccuracy. See explanation in section 5.2.8 of the ERG report.

Issue 28 Model validation and face validity check

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

Pages 15, 91 and 92. The ERG states that the internal validity of the model "lacks credibility", based on an extreme values test that failed to give the expected null result (0 incremental QALY gain for CBD vs CCM). Based on the structure of the model, it would not be expected to give this result under these conditions, and therefore this is not a valid test of internal validity. When extreme values are used that would be expected to give a null result, the model works.	It should be noted that the extreme values test conducted by the ERG is not a valid test of internal validity, as it would not be expected to yield a zero incremental QALY gain for CBD vs CCM. The model does pass this test when input parameters are used that would be expected to yield a null result based on the model's structure (see Appendix 1). To note, the updated model submitted with the Revised Economic Assessment was subjected to a series of internal validity tests as part of its QC, which were detailed in the Company's response to B30c in the ERG's Clarification Questions.	The ERG performed an internal validity test on the model that the ERG expected to give a null result in terms of QALY gain. This test would not be expected to give this result, based on the model structure. When an extreme values test was run that would be expected to deliver a null result, the model passed (see Appendix 1).	Not a factual inaccuracy. See explanation in section 5.2.12 of the ERG report. To clarify this further: the validity checks performed by the ERG should provide zero incremental QALYs whenever there is model symmetry. This is not an extreme condition, indeed model symmetry (ensuring that the disease process is represented consistently across strategies) is recommended as best practice in the ISPOR-SMDM Modelling Good Research Practices Task Force paper on state-transition modelling.

Issue 29 Accuracy of searches

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 12, 14, 97-98. The ERG was concerned about potentially relevant missed evidence as the corrected search strategies were not provided in the clarification	The company has provided details of the amended search strategies, which now approximate to the results from the ERG's searches.	A reputable third party agency with experience and expertise in conducting SLRs conducted the searches on behalf of the company. Amended search strategies have been supplied below (see Appendix 2), together with a response directly from the agency (see below). We do not believe that the errors in the original search led to any relevant studies being omitted from the submission. We originally applied filters for studies in humans with abstracts for the PubMed and Embase searches, and also	Not a factual inaccuracy. The company has provided additional search strategies after the ERG report was written, and the ERG is not able to appraise new searches submitted as part of the FAC.

response.		applied these limits to the revised search in February 2019; we apologise for omitting this information in the submission, which we believe explains some of the discrepancies in search result numbers found by us and the ERG. We re-ran this new search and de-duplicated the original search to identify an additional 4695 studies; these have been screened and we have identified no additional relevant studies. We re-ran the amended search in the Cochrane library on 06 Feb 2019 and identified 207 publications; re-running the identical search on 15 April 2019 identified 341 publications. We cannot explain this discrepancy but have re-screened the 341 studies and have not identified any additional RCTs of relevance. We do not believe that the errors in the original search led to any relevant studies being omitted from the submission. Additional studies identified as [corrected search] NOT [original search] from PubMed, Embase and Cochrane were as follows (new publications are highlighted in green; all are conference abstracts of previously-identified RCTs): Anonymous (2017). "Point-of-care application: 'Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome'." European journal of integrative medicine 14(pp 20-21). **Secondary publication of GWPCARE1** Anonymous (2018). "Cannabidiol (CBD) treatment effect and adverse events (AES) by time in patients with Lennox-Gastaut syndrome (LGS): pooled results from 2 trials." Neurology Conference: 70th Annual Meeting of the American Academy of Neurology, AAN 2018. United States. 90(15 Supplement 1). **Secondary publication of GWPCARE3 and 4** Anonymous (2018). "Exposure-Response Analysis of Cannabidiol (CBD) oral solution for the treatment of Lennox-Gastaut syndrome." Neurology Conference: 70th Annual Meeting of the American Academy of Neurology, AAN 2018. United States. 90(15 Supplement 1). **Secondary publication of GWPCARE3 and 4** Cross, J.H., Devinsky, O., Laux, L., et al. (2017). "Cannabidiol (CBD)	

		reduces convulsive seizure frequency in Dravet syndrome: results of a multi-centre, randomised, double-blind, placebo-controlled trial (GWPCARE1)." Epilepsia 58: S12. **Publication already identified by original search** Cross, J.H., Devinsky, O., Marsh, E., et al. (2017). "Cannabidiol(CBD) reduces convulsive seizure frequency in Dravet syndrome: results of a multi-center, randomized, controlled trial (GWPCARE1." Neurology 88(16). **Publication already identified by original search** Devinsky, O., Cross, J.H., Laux, L., et al. (2017). "Cannabidiol (CBD) reduces convulsive seizure frequency in Dravet syndrome: results of a multi-center, randomized, double-blind, placebo-controlled trial (GWPCARE1)." Neurotherapeutics 14(3): 824. **Secondary publication of GWPCARE1** Devinsky, O., Cross, J.H., Laux, L., et al. (2017). "Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome." New England journal of medicine 376(21): 2011-2020. **Publication already identified by original search** Devinsky, O., Nabbout, R., Miller, I., et al. (2019). "Long-term cannabidiol treatment in patients with Dravet syndrome: an open-label extension trial." Epilepsia 60(2): 294-302. **Secondary publication of GWPCARE5 (2019 publication)** Devinsky, O., Patel, A.D., Cross, J.H., et al. (2018). "Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome." New England journal of medicine 378(20): 1888-1897. **Publication already identified by original search** Devinsky, O., Nabbout, R., Miller, I., et al. (2017). "Maintenance of long-term safety and efficacy of cannabidiol (CBD) treatment in Dravet syndrome (DS): results of the open-label extension (OLE) trial (GWPCARE 5)." Developmental medicine and child neurology 59: 126 **Publication already identified by original search** Devinsky, O., Nabbout, R., Miller, I., et al. (2018). "Maintenance of long-term safety and efficacy of cannabidiol treatment in Dravet syndrome: results of the open-label extension trial (GWPCARE5)." Epilepsia 59: S73 **Secondary publication of GWPCARE5** French, J., Thiele, E., Mazurkiewicz-Beldzinska, M., et al. (2017). "Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): results of a multi-center, randomized, double-blind, placebo-controlled trial (GWPCARE4)." Neurology 88(16). **Publication already identified by original search**	

		Halford, J., Marsh, E., Mazurkiewicz-Beldzinska, M., et al. (2018). "Long-term Safety and Efficacy of Cannabidiol (CBD) in Patients with Lennox-Gastaut Syndrome (LGS): results from Open-label Extension Trial (GWPCARE5)." Neurology 90(15). **Publication already identified by original search** Hancock, E. and Cross, H. (2003). "Treatment of Lennox-Gastaut syndrome." Cochrane database of systematic reviews (online) (3): CD003277. **Old version of SLR already identified by original search** Joshi, C., Thiele, E., Marsh, E., et al. (2017). "Treatment with Cannabidiol (CBD) Significantly Reduces Drop and Total Seizure Frequency in Lennox-Gastaut Syndrome (LGS): results of a Multicenter, Randomized, Double-blind, Placebo Controlled Trial (GWPCARE4)." Annals of neurology 82(S21): S293, Abstract no: 42. **Publication already identified by original search** Marsh, E., Mazurkiewicz-Beldzinska, M., Halford, J., et al. (2018). "Maintained safety and efficacy of cannabidiol in a long-term open-label trial in patients with Lennox-Gastaut syndrome (GWPCARE5)." Epilepsia 59: S9. **Publication already identified by original search** Mazurkiewicz-Beldzinska, M., Thiele, E.A., Benbadis, S., et al. (2017). "Treatment with cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): results of a multi-centre, randomised, double-blind, placebo-controlled trial (GWPCARE4)." Epilepsia 58: S55 **Publication already identified by original search** Mellis, C. (2018). "Cannabidiol for drug-resistant seizures in the Dravet syndrome." Journal of paediatrics and child health 54(1): 101-102. **Secondary publication of GWPCARE3** Patel, A., Devinsky, O., Cross, J.H., et al. (2017). "Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): results of a dose-ranging, multi-center, randomized, double-blind, placebo-controlled trial (GWPCARE3)." Neurology 89(8): e100. **Publication already identified by original search** Patel, A., Devinsky, O., Thiele, E., et al. (2017). "A dose ranging safety and pharmacokinetic study of cannabidiol (CBD) in children with Dravet syndrome (GWPCARE1)." Neurology 88(16). **Publication already identified by original search** Patel, A., Gil-Nagel, A., Chin, R., et al. (2019). "Long-term safety and efficacy of add-on cannabidiol treatment in patients with Lennox Gastaut syndrome in an open-label extension trial	

		(GWPCARE5)." Developmental medicine and child neurology 61: 13. **Publication already identified by original search** Privitera, M., Marsh, E., Mazurkiewicz-Beldzinska, M., et al. (2019). "Time to onset of efficacy of cannabidiol during titration in patients with Lennox - Gastaut syndrome and Dravet syndrome enrolled in three randomised controlled trials." Developmental medicine and child neurology 61: 64. **Publication already identified by original search** Scheffer, I.E., Halford, J., Nabbout, R., et al. (2019). "Long-term safety and efficacy of add-on cannabidiol (CBD) treatment in patients with Dravet syndrome (DS) in an open-label extension (OLE) trial." Developmental medicine and child neurology 61: 63 **Publication already identified by original search** Thiele, E.A., Marsh, E.D., French, J.A., et al. (2018). "Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial." Lancet (London, England) 391(10125): 1085-1096. **Publication already identified by original search** Thiele, E.A., Mazurkiewicz-Beldzinska, M., Benbadis, S., et al. (2017). "Treatment with cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox Gastaut Syndrome (LGS): results of a multi - Center, randomized, double-blind, Placebo-controlled trial (GWPCARE4)." Neurotherapeutics 14(3): 824-825. **Secondary publication of GWPCARE4** Wirrell, E., Devinsky, O., Patel, A., et al. (2017). "Cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox Gastaut syndrome (LGS): results of a dose ranging, multicenter, randomized, double blind, placebo-controlled trial (GWPCARE3)." Annals of neurology 82: S279-S280. **Publication already identified by original search** Wright, S., Devinsky, O., Thiele, E.A., et al. (2017). "Cannabidiol (CBD) in Dravet syndrome: a randomised, dose-ranging pharmacokinetics and safety trial (GWPCARE1)." Epilepsia 58: S56 **Publication already identified by original search** Zuberi, S., Devinsky, O., Patel, A., et al. (2017). "Cannabidiol (CBD) significantly reduces drop and total seizure frequency in Lennox-Gastaut syndrome (LGS): results of a dose-ranging, multi-centre, randomised, double-blind, placebo-controlled trial (GWPCARE3)." Epilepsia 58: S13-S14. **Publication already identified by original search**	

		Rosenberg, E.C., Louik, J., Conway, E., et al. (2017). "Quality of Life in Childhood Epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol." Epilepsia 58(8): e96-e100. **Publication already identified by original search**	

Issue 30 Accuracy of data extraction and quality assurance of included studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 36 and 45. The ERG was uncertain whether the data extraction process was adequately designed to minimise error and bias during data extraction. The ERG was uncertain about the number of reviewers who assessed the quality of included studies.	The company has submitted further details about the data extraction process, which was completed by two researchers to minimise error and bias. The company has submitted further details about the quality assurance process, which was completed by two researchers to minimise error and bias.	One researcher extracted data from all included papers into a pre-determined table shell and a second researcher validated the data extraction. Both researchers independently completed the quality assurance check for RCTs and economic evaluations. The quality assurance for RCTs was taken from the criteria for assessment of risk of bias in RCTs from Systematic Reviews: CRD's guidance for undertaking reviews in health care, 2009 https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf	Not a factual inaccuracy. The company has provided additional information as part of the FAC. The ERG report is based on the company submission and response to clarification questions.

Appendix 1: ERG internal validity test of the model

The ERG performed the following internal validity test on the revised model:

- Seizure frequency health state transition probabilities in cycles 1-9 for CBD were set to 100% on the diagonal trace for CCM (tab #SEIZURES) in each age group
- Seizure-free health sub-state probability assignments for CBD were set to the values for CCM (tab #DAYS) in each age group

The ERG's prediction was that this would result in the distribution of health states at baseline being uniform across the time horizon of the model for all patients (irrespective of treatment allocation), and thus give an incremental QALY gain of 0 for CBD vs CCM.

The model would not be expected to provide this outcome (it gives a gain of 0.13 in the company's revised model). The reason is as follows:

- The model moves all patients in the CCM group back to baseline after cycle 1, whereupon they are re-allocated health states and sub-states in each cycle based on baseline probability assignments (i.e. those at model entry)
- CBD patients by comparison continue in their assigned baseline health state until they discontinue or die
- During this period, CBD patients are assigned health sub-states as if they were on placebo; the placebo effect in the trials means this distribution is "better" than that at baseline - i.e. more patients have more seizure-free days

This results in an incremental QALY accumulation for CBD patients versus those on CCM.

If the probability allocations for health sub-states (tab #DAYS) are set to baseline levels (from tab COHORT DEFINITION) for each age group, this also does not give a zero incremental QALY gain for CBD (actual gain 0.09). This is to be expected, because:

- CCM patients go back to baseline after cycle 1
- As they age, their health state assignment in each cycle will shift from the baseline probability set in the 2-11 year age group to that in the 12-55 year age group
- A CBD patient who started in the age group 2-11 by comparison will continue in their baseline health state until they discontinue or die, even if they become older than 11 years
- The 12-55 year age bracket (i.e. older patients) has a "worse" health state distribution at baseline than those in the 2-11 year bracket (i.e. more patients have more seizures and fewer seizure-free days)

As such, a young CBD patient entering the model below 12 years of age will accumulate more QALYs than a CCM patient starting at the same age, if they do not discontinue before reaching the older age bracket of ≥12 years (because they benefit from the "younger" health state probability distribution for longer).

This results in an incremental QALY gain for CBD patients, even though health state and sub-state distributions are uniform between patients on CCM and CBD in each age group at each time point.

If the probability assignments are set to 100% for any one health state and sub-state (in any combination) in both age groups at baseline (tab COHORT DEFINITION) and in each cycle (tab #DAYS), then the incremental QALY gain for CBD reduces to 0. This is expected, as there is then a totally uniform distribution of health states in all patients at all timepoints over the time horizon.

Thus, the model validity is confirmed under the correct extreme values test.

Appendix 2: Revised search strategies

Search	Hits
PubMed search revised "Lennox Gastaut Syndrome"[Mesh] OR ("Epilepsies, Myoclonic"[Mesh] AND (child* or infan*)) OR "dravet syndrome" OR "lennox gastaut" OR "childhood epileptic encephalopathy" OR "severe myoclonic epilepsy" OR SMEI OR LGS OR Dravet* OR "dravet's syndrome" OR "childhood epileptic encephalopathies" OR "childhood epilepsy encephalopathies" OR "childhood epilepsy encephalopathy" **Limits**: Humans, studies with abstract, publication date to 2018/12/31 search date 06/02/2019	7386 (without limits = 9946)
EMBASE search revised (exact("lennox gastaut syndrome")) OR (exact("dravet like epileptic encephalopathy" OR "dravet syndrome" OR "dravet syndrome spectrum" OR "dravets syndrome")) OR ('Lennox Gastaut' OR Dravet OR 'severe myoclonic epilepsy' OR SMEI OR LGS OR dravet* OR "dravet's syndrome" OR "childhood epileptic encephalopathies" OR "childhood epilepsy encephalopathies" OR "childhood epilepsy encephalopathy") **Limits**: Humans, studies with abstract, publication date to 31/12/2018 Search date 11/02/2019	6114
Cochrane search revised lennox-gastaut OR "lennox gastaut" OR dravet OR "severe myoclonic epilepsy" OR SMEI OR LGS OR MeSH descriptor: [Lennox Gastaut Syndrome] explode all trees OR MeSH descriptor: [Epilepsies, Myoclonic] explode all trees **Limits**: Title, abstract, keywords; Publication date Jan 1890 to Dec 2018 Search date 15/04/2019: identified 342 Trials or Reviews; no additional relevant RCTs were identified	341
CRD Search revised (Lennox Gastaut OR Dravet OR severe myoclonic epilepsy OR SMEI OR LGS (Any Field) in DARE (all), NHS EED (all) and HTA (all)) OR (MeSH DESCRIPTOR Lennox Gastaut Syndrome EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Epilepsies, Myoclonic EXPLODE ALL TREES) **Search date** 06/02/2019	17

NICE National Institute for Health and Care Excellence

Technical engagement response form

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm on 27 June 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**GW Research Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Not applicable**

Questions for engagement

Issue 1: Positioning of cannabidiol in the Dravet syndrome treatment pathway	
Is the suggested position of CBD in the treatment pathway in line with how it is likely to be used in the NHS?	Based on discussions with UK specialist clinicians, the company is confident that the proposed positioning of CBD is in line with anticipated practice in the NHS. The company notes that the NICE technical team also supports this, stating in its Technical Report that the clinical trial population generally reflects the company's proposed positioning of CBD in the treatment pathway.
Issue 2: **Generalisability of the trial results to the NHS**	
Are the characteristics of participants in the GWPCARE trials likely to reflect the characteristics of people with DS seen in practice in the NHS?	The company notes from the NHS England statement in the NICE Technical Papers that "The view of NHS England is that the clinical trial data is generalisable to the UK population". The clinical trials for CBD included UK patients. The diagnostic criteria for DS in the trials were based on international guidelines, which are similar to the NICE guidelines for patients with DS. UK specialist clinicians agree that the participants in the GWPCARE trials reflect the characteristics of people with DS seen in practice in the NHS (based on e.g. age, gender, seizure types, concomitant anti-epileptic drugs).
Issue 3: **Transition to adulthood**	
Would patients continue to be treated into adulthood?	The company notes the statement from the Association of British Neurologists (ABN) in its Professional Organisation Submission: "Adults and children are both suitable candidates, neither should be excluded on age grounds alone". CBD will be prescribed by specialist clinicians. The company assumes that these experienced specialist clinicians will decide which patients to treat based on the Summary of Product Characteristics (SmPC), clinical guidelines and the profile of individual patients.

	The company also notes the following relevant statement from the Patient Organisation Submission (for LGS): "They (the parents) also noted that their son had previously been on the ketogenic diet, funded by the NHS, when he was receiving paediatric care and emphasised their disappointment that similar treatments are not available for adults with the condition on the NHS: 'It is hugely frustrating when it's available for children and not adults'."
Would the efficacy of CBD be expected to be similar in adult patients to paediatric patients?	There is no clinical reason to expect that the efficacy of CBD would be different in adult patients compared with paediatric patients. As noted above, the Association of British Neurologists (ABN) in its Professional Organisation Submission stated that: "Adults and children are both suitable candidates, neither should be excluded on age grounds alone".
How is the transition to adult services managed in the NHS?	
Issue 4: Composition of current clinical management	
Does current clinical management as described in the trial reflect clinical practice in the NHS?	The company notes that the main concern of the NICE technical team for this issue was that, in the company's base case model, the percentage of people with DS on each of the concurrently used anti-epileptic drugs (AEDs) was not based on the trial data (instead it was based on UK market research conducted by the company). The company also notes that "the technical team considers the trial data to be the most appropriate to use in the model base case analysis". For this reason, the company has updated its base case so that the baseline characteristics in the trials have been used to define the mix of AEDs in the CCM basket. Please see the Company's Updated Base Case in the separate 'Response Addendum' document.

If possible please estimate the percentage of people in the specified age groups eligible for treatment with CBD who would be treated with the anti-epileptic drugs specified in the adjacent table.

Anti-epileptic drug	Proportion of patients			
	<12 years		≥12 years	
	Company	Clinical expert	Company	Clinical expert
Clobazam	[redacted]		[redacted]	
Valproate	[redacted]		[redacted]	
Stiripentol	[redacted]		[redacted]	
Levetiracetam	[redacted]		[redacted]	
Topiramate	[redacted]		[redacted]	

Issue 5: Subgroups of patients with additional clinical benefit	
Are there any subgroups where the efficacy of CBD may be different from the overall trial population?	The company is currently investigating scenarios for clinical and cost effectiveness outcomes in subpopulations on certain AEDs. It has not been possible to complete these analyses in time for the submission deadline for responses to the technical report. The company will aim to provide these scenarios for the Appraisal Committee Meeting.
Issue 6: Criteria for stopping treatment	
Would treatment stop if seizure frequency did not improve? How would this be defined, and would this be related to convulsive seizure frequency, total seizure frequency or both? At what time-point(s) would response to treatment be assessed?	In most cases, CBD treatment would be expected to stop if there was no improvement in seizure frequency. In some cases, there may be benefits from CBD that are related to e.g. cognition/behaviour rather than just purely related to seizure reduction. The company assumes that, in those cases, the decision to stop treatment would be based on a discussion between the patient/carer and specialist clinician, especially given the lack of alternative treatment options in this highly refractory population. The company notes that there is now a draft Clinical Commissioning Policy Statement from NHS England, which includes suggested continuation/stopping rules. In response to feedback from the NICE technical team, the Company's Updated Base Case now incorporates the NHSE recommendations for stopping CBD in clinical practice (see Table 3 in the separate 'Response Addendum' document).

	Specifically, the company has implemented a one-off discontinuation at 6 months in each convulsive-seizure health state. This is equal to the proportion of non-withdrawn patients in each health state at 6 months in the GWPCARE5 study who had a <30% reduction from baseline in GWPCARE1/2. The 6 month timepoint represents the earliest time at which a patient is likely to be seen in clinical practice (visits are typically every 3-6 months) after the timepoint at which de-escalation of dose for non-responders to >10 mg/kg/day is recommended in the draft Clinical Commissioning Policy Statement from NHSE. Existing discontinuation rate assumptions, as observed in the GWPCARE5 study, continue to be applied for cycles 2-9. The ERG's preferred assumption has been adopted: see Table 3 in the 'Response Addendum' document. The longer-term discontinuation rates (from cycle 10 onwards) have been adjusted to 5% per cycle in all 'seizure' health states, which is in line with those observed in the US Early Access Program for CBD and reflects long-term non-persistence in a real-world setting. For the convulsive-seizure free health state, long-term discontinuation rates remain at 0.5%.
Issue 7: Ignoring non-convulsive seizures in the model	
Is excluding non-convulsive seizures from the model appropriate?	Convulsive seizures are the seizure types about which parents/caregivers of patients with DS are most concerned, given the risk of injury and SUDEP associated with convulsive seizures. Reduction in convulsive seizures was the primary endpoint in the CBD DS Phase 3 trials. Non-convulsive seizures include myoclonic, partial and absence seizures. These seizures are often more difficult to count. For example, an absence seizure may cause the person to blank out or stare into space for a few seconds, whilst a partial seizure may involve a person's leg or arm twitching briefly. It should be noted that data from the CBD Phase 3 trials shows that the average number of total seizures is lower in health states with fewer convulsive seizures. Therefore, it is the change in QoL in moving from higher to lower convulsive-seizure health states that is important, and there can only be "hidden upside" in terms of QALY gain which is not captured in the model. The magnitude of this hidden upside is explored in the sensitivity analysis presented by the company. Please see the sensitivity analysis in Table 4 of the separate 'Response Addendum' document.

How big an impact do non-convulsive seizures have on individuals' quality of life?	Convulsive seizures are assessed as the primary endpoint in trials for DS because they are clinically identifiable, easy to count, and drive the morbidity. Convulsive seizures were chosen as the basis for the model structure for these reasons, and because it is appropriate that a cost utility study is based on the primary endpoint of the trials. However, as mentioned in the NICE technical report, CBD also showed a treatment effect on total seizures and non-convulsive seizures in the trials. As described in the company's response to question B1a of the ERG's Clarification Questions, the average number of non-convulsive seizures strongly tracks convulsive-seizure health states. As such, there is unrealised patient benefit associated with non-convulsive seizures that is not captured in the model. Providing a deterministic quantification of this benefit is challenging. Non-convulsive seizures are not a homogenous category: both the treatment effect on, and QoL contribution of, each type is distinct. Incorporating their contribution to the model would require a very complex structure with multiple health sub states, and a utility elicitation study that would be unfeasible in such a rare condition due to the number of health state descriptions needed. To account for the uncertainty in this unrealised benefit, the company has performed a sensitivity analysis in which the additional disutility from these seizures required to increase the QALY gain in the updated base case by 5%-20% is estimated (see Table 4 in the separate 'Response Addendum' document). The disutility is assumed to be additive and assigned only in the highest convulsive-seizure health state (i.e. >25 convulsive seizures per month). It is further assumed to apply uniformly across the patient and caregivers. As can be seen in Table 4 of the 'Response Addendum' document, even a 20% increase in QALY gain would require an average disutility of only [redacted], or about a 15% QoL reduction on UK norms. This is within the ranges that might be expected from utility estimates for partial and focal seizures in other forms of epilepsy (see, for example, Kang H, et al. *Epilepsy Res* 2014;108(5):963-971 and Villanueva V, et al. *Neurologia* 2012:28(4):195-204).
Issue 8: Number of days without convulsive seizures	

Is CBD likely to increase the number of convulsive seizure-free days, in addition to reducing convulsive seizure frequency?	CBD showed a statistically and clinically significant treatment effect on the change in seizure frequency from baseline (see Document B, Section B.2.6). CBD also showed a similar effect on the number of seizure-free days per month (see Table 1 in Appendix 1 below). These outcomes were chosen to delineate health states and sub states respectively in the model because they each contribute independently to QoL. This principle was supported by the outcomes of the vignette utility elicitation study. In the NICE technical report, it is noted that the ERG's preferred assumption was to make transition probabilities flat between treatment arms because "it is unclear whether in the model patients maintain any benefit in health state sub-category after stopping CBD, which would bias the results in favour of CBD because patients in the current clinical management arm return to baseline seizure frequency". The model does not treat discontinuing CBD patients differently from CCM patients in this regard. CCM patients are reassigned to the baseline distribution of health states and sub states from cycle 3 onwards (in cycles 1 and 2 they are assigned distributions derived from the placebo arms in the trials - see the company's response to Issue 9 below). Discontinuing CBD patients are assigned to the same distributions at the same timepoints. Therefore, there is no bias in the model structure on the parameter of convulsive-seizure free days, and this assumption has been retained in the Company's Updated Base Case.
Issue 9: Relative treatment effect	
Is it appropriate to only capture placebo response in current clinical management arm for 1 cycle only (the length of the trial), or should the relative efficacy of CBD compared with current clinical management remain constant over time?	The ERG acknowledged in its report that the placebo effect in the GWPCARE trials for CBD was high. The placebo effect seen in clinical trials for both DS and LGS is very variable. In the CBD studies, it was up to 27%. A recent study in DS showed a placebo effect of <2% In LGS trials, it has varied from a 5% worsening to 12% improvement (Ostendorf AP, *et al*. *Neuropsychiatr Dis Treat*. 2017;13:1131-40). The absolute impact of CBD in DS on convulsive seizures from baseline is very consistent across studies at 40-50%, which is also seen on drop seizures in LGS. This magnitude of effect was observed in the open-label GWPCARE5 study for patients entering from the placebo arms of GWPCARE1 and 2 and re-baselined at study entry (see Tables 2 and 3

	in Appendix 1 below), as well as in a real world setting in the US Early Access Program (Laux LC, *et al*. Epilepsy Research 2019;154:13-20 - see Figures 1 and 2 in Appendix 1 below). These observations suggest that the absolute effect on seizure frequency as observed in the clinical trials would be replicated in practice. For these reasons, it is important that CBD is not unduly penalised by virtue of the unusually high placebo effect seen in its trials. This would occur if the relative treatment effect were maintained throughout the time horizon (as preferred by the ERG). The company notes that the NICE technical team considered that "assuming the placebo effect is maintained in subsequent cycles may overestimate the treatment effect of current clinical management". The Company's Updated Base Case has applied outcomes from GWPCARE1 and GWPCARE2 to 6 months (2 cycles) for both the CBD and CCM arms in the model (see Table 3 in the separate 'Response Addendum' document). After this point, CCM patients return to baseline, and outcomes from the GWPCARE5 study are applied to CBD patients. To avoid bias, discontinuing CBD patients are treated identically to CCM patients throughout the model. In a scenario analysis (see Table 4 in the 'Response Addendum' document), the company has extended the Phase 3 outcomes for both arms to cycle 8 in the model (up to 2 years). The ICER remains very stable.
Issue 10: Use of data from open label extension study	
Are the results from the open label extension study (GWPCARE 5), generalisable to the expected maintenance dose?	No dose response was seen in the GWPCARE2 trial in DS or in the GWPCARE3 trial in LGS. This lack of dose response is supported by a *post hoc* sub-group analysis of the GWPCARE5 data. There was no statistically significant difference on the primary and secondary endpoints between patients who were on a low dose (≥[redacted] to <[redacted] mg/kg/day) and those who were on a high dose (≥[redacted] to <[redacted] mg/kg/day), and the ITT population. As such, the Company believes that GWPCARE5 represents a good surrogate for outcomes on the expected maintenance dose of 10 mg/kg/day. The company believes that it is preferable to use long-term data from a clinical trial (i.e. the GWPCARE5 data) rather than extrapolating the 3-month outcomes from the Phase 3 trials (as suggested by the ERG).

	The Company's Updated Base Case extends the Phase 3 GWPCARE1/2 data to 2 cycles (6 months) in both the CBD+CCM and CCM arms, and then applies the GWPCARE5 data up to 2 years for CBD patients (with CCM and discontinued CBD patients returning to baseline). A scenario analysis (see Table 4 in the 'Response Addendum' document) extends the Phase 3 data in both arms to 2 years. The ICER is very stable.
Issue 11: Extrapolating the effects of treatment beyond the follow up period in the clinical trials	
Should the model account for a potential decrease in treatment effect on convulsive seizure- and total seizure frequency over time? If so, how should this be estimated? For example, are seizures likely to return to baseline levels, and over what period – 2 years, 4 years or something else?	As noted by the NICE technical team, the treatment effect of CBD is unlikely to stop abruptly at any given time point. The GWPCARE5 study shows a very consistent effect for CBD from baseline, both in the as-observed and LOCF analyses, over more than 2 years (Thiele E, et al. *Epilepsia* 2019;60(3):419-428, and Devinsky O, et al. *Epilepsia* 2019;60(2):294-302). Any assumption on cut-off or waning of transition probabilities within the model would be arbitrary. The company considers that it is more appropriate to account for any evolution in the drug's efficacy over time through discontinuation assumptions. This reflects clinical practice, and is evidence-led. Any attenuations in treatment effect are already accounted for in cycles 2-9 of the model through the application of the discontinuation rates as observed in the GWPCARE5 study, as well as stopping criteria (see Issue 5 above). Long-term discontinuations are captured by applying 3-month discontinuation rates as observed in the US Early Access Program ([redacted]%), which is the best long-term real-world data set currently available (Laux LC, et al. *Epilepsy Research* 2019;154:13-20). In the Company's Updated Base Case, [redacted]% of patients are on treatment by 3 years, and [redacted]% by 5 years. Increasing discontinuation rate assumptions in the model, which would account for any potential underestimation of treatment waning, reduces the ICER (see scenarios in Table 4 the separate 'Response Addendum' document).
If the dose of other anti-epileptic drugs had been reduced (see issue 18) would the dose be increased	To reduce uncertainty about how the dose of concomitant AEDs would vary when taking CBD, the company has removed the assumption that there would be a dose reduction of certain concomitant AEDs with CBD from its Updated Base Case (see response to Issue 18 below).

back to standard levels if the efficacy of CBD was reduced?	
Issue 12: Increasing the dose of cannabidiol	
Would a higher dose of CBD (eg the maximum recommended dose of 20 mg/kg/day) be considered for any of the following: • people who did not respond to a 10 mg/kg/day dose? • people whose response to a 10 mg/kg/day dose had lessened over time (see issue 11)? • people who responded to a 10 mg/kg/day dose to try and further reduce seizure frequency? If so, which patients would be considered for this dose and what proportion of responders/non-responders would this be?	CBD will be prescribed by specialist clinicians. The company assumes that these specialist clinicians will decide, in conjunction with the patient/carer, when/if to escalate the dose based on the Summary of Product Characteristics (SmPC), clinical guidelines and the risk profile of individual patients. Clinicians who treat epilepsy are experienced in doing this for AEDs. The SmPC defines 10mg/kg/day as the preferred maintenance dose for CBD. The company anticipates that the majority of patients will be on this dose in clinical practice. With regard to the groups described here in Issue 11: • People who did not respond to a 10 mg/kg/day dose of CBD should not be considered for a higher dose. (There was no dose response in the CBD clinical trials). • People who are not responding to a 10 mg/kg/day dose of CBD should not be considered for a higher dose. • People who responded to a 10 mg/kg/day dose have the option of being considered for a higher dose of CBD in order to try to further reduce seizure frequency or possibly achieve seizure freedom. The company notes that the draft Clinical Commissioning Policy Statement from NHS England supports this principle, i.e. it recommends escalation only where there is a response to a 10 mg/kg/day dose. The company acknowledges the NICE technical team's comment that scenario analyses relating to dose escalation should consider both the costs and benefits of dose escalation. The company has implemented scenario analyses in a population that includes some patients who receive a dose above 10 mg/kg/day, including both the costs and benefits. Please see the scenario analyses in Table 4 of the separate 'Response Addendum' document
At which timepoint(s) would people be assessed to determine if an increased dose could be of benefit?	The company notes that the draft Clinical Commissioning Policy Statement from NHS England states that the CBD dose should be reviewed at a minimum of 3 months or maximum of 6 months after initiation.
Issue 13: Time horizon	

<table>
<tr><td>Are all differences in costs and effects attributable to CBD likely to be captured in a 15-year time horizon?</td><td>In line with the recommendations in the NICE technical report, the Company's Updated Base Case extends the time horizon to 50 years.
The company considers that a lifetime horizon in this therapy area should be based on the time required for most patients to discontinue therapy.
In the Company's Updated Base Case, only [redacted]% of patients are still on therapy at 50 years. As such, this is considered to be a reasonable lifetime horizon. Scenario analyses are also provided on time horizons between 15 and 40 years.</td></tr>
<tr><td colspan="2">Issue 14: Relationship between mortality rates and number of seizures</td></tr>
<tr><td>Is an association between number of convulsive seizures and increased epilepsy-related mortality rates plausible? If possible, please estimate the increased (value greater than 1) or reduced risk (value less than 1) compared with the >8 and ≤ 25 seizures category in the adjacent table:</td><td>In the original economic model submitted to NICE, the company attempted to consider the impact on mortality of improved seizure control, as this is cited as an important area of unmet need. However, the company has accepted the ERG's assumption that mortality should be the same in all health states except in seizure-free patients and has updated the company base case to reflect this.
<table>
<tr><td></td><td colspan="4">Risk ratio</td></tr>
<tr><td></td><td>Seizure free</td><td>≤ 8 seizures</td><td>>8 to ≤ 25 seizures (reference)</td><td>> 25 seizures</td></tr>
<tr><td>Company</td><td>0.42</td><td>[redacted]</td><td>1.0</td><td>[redacted]</td></tr>
<tr><td>ERG</td><td>0.42</td><td>1.0</td><td>1.0</td><td>1.0</td></tr>
<tr><td>Clinical expert estimate</td><td></td><td></td><td>1.0</td><td></td></tr>
</table></td></tr>
<tr><td>What proportion of patients with Dravet syndrome treated with current clinical management would be expected to be alive:
15 years after starting treatment,
20 years after starting treatment,
50 years after starting treatment.</td><td></td></tr>
</table>

Issue 15: Health-related quality of life of people with Dravet syndrome	
Are the quality of life values presented by the company plausible?	The company considers the quality of life values presented to be plausible. See response below.
Are there any sources of evidence from the literature which could be used to validate the proposed quality of life values?	The systematic literature review for both DS and LGS performed by the company identified a single study that provided utility analogues broken out by health state (Verdian *et al*, 2008). This study was done in a UK setting for LGS patients. All other identified cost-utility studies in both DS and LGS used these analogues. The health states investigated in Verdian *et al* were not close surrogates for the CBD model, as they assessed HRQoL associated with relative changes in seizure frequency over time and not absolute seizure frequency. In the company's model, using absolute seizure frequency was a deliberate choice, since QoL is more likely to be determined by absolute and not relative seizure status. In addition, the literature does not report on the contribution of seizure-free days to utilities, which is another key parameter affecting QoL. For these reasons, the company conducted a bespoke vignette study to elicit utility estimates for its model. Utility scores for patients with a high response in Verdian (≥75% reduction) align to the convulsive seizure-free health state in the CBD model. Furthermore, average utility scores for DS populations reported in the large DISCUSS survey showed similar values to the company's health states, both at a European level (Lagae L, et al. Developmental Medicine & Child Neurology 2018;60:63-72) and in the UK (Pagano K, et al. Developmental Medicine and Child Neurology 2019;61: 62). A scenario analysis using the utility estimates from Verdian *et al* applied as closely as possible to the health states in the company's model shows a similar ICER to the Company's Updated Base Case. (See the scenario in Table 4 the separate 'Response Addendum' document).
Issue 16: Health-related quality of life of carers of people with Dravet syndrome	

Should carer quality of life be included in the model?	The company notes that the technical team concluded that carer quality of life should be included in the model. From the Technical Report: "The technical team agrees that it is important to capture the impact of caring for someone with DS in the model in line with the NICE methods guide." In the "Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)" for this appraisal, NICE also commented that "Caregiver related quality could be considered under health-related quality of life".
Are the quality of life values presented by the company for carer quality of life plausible?	The quality of life values presented by the company for carer quality of life are in line with those found in the literature (see response below).
Are there any sources of evidence from the literature which could be used to validate the proposed quality of life values?	In DS, a survey (Campbell JD, et al. *Epilepsy & Behavior* 2018;80:152-156) assessed caregiver utilities. The disutility (0.22 +/- 0.17) is closely aligned to those measured in the company's vignette study ([redacted] and [redacted] for the two health states with the highest numbers of seizures), validating the plausibility of the company's disutility estimates.
How many carers would a child with Dravet syndrome be expected to have? Would this be expected to remain the same after the person reaches adulthood?	The literature suggests that ≥1 carer for patients with DS is usual. For example, in the large pan-European DISCUSS survey of DS patients (Lagae, L. et al. *Developmental Medicine & Child Neurology* 2017), almost 80% of households had more than one adult caregiver. For the majority of children with DS, this remains the same after they reach adulthood. DS is a severe, lifelong, treatment-resistant form of epilepsy affecting children from 2 years of age. It is associated with many consequences/co-morbidities that can result in lifelong intellectual and physical impairment, and complete dependence upon caregivers for daily activities. The company notes from the NICE technical report that "the technical team considers that the company may have underestimated the number of carers". (In the Revised Base Case, March 2019, the company included only 1 caregiver per patient). Therefore, in the Company's Updated Base Case, in line with Lagae et al, 2017, it has been assumed that each patient with DS has 1.8 carers.
Issue 17: Impact of adverse events on quality of life	
Would the adverse events (AEs) associated with CBD be expected to have a substantial negative impact on health-related quality of life?	The majority of adverse events (AEs) associated with CBD reported in the clinical trials were mild to moderate in severity. The ERG noted that "Safety data appeared to indicate a pattern of gastrointestinal and 'tiredness'-related adverse events".

	Any negative impact on health-related quality of life is likely to be very small compared to the loss of quality of life associated with the severe seizures experienced by patients with DS. In addition, any AEs are occurring against a background of AEs from the other anti-epileptic drugs in the CCM mix. Therefore, the costs associated with AEs have been included in the model, but the disutilities that may be associated with any AEs have not.
Issue 18: Reduction in the concomitant use of anti-epileptic drugs	
Is using CBD likely to reduce concomitantly used anti-epileptic drugs? Is a 33% reduction plausible?	Clinically, a reduction in concomitant AEDs is relevant to patients and their carers, as there may be benefits associated with dose reductions through an improvement in side effects. Nonetheless, based on the comments from the ERG and the NICE technical team, in the Company's Updated Base Case, the company assumed that there are no reductions in concomitant AEDs. The dose reduction of concomitant AEDs is included as a scenario in the economic analysis. Please see the scenario analyses in Table 4 of the separate 'Response Addendum' document.
If dose reductions are likely please estimate the percentage of patients who would have a dose reduction and the size of this reduction in the adjacent table:	

Drug	% of patients	% dose reduction
Clobazam		
Stiripentol		
Valproate		
Levetiracetam		
Topiramate		

Are there situations where increasing the dose of a concomitant anti-epileptic drug after starting CBD is appropriate?	

Appendix 1

Issue 8
Table 1: Mean number of convulsive seizure-free days per 28 days over the treatment period

	GWPCARE2 Study 1424			GWPCARE1 Study 1332	
	CBD 20 mg/kg/day (n= 67)	CBD 10 mg/kg/day (n= 66)	Placebo (n= 65)	CBD 20 mg/kg/day (n= 61)	Placebo (n= 59)
Treatment period P-value (vs placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NR – Not reported

Issue 9
Table 2: Outcomes on the primary endpoint for patients in GWPCARE1 and 2 versus those re-baselined in GWPCARE5

	N	Mean	SD	Median	Comparison between groups	
					T-test	Wilcoxon
Received CBD (14 weeks outcomes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Received placebo (12 week outcomes)	[redacted]	[redacted]	[redacted]	[redacted]		

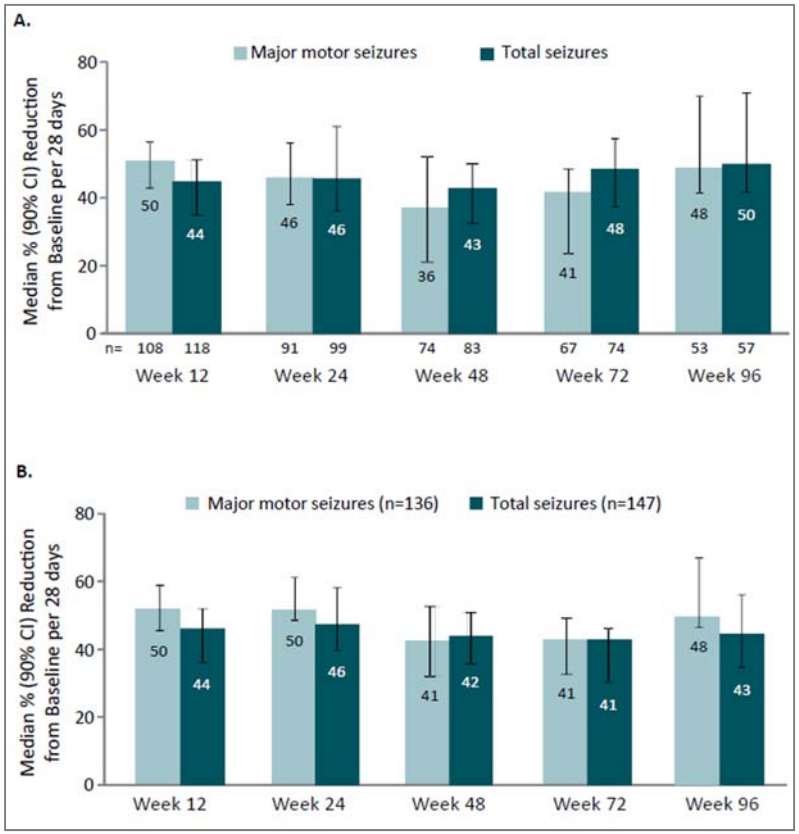
Percent reduction in convulsive-seizure frequency for patients on CBD in GWPCARE1 and 2, and for patients on a maintenance dose of <21 mg/kg/day of CBD in GWPCARE5 who were previously on placebo in GWPCARE1 and 2. Outcomes for transitioning placebo patients are re-baselined to the start of the GWPCARE5 study and measured at 12 weeks (vs 14 weeks for patients on CBD in the GWPCARE1 and 2 studies).

Issue 9
Table 3: Outcomes on the key secondary endpoint for patients in GWPCARE1 and 2 versus those re-baselined in GWPCARE5

	N	≥50% reduction from baseline		Chi-squared
		N	%	
Received CBD (14 weeks outcomes)	[redacted]	[redacted]	[redacted]	[redacted]
Received placebo (12 week outcomes)	[redacted]	[redacted]	[redacted]	

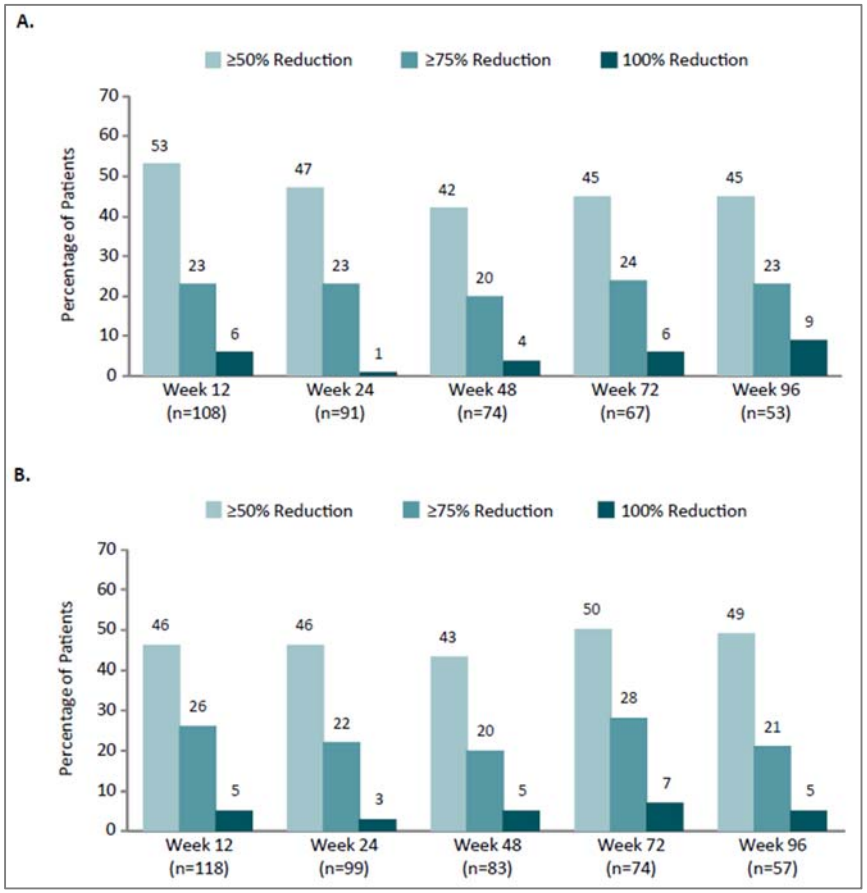
Proportion of patients achieving ≥50% reduction in convulsive-seizure frequency on CBD in GWPCARE1 and 2, and for patients on a maintenance dose of <21 mg/kg/day of CBD in GWPCARE5 who were previously on placebo in GWPCARE1 and 2. Outcomes for transitioning placebo patients are re-baselined to the start of the GWPCARE5 study and measured at 12 weeks (vs 14 weeks for patients on CBD in the GWPCARE1 and 2 studies).

Issue 9
Figure 1: Primary endpoint on CBD in the US Early Access Program



Percentage reduction from baseline in major motor and total seizures among patients with LGS and DS for the efficacy analysis set (A) and under LOCF analysis (B).
Major motor seizures include tonic, clonic, tonic-clonic, atonic, or focal seizures that evolved to generalized tonic, clonic, or tonic-clonic components. These are a close surrogate for drop (LGS) and convulsive seizures (DS). Other seizure types included in total seizures are myoclonic, absence, myoclonic-absence, focal with and without impaired consciousness.

Issue 9
Figure 2: Key secondary endpoint on CBD in the US Early Access Program



Percentage reduction from baseline in major motor (A) and total seizures (B) among patients with LGS and DS for the. Major motor seizures include tonic, clonic, tonic-clonic, atonic, or focal seizures that evolved to generalized tonic, clonic, or tonic-clonic components. These are a close surrogate for drop (LGS) and convulsive seizures (DS). Other seizure types included in total seizures are myoclonic, absence, myoclonic-absence, focal with and without impaired consciousness.

Technical engagement response form – Addendum update Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

This document is as an update of the Addendum to the company's responses provided in the Technical engagement response form, as submitted on 27th June 2019.

This update is in response to the communication from NICE (signed by Nicole Elliott) on 9th July 2019, requesting further clarification on model symmetry.

Company's Updated Base Case

The company's response to Issue 28 in the Pro-forma Response to the ERG Report (18th April 2019) outlined why the ERG's validity tests would not be expected to give zero QALY gain in the Company's Revised Base Case Model (issued March 2019). It relates to how the model manages the effect of aging (moving from 2-11 years to ≥12 years) on the distribution of convulsive seizure health states for patients on and not on CBD. The company feels that this was a reasonable design choice to account for likely changes in convulsive seizure frequency over time in DS as it is currently treated (and as observed at baseline in the GWPCARE trials).

This design feature was maintained in the model accompanying the Company's Updated Base Case (submitted 27th June 2019).

Following an email from NICE (signed by Nicole Elliott) on 9th July 2019, the company has removed this design feature.

In its response to Issue 9 of the technical report, the company provided an explanation as to why applying the relative treatment effect observed in the GWPCARE1 and GWPCARE2 studies beyond the first cycle is likely to considerably underestimate the cost effectiveness of CBD.

Nonetheless, in recognition of the uncertainty cited in the technical report relating to this issue (and issue 10), the company applied outcomes from the phase III studies for an extra cycle (i.e. cycles 1-2) in both CBD+CCM and CCM arms. To avoid bias, outcomes in the placebo arms of the studies were also applied to discontinuing CBD patients over the same time period.

[redacted]

As such, the new model provided with this Addendum update now manages CCM patients in the following way in the base case:

- Transition probabilities, as specified for "Placebo + CCM" in tab "# SEIZURES" for "Cycle 1", are applied for the first cycle. These are derived from the placebo arms of the GWPCARE1 and GWPCARE2 trials

- Patients are maintained in this health state distribution for [redacted] (see tab "# SEIZURES" for "Subsequent Cycles")
- In [redacted], patients are assigned the distribution of health substates (defining the number of seizure free days) as specified for "Placebo + CCM" in the tab "# DAYS"
- Patients are re-assigned the baseline distribution of heath states and health substates as of [redacted] (see tab "COHORT DEFINITION") for the age at which they entered the model. This is maintained until the end of the time horizon.

Patients who discontinue CBD are treated in the same way:

- If they discontinue CBD in [redacted], they are assigned to the health state distribution for CCM patients at the end of cycle 1, and health substate distribution as defined in tab "# DAYS" for "Placebo + CCM"
- As of [redacted], they are assigned the baseline health state and substate distributions for the age at which they entered the model, no matter when they discontinue. This is maintained until the end of the time horizon.

This revised model structure removes "aging" as a feature of the model.

This Addendum update provides the following information:

- Tables 1 and 2 show the Company's Updated Base Case with this revised model structure. All other structural changes and assumptions are as described in the company's response to the technical report on 27th June 2019
- Table 3 shows scenario analyses for the Company's Updated Base Case with this revised model structure. These scenarios are the same as those submitted in the company's response to the technical report on 27th June 2019
- Table 4 lists the validity tests requested by the ERG and the NICE technical team on the company's base case with this revised model structure, demonstrating model symmetry under the correct conditions
- Table 5 provides a summary of the coding updates done to the model to accommodate this new structure
- Tables 6-8 and Figures 1-3 provide sensitivity analyses for the base case
- The attached document "QC Tests Revised Model" repeats quality assurance tests done for the previous model

These results should now be considered as the company's base case.

Updated Economic Outcomes

Table 1. Company's Updated Base Case (no aging function)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Patients still on CBD at:	
						2 years	50 years
CCM	[redacted]	[redacted]	-	-	-	-	-
CCM + CBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2. Costs in the Company's Updated Base Case (no aging function)

Cost categories	CCM + CBD	CCM	Difference
Total costs per patient	[redacted]	[redacted]	[redacted]
Treatment costs per patient	[redacted]	[redacted]	[redacted]
Adverse Events costs per patient	[redacted]	[redacted]	[redacted]
Management costs per patient	[redacted]	[redacted]	[redacted]
SUDEP cost per patient	[redacted]	[redacted]	[redacted]
Non-SUDEP cost per patient	[redacted]	[redacted]	[redacted]

Table 3. Scenario analyses on the Company's Updated Base Case (no aging function)

Scenario	Rationale	Inc. Costs	Inc. QALYs	ICER
Company's Updated Base Case	-	[redacted]	[redacted]	[redacted]
CCM mix based on the company's market research survey from Q1 2018 (as per the Company's Revised Base Case March 2019; see Table 16 p59 of Document B)	Issue 4	[redacted]	[redacted]	[redacted]
Outcomes from GWPCARE1/2 (used in cycle 1 of Company's Updated Base Case) applied for cycles 1-8 for both the CBD+CCM and CCM arms (ERG's scenario)	Issues 9 and 10	[redacted]	[redacted]	[redacted]
Relative treatment effect applied for cycles 1-2 only (as per the base case in the company's response to the technical report 27th June 2019).	Issue 9	[redacted]	[redacted]	[redacted]
Long-term discontinuation rates (cycles 10 onwards) increased from 5% to 10% per cycle for all health states other than convulsive-seizure free patients.	Issue 11	[redacted]	[redacted]	[redacted]
Time horizon (% patients still on CBD, % patients alive on CBD+CCM/CCM): • 15 years (8.43%, 79.5%/78.8%) • 20 years (6.39%, 73.5%/72.6%) • 30 years (4.95%, 62.6%/61.4/%) • 40 years (4.33%, 52.5%/51.5%)	Issue 13	[redacted]	[redacted]	[redacted]
Utilities for health states taken from LGS analogues in Verdian *et al* 2018[1]. Utilities across seizure free day health sub states made uniform.	Issue 15	[redacted]	[redacted]	[redacted]
Concomitant AED doses reduced for patients on CBD (as per the Company's Revised Base Case March 2019; see Table 27 p82 of Document B)	Issue 18	[redacted]	[redacted]	[redacted]
Incident population only (age 2-5 years at model entry)	Existing scenario	[redacted]	[redacted]	[redacted]

Scenario	Rationale	Inc. Costs	Inc. QALYs	ICER
Average dose of 12.88 mg/kg/day (as per the Company's Revised Base Case March 2019; see Table 40 p108 of Document B)	Existing scenario	[redacted]	[redacted]	[redacted]
Mean instead of median body weight across age ranges in the weight table	Table 3 Technical Report	[redacted]	[redacted]	[redacted]
Sensitivity analysis - QoL impact of non-convulsive seizure reductions. Additive disutility per person* required to increase incremental QALY gain in base case by: • 5% - 0.034 • 10% - 0.068 • 20% - 0.102	Issue 7	[redacted]	[redacted]	[redacted]

1. Verdian L, *et al*. Abstract 1.352 presented at the 62nd meeting of the American Epilepsy Society 2008.

*Both scenarios assume 1 patient and an average of 1.8 caregivers. Disutilities assigned only to patients in the highest convulsive-seizure health state (>25 convulsive-seizures per month).

The sensitivity analyses to address Issue 7 (last row) would require an additive QoL decrease of about 15% on UK norms to increase QALY gain by 20% in the base case. This disutility is within the ranges that might be expected from utility estimates for partial and focal seizures in other forms of epilepsy (see, for example, Kang H, et al. Epilepsy Res 2014;108(5):963-971 and Villanueva V, et al. Neurologia 2012:28(4):195-204).

Table 4. Validity Tests

Tests show changes versus the company's updated base case. Null results hold true over all time horizons and age groups, unless otherwise stated. Non-zero results are quoted for the overall population at 50 years.

Test	Result (QALY gain)	Expected
ERG's Test: • All transition probabilities (TPs) set to 0%/100% on the diagonal trace for all cycles in tab "# SEIZURES" • Probabilities by health state for seizure free day (SFD) substates set to the values in the "Placebo + CCM" table for all CBD tables in tab "# DAYS"	CBD+CCM: 3.42 CCM: 3.10 Total QALY gain: 0.31	Yes. A non-zero QALY gain is expected for CBD. This is expected for 3 reasons: • The distribution of SFD heath substates across health states is not set to be the same for each cycle (tab "# DAYS") and at baseline (tab "COHORT DEFINITION") within each age group. As patients in the CCM arm go back to baseline from cycle 3, and CBD patients do not, this results in different QALY gains in each cohort, even if convulsive seizure health state distributions are kept uniform over time • Discontinuation rates are not set to be uniform across all health states at each time point in each age group. This creates different distributions of health states over time between CBD and CCM/discontinued CBD patients, even though they start out uniform • Stopping rules are not switched off (tab "Global Settings"); this has the same effect as non-uniform discontinuation rates (as above)
Full model symmetry test: • All transition probabilities (TPs) set to 0%/100% on the diagonal trace for all cycles in tab "# SEIZURES" • Probabilities by health state for SFD substates set to the values at baseline for all tables ("placebo + CCM" and "CBD + CCM") in each age group in the tab "# DAYS" • Discontinuation rates set to 5% for health states in all cycles across both age groups in tab "DISCONTINUATION" • Stopping rules switched off in tab "GLOBAL SETTINGS"	Zero QALY gain	Yes. A zero QALY gain is expected. Note – failing to apply all these conditions results in a non-zero QALY gain, as expected (see ERG's test above) Note – changing the distribution of health states and SFD health substates at baseline in each age group independently retains a null QALY gain, as long as the distribution of SFD substates is the same at baseline (tab "COHORT DEFINITION") and in all tables in the tab "# DAYS" for each age group. This highlights that that the age groups are now "separated", and discontinuing CBD patients are not "aging" Note – setting the distribution of health states and substates at baseline (tab "COHORT DEFINITION") to be the same for both age groups gives a zero QALY gain overall and in each age group independently (tab "BASE CASE RESULTS"), as long as the other conditions are met.
Company's prior model symmetry test: As noted in the email from NICE (Nicole Elliott) *"The company further stated that if the probability assignments are set to 100% for any one health state and sub-state in both age groups at baseline then the incremental QALY gain for*	Zero QALY gain	Yes. A zero QALY gain is maintained under this change, as expected. Note – this result is maintained irrespective of which health state (at baseline) and health substate (at baseline and in tab "# DAYS") is assigned a 100% value (with all others set to 0%).

Test	Result (QALY gain)	Expected
CBD+CCM is 0. The ERG have noted that it is not clear which settings have been used in the model from this description". This test is achieved by setting all parameters as per the "Full model symmetry test" (above), with the exception that: • Baseline health state probabilities set to "100%" for the health state "≤8 seizures", and 0% for all others, for both age groups in tab "COHORT DEFINITION" • Probabilities are set to 100% for the SFD substates "≤18 days", and 0% in all others, in both age groups at baseline in tab "COHORT DEFINITION", and in tab "# DAYS"		
Model symmetry for CCM and discontinuing CBD patients (NICE technical team's test): All parameters as per the "Full model symmetry test" (above), with the exception that: • Discontinuation rates in tab "DISCONTINUATIONS" are set to 0%, 10%, 15%, 20% (variably) for all health states in all cycles	Zero QALY gain	Yes. A zero QALY gain is maintained under all changes, as expected. Note – the null result is maintained if discontinuation rates are changed for only one set of cycle time points (e.g. "Cycle 1", "Subsequent cycles" or "Long-Term") and all other timepoints remain at 5%, as long as discontinuation rates are uniform across health states. Furthermore, this holds true if all discontinuation rates are set to 100% for one set of cycle time points, and all others are set to 0%.
Model symmetry for CCM and discontinuing CBD patients (discontinuation test): All parameters as per the "Full model symmetry test" (above), with the exception that: • Discontinuation rates are set to 5% for all health states in all cycles for patients 2-11 years old, and 10% in patients ≥12 years old.	Zero QALY gain	Yes. A zero QALY gain is maintained under this change, as expected. Note – changing the discontinuation rates in each age group independently maintains a null result, as long as they are uniform across health states for any given set of cycle time points in each age group.
Model symmetry for CCM and discontinuing CBD patients (parameters test 1): All parameters as per the "Full model symmetry test" (above), with the exception that: • Discontinuation rates set to 5% for all cohorts and cycles, except for the health state "≤8 seizures" in "Long-Term" cycles (10%)	Zero QALY gain at 2 years At 50 years: CBD + CCM 2.94 CCM 3.09 Total QALY gain -0.15	Yes. A zero QALY gain is expected up to 2 years, and a non-zero gain thereafter. The application of the split of health states at the end of cycle 1 in the CCM arm to all patients on CCM and discontinuing CBD over 8 cycles (2 years), alongside the uniform discontinuation rates in cycles 1-8, would be expected to give a null result over a 2-year time horizon. From cycle 10 onwards patients not on CBD go back to baseline, and those on CBD have non-uniform discontinuation rates. This gives a non-zero result. Note – changing the long-term discontinuation rate for the "≤8 seizures" health state in "Long-Term" cycles to 5% returns a null result at all time points.

Test	Result (QALY gain)	Expected
		Note – any non-uniform set of long-term discontinuation rates across health states returns this non-zero result for time horizons beyond 2 years.
Model symmetry for CCM and discontinuing CBD patients (parameters test 2): All parameters as per the "Full model symmetry test" (above), with the exception that: • The user option "Maintain benefit of placebo effect after the 1st cycle" is set to "For 1 additional cycles" (tab "COHORT DEFINITION")	Zero QALY gain	Yes. A zero QALY gain is maintained under this change, as expected. This parameter increases the number of cycles over which the health state distribution at the end of cycle 1 is applied to CCM patients, before they go back to baseline. Note – A null result is maintained irrespective of the number of additional cycles selected for this parameter
Model symmetry for CCM and discontinuing CBD patients (parameters test 3): All parameters as per the "Full model symmetry test" (above), with the exception that: • The user option "Split used when patients discontinued treatment" set to "split at baseline" (tab "COHORT DEFINITION")	Zero QALY gain	Yes. A zero QALY gain is maintained under this change, as expected. This parameter determines whether discontinuing CBD patients are returned to baseline by default, or assigned the health state distribution at the end of cycle 1 in CCM patients, for as long as this is applied to the latter.

Table 5. Coding changes

The document "Technical engagement response form – Appendix: Sensitivity Analyses and Coding Changes to the Model" (issued 1st July 2019) provides a description of the coding changes made to the model submitted with the company's responses to the NICE technical report.

The following table lists the additional changes made to the model provided with this document. The removal of the aging function is facilitated by the functional change in the first row. The second functional update makes no difference to the outcomes versus the model submitted on 27th June 2019, and is for simplicity only.

Function	Changes
Discounting Function: Initial function not accounting for aging	• Additional variables are defined in Module **A1_Main**: ○ *agingFunction*: discontinuation function not accounting for aging (set to False) • The macro *get_ModelSettings* from Module **A2_GetValuesInputs** has been updated to disregard aging in the Discontinuation function (initial function not accounting for aging). • The macro *calculate_patientMatrix* from Module **A4_PatientTraces** has been updated to put back patients who discontinued to baseline split of the baseline age group (age group when entering the model). • The macro *calculate_patientMatrix2* from Module **A4_PatientTraces** has been updated to put back patients who discontinued to baseline split of the baseline age group (age group when entering the model).
Number of Caregivers	The macro *get_Utilities* from Module **A2_GetValuesInputs** has been updated to account for the number of caregivers. The caregiver utilities are multiplied by the number of caregivers provided by the user.

Deterministic Sensitivity Analysis

Table 6: Parameter variations in the DSA

Parameter	Base Case	Lower Bound	Upper Bound	References
Discount Rates				
Costs	3.5%	0.0%	6.0%	NICE recommendation
Outcomes	3.5%	0.0%	6.0%	
Weight (kg)				
2 - 5 years	[redacted]	[redacted]	[redacted]	Based on the patient level data from the GWPCARE1 & 2 studies, using 40th and 60th percentiles
6 - 11 years	[redacted]	[redacted]	[redacted]	
12 - 17 years	[redacted]	[redacted]	[redacted]	
18 - 55 years	[redacted]	[redacted]	[redacted]	
Dose reduction concomitant valproate and clobazam				
All age groups	0%	0%	-100%	Assumption
Discontinuation rates				
All cycles	As below	-10%	+10%	Assumption
Subsequent cycles	As observed in GWPCARE5	-50%	+50%	Assumption
Long-term	[redacted]	-50%	+50%	Assumption
Stopping rules				
% patients stopping at 6 months per health state	As observed in GWPCARE5	-20%	+20%	Assumption
Management Unit Costs				
Visits Costs	Between £106 and £3,529	-20%	+20%	Assumption

Parameter	Base Case	Lower Bound	Upper Bound	References
Hospitalisation Costs	Between £0 and £5,817	-20%	+20%	Assumption
Rescue Med Costs	Between £0 and £408	-20%	+20%	Assumption
Institutionalisation Costs	Between £0 and £1,604	-20%	+20%	Assumption
Daily Cost ICU				
Adults	£1,299	£643	£4,482	Tables 32 & 38 of Document B
Paediatric	£1,583	£784	£5,867	
Daily Cost General Ward				
Adults	£460	£402	£807	Tables 32 & 38 of Document B
Paediatric	£597	£560	£760	
Phone Call Follow-up				
Neurologist	£107	£57	£153	Tables 32 & 38 of Document B
Paediatric neurologist	£258	£55	£234	
Emergency Department Visit				
Per episode	£237	£56	£838	Tables 32 & 38 of Document B
Non-SUDEP costs, days in ICU				
2 - 11 years	7.00	-20%	+20%	Tables 32 & 38 of Document B
12 - 55 years	7.00	-20%	+20%	
% of institutionalisation				
Seizure-Free	2.00%	1.6%	2.4%	Table 32 of Document B
≤8 seizures	10.00%	8.00%	12.00%	
>8 - ≤25 seizures	10.00%	8.00%	12.00%	
>25 seizures	10.00%	8.00%	12.00%	
CBD average dosage per patient (mg/kg/day)				

Parameter	Base Case	Lower Bound	Upper Bound	References
All age groups	10	N/A	12.88	Table 41 of Document B
Epilepsy-related Mortality				
SUDEP – RR				
Seizure-Free				
2 - 11 years	0.42	-10%	+10%	Assumption
12 - 55 years	0.42	-10%	+10%	
≤8 seizures				
2 - 11 years	1	-10%	+10%	Assumption
12 - 55 years	1	-10%	+10%	
>25 seizures				
2 - 11 years	1	-10%	+10%	Assumption
12 - 55 years	1	-10%	+10%	
SUDEP – Probabilities				
>8 - ≤25 seizures				
2 - 11 years	0.23%	0.11%	0.49%	Based on 98% CIs in Cooper MS, *et al*. 2016 Epil Res 128:43-7.
12 - 55 years	0.23%	0.11%	0.49%	
Non-SUDEP – RR				
Seizure-Free				
2 - 11 years	0.42	-10%	+10%	Assumption
12 - 55 years	0.42	-10%	+10%	
≤8 seizures				
2 - 11 years	1	-10%	+10%	Assumption
12 - 55 years	1	-10%	+10%	
>25 seizures				
2 - 11 years	1	-10%	+10%	Assumption
12 - 55 years	1	-10%	+10%	
Non-SUDEP – Probabilities				
>8 - ≤25 seizures				

Parameter	Base Case	Lower Bound	Upper Bound	References
2 - 11 years	0.16%	0.11%	0.21%	Based on 98% CIs in Cooper MS, *et al*. 2016 Epil Res 128:43-7.
12 - 55 years	0.16%	0.11%	0.21%	
Utilities				
Patient utilities				
Seizure-Free; >24 days	[redacted]	[redacted]	[redacted]	Based on standard errors from vignette study Table 25 of Document B
≤8 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
≤8 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>18 - ≤25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>18 - ≤25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>18 - ≤25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
Caregiver utility decrements				
Seizure-Free; >24 days	[redacted]	[redacted]	[redacted]	Based on standard errors from vignette study
≤8 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
≤8 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>18 - ≤25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>18 - ≤25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>18 - ≤25 seizures; >24 days	[redacted]	[redacted]	[redacted]	

Parameter	Base Case	Lower Bound	Upper Bound	References
>25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >24 days	[redacted]	[redacted]	[redacted]	

Figure 1: Tornado Diagramme

Probabilistic Sensitivity Analysis

Table 7: Parameter variations in the PSA

Parameters		Base case	Min	Max	SE	Alpha	Beta	Distribution
Transition probabilities								
Transition probabilities		N/A	Bootstrap from trial data					
Weight								
2 - 5 years		[redacted]	N/A	N/A	[redacted]	1465.26	0.01	Gamma
6 - 11 years		[redacted]	N/A	N/A	[redacted]	867.04	0.03	Gamma
12 - 17 years		[redacted]	N/A	N/A	[redacted]	1055.73	0.05	Gamma
18 - 55 years		[redacted]	N/A	N/A	[redacted]	405.42	0.13	Gamma
Subsequent cycle discontinuation								
2 - 11 years	Seizure-Free	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	≤8 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>8 - ≤25 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>25 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
12 - 55 years	Seizure-Free	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	≤8 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>8 - ≤25 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>25 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
Long-term discontinuation								
Seizure-Free		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
≤8 seizures		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
>8 - ≤25 seizures		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
>25 seizures		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
Stopping rules								
2 - 11 years	Seizure-Free	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	≤8 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>8 - ≤25 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>25 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
12 - 55 years	Seizure-Free	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	≤8 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>8 - ≤25 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>25 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
Management Unit Costs								
Visits Costs								
2 - 11 years	Seizure-Free	£275	£138	£413	70,15	15,37	17,90	Gamma

Parameters		Base case	Min	Max	SE	Alpha	Beta	Distribution
	≤8 seizures	£971	£486	£1,457	247.71	15.37	63.19	Gamma
	>8 - ≤25 seizures	£2,008	£1,004	£3,011	512.13	15.37	130.65	Gamma
	>25 seizures	£3,529	£1,764	£5,293	900.14	15.37	229.63	Gamma
12 - 55 years	Seizure-Free	£106	£53	£160	27.14	15.37	6.92	Gamma
	≤8 seizures	£311	£155	£466	79.31	15.37	20.23	Gamma
	>8 - ≤25 seizures	£560	£280	£839	142.74	15.37	36.42	Gamma
	>25 seizures	£1,192	£596	£1,788	304.15	15.37	77.59	Gamma
Hospitalisation Costs								
2 - 11 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤8 seizures	£1,454	£727	£2,181	370.98	15.37	94.64	Gamma
	>8 - ≤25 seizures	£2,908	£1,454	£4,363	741.96	15.37	189.28	Gamma
	>25 seizures	£5,817	£2,908	£8,725	1483.92	15.37	378.56	Gamma
12 - 55 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤8 seizures	£188	£94	£282	48.02	15.37	12.25	Gamma
	>8 - ≤25 seizures	£376	£188	£565	96.04	15.37	24.50	Gamma
	>25 seizures	£753	£376	£1,129	192.08	15.37	49.00	Gamma
Rescue Med Costs								
2 - 11 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤8 seizures	£102	£51	£153	26.02	15.37	6.64	Gamma
	>8 - ≤25 seizures	£204	£102	£306	52.04	15.37	13.28	Gamma
	>25 seizures	£408	£204	£612	104.08	15.37	26.55	Gamma
12 - 55 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤8 seizures	£51	£26	£77	13.01	15.37	3.32	Gamma
	>8 - ≤25 seizures	£102	£51	£153	26.02	15.37	6.64	Gamma
	>25 seizures	£204	£102	£306	52.04	15.37	13.28	Gamma
Institutionalisation Costs								
18 - 55 years	Seizure-Free	£321	£160	£481	81.86	15.37	20.88	Gamma
	≤8 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
	>8 - ≤25 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
	>25 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
Daily Cost ICU								
Adults		£1,299	£643	£4,482	979.49	1.76	738.39	Gamma
Paediatric		£1,583	£784	£5,867	1296.58	1.49	1061.73	Gamma
Daily Cost General Ward								
Adults		£460	£402	£807	103.43	19.78	23.26	Gamma
Paediatric		£597	£560	£760	51.01	137.00	4.36	Gamma
Emergency Department Visit								
Per episode		£237	£56	£838	199.33	1.41	167.64	Gamma
Epilepsy-related Mortality – SUDEP								
2 – 11 years (>45 - ≤110 seizures)		0.23%	0.11%	0.49%	0.00	5.80	0.00	Gamma

Parameters		Base case	Min	Max	SE	Alpha	Beta	Distribution
12 – 55 years (>45 - ≤110 seizures)		0.23%	0.11%	0.49%	0.00	5.80	0.00	Gamma
Epilepsy-related Mortality – Non-SUDEP								
2 – 11 years (>45 - ≤110 seizures)		0.16%	0.11%	0.21%	0.00	43.86	0.00	Gamma
12 – 55 years (>45 - ≤110 seizures)		0.16%	0.11%	0.21%	0.00	43.86	0.00	Gamma
% of institutionalization								
Seizure-Free		2.00%	1.60%	2.40%	N/A	N/A	N/A	Uniform
≤8 seizures		10.00%	8.00%	12.00%	N/A	N/A	N/A	Uniform
>8 - ≤25 seizures		10.00%	8.00%	12.00%	N/A	N/A	N/A	Uniform
>25 seizures		10.00%	8.00%	12.00%	N/A	N/A	N/A	Uniform
Utilities								
Patient utilities - Values estimated based on SE								
No seizures	>24 days	[redacted]	N/A	N/A	[redacted]	57.46	18.82	Beta
≤8 seizures	≤18 days	[redacted]	N/A	N/A	[redacted]	N/A	N/A	Beta
	>18 - ≤24 days	[redacted]	N/A	N/A	[redacted]	82.25	61.65	Beta
	>24 days	[redacted]	N/A	N/A	[redacted]	67.51	42.92	Beta
>8 - ≤25 seizures	≤18 days	[redacted]	N/A	N/A	[redacted]	75.56	133.56	Beta
	>18 - ≤24 days	[redacted]	N/A	N/A	[redacted]	73.17	91.89	Beta
	>24 days	[redacted]	N/A	N/A	[redacted]	42.76	49.06	Beta
>25 seizures	≤18 days	[redacted]	N/A	N/A	[redacted]	76.04	247.54	Beta
	>18 - ≤24 days	[redacted]	N/A	N/A	[redacted]	77.95	130.22	Beta
	>24 days	[redacted]	N/A	N/A	[redacted]	46.36	57.78	Beta
Caregiver utility decrements – values based on SE								
>8 - ≤25 seizures	≤18 days	[redacted]	N/A	N/A	[redacted]	14.990	0.013	Gamma
	>18 - ≤24 days	[redacted]	N/A	N/A	[redacted]	14.990	0.013	Gamma
	>24 days	[redacted]	N/A	N/A	[redacted]	14.990	0.013	Gamma
>25 seizures	≤18 days	[redacted]	N/A	N/A	[redacted]	20.717	0.012	Gamma
	>18 - ≤24 days	[redacted]	N/A	N/A	[redacted]	20.717	0.012	Gamma
	>24 days	[redacted]	N/A	N/A	[redacted]	20.717	0.012	Gamma

Table 8: PSA results compared to base case (1000 simulations)

	Inc. Costs	Inc. QALYs	ICER
Base Case	[redacted]	[redacted]	[redacted]
PSA	[redacted]	[redacted]	[redacted]

Figure 2: Cost-effectiveness plane

[redacted]

Figure 3: Cost-effectiveness acceptability curve

[redacted]

Clinical Outcomes – On-Clobazam Population
Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

The company expects to receive CHMP positive opinion for Epidyolex (cannabidiol) on [redacted]. The indication in section 4.1 of the SmPC is likely to be as follows:

- Epidyolex is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), [redacted], for patients 2 years of age and older.

This document provides the main clinical outcomes (efficacy and safety) for the population of patients who were on clobazam (CLB) at baseline in the GWPCARE1 and GWPCARE2 trials.

Efficacy

The efficacy of cannabidiol for the adjunctive therapy of seizures associated with DS was evaluated in two Phase 3 studies, GWPCARE1 and GWPCARE2.

Approximately 65% of patients were taking concomitant clobazam. Of the patients who were not taking clobazam, the majority had previously taken and subsequently discontinued clobazam treatment.

Results of the subgroup analysis of patients treated with clobazam are shown below.

Key outcome measures and subgroup analysis in DS studies

		Overall	N	Subgroup With Clobazam	N
CONVULSIVE SEIZURES PER 28 DAYS Percentage Reduction from Baseline[a]					
GWPCARE2	Placebo	26.9%	65	[redacted]	[redacted]
	10 mg/kg/day	48.7%	66	[redacted]	[redacted]
	20 mg/kg/day	45.7%	67	[redacted]	[redacted]
GWPCARE1	Placebo	13.3%	59	[redacted]	[redacted]
	20 mg/kg/day	38.9%	61	[redacted]	[redacted]
Difference or Percent Reduction Compared with Placebo (95% CI), p-value[b]					
GWPCARE2	10 mg/kg/day	29.8%		[redacted]	
		(8.4%, 46.2%)		[redacted]	
		p=0.0095		[redacted]	
	20 mg/kg/day	25.7%		[redacted]	
		(2.9%, 43.2%)		[redacted]	
		p=0.0299		[redacted]	
GWPCARE1	20 mg/kg/day	22.8%		[redacted]	
		(5.4%, 41.1%)		[redacted]	
		p=0.0123		[redacted]	
≥50% REDUCTION IN CONVULSIVE SEIZURES (RESPONDER ANALYSIS) Percentage of ≥50% Responders, p-value[d]					
GWPCARE2	Placebo	26.2%	65	[redacted]	[redacted]
	10 mg/kg/day	43.9%	66	[redacted]	[redacted]

		p=0.0332		[redacted]	
	20 mg/kg/day	49.3%	67	[redacted]	[redacted]
		p=0.0069		[redacted]	
GWPCARE1	Placebo	27.1%	59	[redacted]	[redacted]
	20 mg/kg/day	42.6%	61	[redacted]	[redacted]
		p=0.0784		[redacted]	
TOTAL SEIZURES PER 28 DAYS					
Percentage Reduction from Baseline[a]					
GWPCARE2	Placebo	29.7%	65	[redacted]	[redacted]
	10 mg/kg/day	56.4%	66	[redacted]	[redacted]
	20 mg/kg/day	47.3%	67	[redacted]	[redacted]
GWPCARE1	Placebo	9.0%	59	[redacted]	[redacted]
	20 mg/kg/day	28.6%	61	[redacted]	[redacted]
Difference or Percent Reduction Compared with Placebo, p-value[b]					
GWPCARE2	10 mg/kg/day	38.0%		[redacted]	
		P=0.0003		[redacted]	
	20 mg/kg/day	25.1%		[redacted]	
		P=0.0255		[redacted]	
GWPCARE1	20 mg/kg/day	19.20		[redacted]	
		P=0.0335		[redacted]	
MEAN CGIC SCORE AT LAST VISIT					
Percentage patients with any improvement, p-value					
GWPCARE2	Placebo	42%	65	[redacted]	[redacted]
	10 mg/kg/day	68%	66	[redacted]	[redacted]
		P=0.0009		[redacted]	
	20 mg/kg/day	60%	67	[redacted]	[redacted]
		P=0.0279		[redacted]	
GWPCARE1	Placebo	34%	59	[redacted]	[redacted]
	20 mg/kg/day	62%	61	[redacted]	[redacted]
		P=0.02		[redacted]	
EXPLORATORY ENDPOINT - CONVULSIVE SEIZURE-FREE DAYS GAINED					
Mean number of convulsive seizure-free days gained versus baseline					
GWPCARE2	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	10 mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]
	20 mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference, p-value					
GWPCARE2	10 mg/kg/day	[redacted]		[redacted]	
		[redacted]		[redacted]	
	20 mg/kg/day	[redacted]		[redacted]	
		[redacted]		[redacted]	

CI = 95% confidence interval.
[a] Data for the overall population are presented as median percent reduction from baseline. Data for the with clobazam subgroup are presented as percent reduction from baseline estimated from a negative binomial regression analysis.
[b] Overall data are presented as estimated median difference and p-value from a Wilcoxon rank-sum test. Data for the with clobazam subgroup are estimated from a negative binomial regression analysis.
[c] nominal p value.
[d] The Overall p-value is based on Cochran–Mantel–Haenszel test; the nominal p-values for the with clobazam subgroup are based on logistic regression analysis.

Safety

Results of the subgroup analysis of patients treated with concomitant clobazam are shown below.

Summary of adverse events from pooled DS trial data

Pooled DS trial data	**Overall**		**Subgroup with clobazam**	
	All CBD (N=221) n (%)	**Placebo (N=131) n (%)**	**All CBD (N=[redacted]) n (%)**	**Placebo (N=[redacted]) n (%)**
AEs	**195 (88.2)**	**108 (82.4)**	[redacted]	[redacted]
Mild	96 (43.4)	80 (61.1)	Data N/A	Data N/A
Moderate	75 (33.9)	23 (17.6)	Data N/A	Data N/A
Severe	24 (10.9)	5 (3.8)	Data N/A	Data N/A
AEs leading to discontinuation	16 (7.2)	1 (0.8)	[redacted]	[redacted]
SAEs	44 (19.9)	14 (10.7)	[redacted]	[redacted]
Deaths	0	0	0	0

Selected adverse events in pooled DS patients

Adverse reaction	**Overall**		**Subgroup with clobazam**	
	All CBD (N=221) n (%)	**Placebo (N=131) n (%)**	**All CBD (N=[redacted]) n (%)**	**Placebo (N=[redacted]) n (%)**
Somnolence / sedation	**61 (27.6)**	**11 (8.4)**	[redacted]	[redacted]
Decreased appetite	53 (24.0)	14 (10.7)	[redacted]	[redacted]
Diarrhoea	48 (21.7)	15 (11.5)	[redacted]	[redacted]
Pyrexia	45 (20.4)	16 (12.2)	[redacted]	[redacted]
Fatigue	33 (14.9)	11 (8.4)	[redacted]	[redacted]
Vomiting	27 (12.2)	7 (5.3)	[redacted]	[redacted]

Technical engagement response form – Addendum update Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

This document replaces the document entitled "Technical engagement response form – Addendum update" (issued on 17th July 2109). It follows the company's responses in the Technical engagement response form, submitted on 27th June 2019.

Company's Updated Base Case in the On-Clobazam Subpopulation

The company anticipates receiving CHMP positive opinion for Epidyolex (cannabidiol) on [redacted]. The indication in section 4.1 of the SmPC will be as follows:

- Epidyolex is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), [redacted], for patients 2 years of age and older.

In light of this label, this document provides cost-utility outcomes for the population of patients who were on clobazam (CLB) at baseline in the GWPCARE1 and GWPCARE2 trials. These outcomes also serve as the company's response to Issue 5 of the NICE technical report.

These outcomes align to the indicated population, and serve as the company's Updated Base Case. They replace those previously provided for the overall trial populations.

The structure of the model is the same as that provided in the addendum update issued on 17th July 2019. In particular, "aging" is removed. The relevant validity tests and coding changes specified in that document still apply. In the model provided with this document, clinical parameters have been replaced with those from the on-CLB population from the trials.

This document provides the following information:

- Tables 1-2 show the Company's Updated Base Case in the on-CLB subpopulation.
- Table 3 shows scenario analyses for the Company's Updated Base Case in the on-CLB subpopulation.
- Table 4 provides a summary of the parameters in the model that have been updated since the model provided for the overall trial populations on 27th June 2019

Updated Economic Outcomes

Table 1. Company's Updated Base Case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Patients still on CBD at:	
						2 years	50 years
CCM	£356,822	3.25	-	-	-	-	-
CCM + CBD	£395,585	4.68	**£38,763**	**1.43**	**£27,181**	54.81%	4.99%

Table 2. Costs in the Company's Updated Base Case

Cost categories	CCM + CBD	CCM	Difference
Total costs per patient	£395,585	£356,822	£38,763
Treatment costs per patient	[redacted]	[redacted]	[redacted]
Adverse Events costs per patient	[redacted]	[redacted]	[redacted]
Management costs per patient	[redacted]	[redacted]	[redacted]
SUDEP cost per patient	[redacted]	[redacted]	[redacted]
Non-SUDEP cost per patient	[redacted]	[redacted]	[redacted]

Table 3. Scenario analyses on the Company's Updated Base Case

Scenario	Rationale	Inc. Costs	Inc. QALYs	ICER
Company's Updated Base Case	-	£38,763	1.43	£27,181
CCM mix based on the company's market research survey from Q1 2018 (as per the Company's Revised Base Case March 2019; see Table 16 p59 of Document B)	Issue 4	[redacted]	[redacted]	[redacted]
Outcomes from GWPCARE1/2 (used in cycle 1 of Company's Updated Base Case) applied for cycles 1-9 for both the CBD+CCM and CCM arms (ERG's scenario)	Issues 9 and 10	[redacted]	[redacted]	[redacted]
Long-term discontinuation rates (cycles 10 onwards) increased from 5% to 10% per cycle for all health states other than convulsive-seizure free patients.	Issue 11	[redacted]	[redacted]	[redacted]
Time horizon (% patients still on CBD, % patients alive on CBD+CCM/CCM): • 15 years ([redacted]%, [redacted]% / [redacted]%) • 20 years ([redacted]%, [redacted]% / [redacted]%) • 30 years ([redacted]%, [redacted]% / [redacted]%) • 40 years ([redacted]%, [redacted]% / [redacted]%)	Issue 13	[redacted]	[redacted]	[redacted]
Utilities for health states taken from LGS analogues in Verdian *et al* 2018[1]. Utilities across seizure free day health sub states made uniform.	Issue 15	[redacted]	[redacted]	[redacted]
Concomitant AED doses reduced for patients on CBD (as per the Company's Revised Base Case March 2019; see Table 27 p82 of Document B)	Issue 18	[redacted]	[redacted]	[redacted]
Incident population only (age 2-5 years at model entry)	Existing scenario	[redacted]	[redacted]	[redacted]

Average dose of [redacted] mg/kg/day (as per the Company's Revised Base Case March 2019; see Table 40 p108 of Document B)	Existing scenario	[redacted]	[redacted]	[redacted]
Sensitivity analysis - QoL impact of non-convulsive seizure reductions. Additive disutility per person* required to increase incremental QALY gain in base case by: • 5% - [redacted] • 10% - [redacted] • 20% - [redacted]	Issue 7	[redacted]	[redacted]	[redacted]

The sensitivity analyses to address Issue 6 (last row) would require an additive QoL decrease of about 15% on UK norms to increase QALY gain by 20% in the base case. This disutility is within the ranges that might be expected from utility estimates for partial and focal seizures in other forms of epilepsy (see, for example, Kang H, et al. Epilepsy Res 2014;108(5):963-971 and Villanueva V, et al. Neurologia 2012:28(4):195-204).

Table 4. Parameter updates for the On-CLB model

Only the clinical inputs have been changed in the "On-CLB" model relative to the model for the overall patient population, issued on 27th June 2019 in response to the NICE technical report. In all cases, these clinical parameters have been derived from the subpopulation of patients who were on concomitant CLB at baseline, instead of the ITT population, in GWPCARE1, GWPCARE2 and GWPCARE5.

The following table lists out which clinical inputs have changed, and in which tabs, within the model.

Parameter	Tab
Age Groups: % patients, mean age and median weight within each age category.	COHORT DEFINITION
Frequency of Seizures at Baseline: Distribution of patients amongst health states based on convulsive seizure frequency at model entry	COHORT DEFINITION
Frequency of Number of Days Without Seizures at Baseline: Distribution of patients amongst health sub states (based on the number of convulsive seizure free days) in each health state at model entry	COHORT DEFINITION
Current Clinical Management: % patients on each concomitant AED	COHORT DEFINITION
Sub-tabs Cycle 1 and subsequent cycles: Transition probabilities per cycle and age group	# SEIZURES
Distribution of patients amongst health sub states (based on the number of convulsive seizure free days) in each health state across cycles	# DAYS
Cycle 1 and subsequent cycles: Discontinuation rates per cycle by health state *Stopping rules:* % patients in whom treatment is stopped at a given time point (due to lack of response)	DISCONTINUATION

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Technical engagement response form

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm on 27 June 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.

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We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Professor Sanjay Sisodiya**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Association of British Neurologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Positioning of cannabidiol in the Dravet syndrome treatment pathway	
Is the suggested position of CBD in the treatment pathway in line with how it is likely to be used in the NHS?	CBD is likely initially to be used in practice in patients who have not responded, or not tolerated, other standard treatments. It may end up being used before stiripentol in adults as it is currently a significant challenge to get stiripentol started in adults.
Issue 2: Generalisability of the trial results to the NHS	
Are the characteristics of participants in the GWPCARE trials likely to reflect the characteristics of people with DS seen in practice in the NHS?	I can comment only on adults. In adults, not all Dravet patients have at least 4 convulsive seizures per week. Patients in adulthood are likely to be on polytherapy. Adults were not included in the trials.
Issue 3: Transition to adulthood	
Would patients continue to be treated into adulthood?	Dravet Syndrome is a lifelong condition. Its cause does not change with age. If cannabidiol is effective, yes its use should continue into adulthood as long as required, noting that for some individuals with Dravet Syndrome, seizure frequency may fall and control improve in adulthood, but also that this is not universal. It must not be the case that (a) it would have to be stopped at some arbitrary age and (b) that it could not be initiated in adulthood, as there are people in whom the diagnosis is made in adulthood. The latter limitation in the marketing authorisation of stiripentol is unnecessary and wrong.
Would the efficacy of CBD be expected to be similar in adult patients to paediatric patients?	This cannot be predicted with the available data. However, the underlying cause of Dravet Syndrome does not change with age, and neither, to our knowledge, does expression of SCN1A

<table>
<tr><td></td><td>(the protein whose mutation causes Dravet in the majority of cases). So there is no a priori reason to think its efficacy would change.</td></tr>
<tr><td>How is the transition to adult services managed in the NHS?</td><td>This is a contentious area. Most children with an existing diagnosis of Dravet will be referred to specialist adult care, but it must be recognised that expertise and experience amongst adult neurologists is limited. In addition, the broad support umbrella available to children tends to largely disappear on transition – for example, multidisciplinary hospital clinics are rarely available in adulthood.</td></tr>
<tr><td colspan="2">Issue 4: Composition of current clinical management</td></tr>
<tr><td>Does current clinical management as described in the trial reflect clinical practice in the NHS?</td><td>This partly depends on the nation. In addition, no adults were included in the trial. So the trials may well not reflect adult NHS treatment practice.</td></tr>
<tr><td>If possible please estimate the percentage of people in the specified age groups eligible for treatment with CBD who would be treated with the anti-epileptic drugs specified in the adjacent table.</td><td>
<table>
<tr><th rowspan="3">Anti-epileptic drug</th><th colspan="4">Proportion of patients</th></tr>
<tr><th colspan="2"><12 years</th><th colspan="2">≥12 years</th></tr>
<tr><th>Company</th><th>Clinical expert</th><th>Company</th><th>Clinical expert</th></tr>
<tr><td>Clobazam</td><td>[redacted]</td><td></td><td>[redacted]</td><td>70</td></tr>
<tr><td>Valproate</td><td>[redacted]</td><td></td><td>[redacted]</td><td>80</td></tr>
<tr><td>Stiripentol</td><td>[redacted]</td><td></td><td>[redacted]</td><td>15 (growing)</td></tr>
<tr><td>Levetiracetam</td><td>[redacted]</td><td></td><td>[redacted]</td><td>30</td></tr>
<tr><td>Topiramate</td><td>[redacted]</td><td></td><td>[redacted]</td><td>30</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Issue 5: Subgroups of patients with additional clinical benefit</td></tr>
<tr><td>Are there any subgroups where the efficacy of CBD may be different from the overall trial population?</td><td>Most patients in the trials will have carried mutation in SCN1A. Having such a mutation is not a prerequisite to make a clinical diagnosis of Dravet Syndrome (though ~85% of patients do). We there have less information about how patients with Dravet due to other gene mutations will</td></tr>
</table>

	respond to CBD. In addition, there may be pharmacogenetic variation that influences CBD response that is independent of the disease-causing mutation.
Issue 6: Criteria for stopping treatment	
Would treatment stop if seizure frequency did not improve? How would this be defined, and would this be related to convulsive seizure frequency, total seizure frequency or both? At what time-point(s) would response to treatment be assessed?	I respond as an adult neurologist. For most (but not all) adults, many of whom are in residential care, it is only the convulsive seizures that are reliably documented, and are also arguably the most important to control and those that affect quality of life and premature mortality risk the most. Therefore for adults, in my opinion, outcome for seizures would be measured by convulsive seizure frequency. We are still learning about CBD use in adults, but it would seem reasonable to determine this outcome at a minimum of three months on a stable dose, then at six months, a year and with each subsequent follow-up, as we do with current treatments. In general, treatment would stop if CBD were ineffective, unless it proved better tolerated than existing treatments that might be withdrawn leaving CBD in their place.
Issue 7: Ignoring non-convulsive seizures in the model	
Is excluding non-convulsive seizures from the model appropriate?	See Issue 6. Yes for adults in my view. Some adults also have drop seizures, in which case these should be include in the evaluation.
How big an impact do non-convulsive seizures have on individuals' quality of life?	See Issue 6 and point immediately above.
Issue 8: Number of days without convulsive seizures	

Is CBD likely to increase the number of convulsive seizure-free days, in addition to reducing convulsive seizure frequency?	This will vary from patient to patient. In adulthood, convulsive seizures may occur mainly or solely during sleep. A minority of adult patients have convulsive seizures every day; most have them with seizure-free days in between, and when they occur, they may do so in clusters. CBD may therefore increase the number of convulsive seizure-free days, but this is currently difficult to predict in adults in the absence of extensive data.
Issue 9: Relative treatment effect	
Is it appropriate to only capture placebo response in current clinical management arm for 1 cycle only (the length of the trial), or should the relative efficacy of CBD compared with current clinical management remain constant over time?	I am not sure I understand this question. Trials are inevitably of limited duration. This is one limit to their generalisability. Both placebo and drug effects may vary over time, typically with regression to the mean.
Issue 10: Use of data from open label extension study	
Are the results from the open label extension study (GWPCARE 5), generalisable to the expected maintenance dose?	Not necessarily.
Issue 11: Extrapolating the effects of treatment beyond the follow up period in the clinical trials	
Should the model account for a potential decrease in treatment effect on convulsive seizure- and total seizure frequency over time? If so, how should this be estimated? For example, are seizures likely to return to baseline levels, and over what period – 2 years, 4 years or something else?	Ideally this should be possible to evaluate within the model, yes. Return to baseline levels, in my general experience, should be apparent within a year.
If the dose of other anti-epileptic drugs had been reduced (see issue 18) would the dose be increased	Yes, probably.

back to standard levels if the efficacy of CBD was reduced?	
Issue 12: Increasing the dose of cannabidiol	
Would a higher dose of CBD (eg the maximum recommended dose of 20 mg/kg/day) be considered for any of the following: • people who did not respond to a 10 mg/kg/day dose? • people whose response to a 10 mg/kg/day dose had lessened over time (see issue 11)? • people who responded to a 10 mg/kg/day dose to try and further reduce seizure frequency? If so, which patients would be considered for this dose and what proportion of responders/non-responders would this be?	It is not easy to be definitive about this. Even a syndrome as well-defined as Dravet still presents extensive inter-individual variation in many aspects. Keeping this in mind, I consider it unlikely that a higher dose would routinely be tried if 10mg/kg/day had had no effect, but there will be patients for whom there are no other options at all (there are patients in this position already). Yes, I would think it likely the dose would be increased if the effect appeared to lessen over time, and yes also if there had been a partial response, all within the limits of tolerability.
At which timepoint(s) would people be assessed to determine if an increased dose could be of benefit?	3, 6, 12 months after initiation and at each follow-up thereafter
Issue 13: Time horizon	
Are all differences in costs and effects attributable to CBD likely to be captured in a 15-year time horizon?	Not in my opinion. If effective, CBD is likely to be continued, which may increase actual costs if control of seizures improved with age in any case (which seems to occur for some, but not all, patients).
Issue 14: Relationship between mortality rates and number of seizures	

Is an association between number of convulsive seizures and increased epilepsy-related mortality rates plausible? If possible, please estimate the increased (value greater than 1) or reduced risk (value less than 1) compared with the >8 and ≤ 25 seizures category in the adjacent table:	

	Risk ratio			
	Seizure free	≤ 8 seizures	>8 to ≤ 25 seizures (**reference**)	> 25 seizures
Company	0.42	[redacted]	1.0	[redacted]
ERG	0.42	1.0	1.0	1.0
Clinical expert estimate			1.0	

What proportion of patients with Dravet syndrome treated with current clinical management would be expected to be alive: • 15 years after starting treatment, • 20 years after starting treatment, • 50 years after starting treatment.	Approximately 20% of children diagnosed with Dravet are deceased by the age of 20 years (this figure may change as earlier and better treatments are initiated). Beyond that, in my view it is not possible to answer this question currently. I have patients in their 5th, 6th, and 7th decades who have survived despite late diagnosis, the 'wrong' drugs, and frequent convulsive seizures and episodes of status epilepticus.
Issue 15: Health-related quality of life of people with Dravet syndrome	
Are the quality of life values presented by the company plausible?	I do not feel qualified to address this issue.
Are there any sources of evidence from the literature which could be used to validate the proposed quality of life values?	I do not feel qualified to address this issue.
Issue 16: Health-related quality of life of carers of people with Dravet syndrome	
Should carer quality of life be included in the model?	Yes it should, but this does not mean it has been done properly.
Are the quality of life values presented by the company for carer quality of life plausible?	I do not feel qualified to address this issue.

Are there any sources of evidence from the literature which could be used to validate the proposed quality of life values?	Lagae L, Irwin J, Gibson E, Battersby A. Caregiver impact and health service use in high and low severity Dravet syndrome: A multinational cohort study. Seizure. 2019 Feb;65:72-79 Not much other evidence especially for adult patients.
How many carers would a child with Dravet syndrome be expected to have? Would this be expected to remain the same after the person reaches adulthood?	I cannot comment on children. Adults living with parents may have additional care providers. Those in residential care typically are accompanied to clinic by two carers
Issue 17: Impact of adverse events on quality of life	
Would the adverse events (AEs) associated with CBD be expected to have a substantial negative impact on health-related quality of life?	We are still learning about this in adult patients. Loss of appetite may be an important issue, as some adults with Dravet may have lack of appetite (possibly aggravated by stiripentol or topiramate treatment) and some develop dysphagia (Catarino et al. Brain 2012).
Issue 18: Reduction in the concomitant use of anti-epileptic drugs	
Is using CBD likely to reduce concomitantly used anti-epileptic drugs? Is a 33% reduction plausible?	Too early to say in adulthood, but conceivable. I do not think it feasible to provide meaningful estimates given the lack of data available.
If dose reductions are likely please estimate the percentage of patients who would have a dose reduction and the size of this reduction in the adjacent table:	

Drug	% of patients	% dose reduction
Clobazam		
Stiripentol		

	Valproate			
	Levetiracetam			
	Topiramate			
Are there situations where increasing the dose of a concomitant anti-epileptic drug after starting CBD is appropriate?	I consider this unlikely, but not impossible.			

NICE National Institute for Health and Care Excellence

Technical engagement response form

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm on 27 June 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.

NICE National Institute for Health and Care Excellence

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Professor Helen Cross
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	NHS England
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Positioning of cannabidiol in the Dravet syndrome treatment pathway	
Is the suggested position of CBD in the treatment pathway in line with how it is likely to be used in the NHS?	It is likely that the position would be after three antiepileptic drugs, as it is likely stiripentol with sodium valproate and/or clobazam would be trialled first.
Issue 2: Generalisability of the trial results to the NHS	
Are the characteristics of participants in the GWPCARE trials likely to reflect the characteristics of people with DS seen in practice in the NHS?	They are – children with Dravet syndrome with continuing convulsive seizures
Issue 3: Transition to adulthood	
Would patients continue to be treated into adulthood?	They would – children with dravet syndrome live into adulthood, and are known to continue with seizures
Would the efficacy of CBD be expected to be similar in adult patients to paediatric patients?	There would be no suggestion there would be a different response in adults with Dravet syndrome to children~~adults~~
How is the transition to adult services managed in the NHS?	This is difficult and variable according to centre. Children should go through transition, and be followed in adulthood by a physician with experience in rare and complex epilepsies, preferably a neurologist
Issue 4: Composition of current clinical management	
Does current clinical management as described in the trial reflect clinical practice in the NHS?	The clinical management described reflects current clinical practice

If possible please estimate the percentage of people in the specified age groups eligible for treatment with CBD who would be treated with the anti-epileptic drugs specified in the adjacent table.

Anti-epileptic drug	Proportion of patients			
	<12 years		≥12 years	
	Company	Clinical expert	Company	Clinical expert
Clobazam	[redacted]	70%	[redacted]	40%
Valproate	[redacted]	90%	[redacted]	50%
Stiripentol	[redacted]	70%	[redacted]	40%
Levetiracetam	[redacted]	10%	[redacted]	20%
Topiramate	[redacted]	40%	[redacted]	30%

Issue 5: Subgroups of patients with additional clinical benefit	
Are there any subgroups where the efficacy of CBD may be different from the overall trial population?	Not that has become apparent
Issue 6: Criteria for stopping treatment	
Would treatment stop if seizure frequency did not improve? How would this be defined, and would this be related to convulsive seizure frequency, total seizure frequency or both? At what time-point(s) would response to treatment be assessed?	It is difficult to count nonconvulsive seizures. It would be suggested that seizure charts are maintained, and overall medication not continued if <30% reduction in countable seizures was seen over a three month period
Issue 7: Ignoring non-convulsive seizures in the model	
Is excluding non-convulsive seizures from the model appropriate?	Ideally they should not be ignored, but difficult to count – more reliable to use 'countable' seizures – this could include some forms of nonconvulsive seizures
How big an impact do non-convulsive seizures have on individuals' quality of life?	They have a high degree of impact, particularly if the individual is prone to prolonged periods of nonconvulsive seizure

Issue 8: Number of days without convulsive seizures	
Is CBD likely to increase the number of convulsive seizure-free days, in addition to reducing convulsive seizure frequency?	This is possible
Issue 9: Relative treatment effect	
Is it appropriate to only capture placebo response in current clinical management arm for 1 cycle only (the length of the trial), or should the relative efficacy of CBD compared with current clinical management remain constant over time?	Appropriate
Issue 10: Use of data from open label extension study	
Are the results from the open label extension study (GWPCARE 5), generalisable to the expected maintenance dose?	Yes
Issue 11: Extrapolating the effects of treatment beyond the follow up period in the clinical trials	
Should the model account for a potential decrease in treatment effect on convulsive seizure- and total seizure frequency over time? If so, how should this be estimated? For example, are seizures likely to return to baseline levels, and over what period – 2 years, 4 years or something else?	There is no evidence of a decreased effect over time
If the dose of other anti-epileptic drugs had been reduced (see issue 18) would the dose be increased back to standard levels if the efficacy of CBD was reduced?	Possibly, but difficult to know whether reduced efficacy of CBD or synergistic effect? Dependent on concomitant medication eg valproate or clobazam or stiripentol

Issue 12: Increasing the dose of cannabidiol	
Would a higher dose of CBD (eg the maximum recommended dose of 20 mg/kg/day) be considered for any of the following: • people who did not respond to a 10 mg/kg/day dose? • people whose response to a 10 mg/kg/day dose had lessened over time (see issue 11)? • people who responded to a 10 mg/kg/day dose to try and further reduce seizure frequency? If so, which patients would be considered for this dose and what proportion of responders/non-responders would this be?	Unlikely Unlikely Yes I would suggest about 20% of patients may move to a higher dose – those who had responded in part but not fully to 10mg/kg/day
At which timepoint(s) would people be assessed to determine if an increased dose could be of benefit?	At 3 months of treatment
Issue 13: Time horizon	
Are all differences in costs and effects attributable to CBD likely to be captured in a 15-year time horizon?	Yes
Issue 14: Relationship between mortality rates and number of seizures	

Is an association between number of convulsive seizures and increased epilepsy-related mortality rates plausible? If possible, please estimate the increased (value greater than 1) or reduced risk

	Risk ratio			
	Seizure free	≤ 8 seizures	>8 to ≤ 25 seizures (**reference**)	> 25 seizures
Company	0.42	[redacted]	1.0	[redacted]

<table>
<tr><td>(value less than 1) compared with the >8 and ≤ 25 seizures category in the adjacent table:</td><td><table>
<tr><td>ERG</td><td>0.42</td><td>1.0</td><td>1.0</td><td>1.0</td></tr>
<tr><td>Clinical expert estimate</td><td></td><td>0.75</td><td>1.0</td><td>1.25</td></tr>
</table></td></tr>
<tr><td>What proportion of patients with Dravet syndrome treated with current clinical management would be expected to be alive:
• 15 years after starting treatment,
• 20 years after starting treatment,
• 50 years after starting treatment.</td><td>80%

70%

50%</td></tr>
<tr><td colspan="2">Issue 15: Health-related quality of life of people with Dravet syndrome</td></tr>
<tr><td>Are the quality of life values presented by the company plausible?</td><td>The company have utilised standardised measures of quality of life – it is generally accepted that this population remains difficult with regard to assessing QoL</td></tr>
<tr><td>Are there any sources of evidence from the literature which could be used to validate the proposed quality of life values?</td><td>Comorbidities and predictors of health-related quality of life in Dravet syndrome Brunklaus et al Epilepsia 2011; 52: 1476-1482</td></tr>
</table>

	Development and content validation of a preliminary core set of patient- and caregiver-relevant outcomes for inclusion in a potential composite endpoint for Dravet Syndrome Nabbout et al Epilepsy & Behavior 78 (2018) 232–242
Issue 16: Health-related quality of life of carers of people with Dravet syndrome	
Should carer quality of life be included in the model?	Yes
Are the quality of life values presented by the company for carer quality of life plausible?	The trial utilised care giver impression of change, which does not really give quality of life
Are there any sources of evidence from the literature which could be used to validate the proposed quality of life values?	Development and content validation of a preliminary core set of patient- and caregiver-relevant outcomes for inclusion in a potential composite endpoint for Dravet Syndrome Nabbout et al Epilepsy & Behavior 78 (2018) 232–242
How many carers would a child with Dravet syndrome be expected to have? Would this be expected to remain the same after the person reaches adulthood?	It is likely a child with Dravet would have at least 2, possibly 4 carers Parents x1-2 Grandparents –x1-2 Respite – additional support Most children would have the same carers in adulthood, although some may be in a 52 week placement

<table>
<tr><td></td><td></td></tr>
<tr><td colspan="2">Issue 17: Impact of adverse events on quality of life</td></tr>
<tr><td>Would the adverse events (AEs) associated with CBD be expected to have a substantial negative impact on health-related quality of life?</td><td>Unlikely</td></tr>
<tr><td colspan="2">Issue 18: Reduction in the concomitant use of anti-epileptic drugs</td></tr>
<tr><td>Is using CBD likely to reduce concomitantly used anti-epileptic drugs? Is a 33% reduction plausible?</td><td>Yes</td></tr>
<tr><td>If dose reductions are likely please estimate the percentage of patients who would have a dose reduction and the size of this reduction in the adjacent table:</td><td>
<table>
<tr><th>Drug</th><th>% of patients</th><th>% dose reduction</th></tr>
<tr><td>Clobazam</td><td>50%</td><td>30%</td></tr>
<tr><td>Stiripentol</td><td>50%</td><td>wean</td></tr>
<tr><td>Valproate</td><td>20%</td><td>30%</td></tr>
<tr><td>Levetiracetam</td><td>40%</td><td>wean</td></tr>
<tr><td>Topiramate</td><td>50%</td><td>wean</td></tr>
</table>
</td></tr>
<tr><td>Are there situations where increasing the dose of a concomitant anti-epileptic drug after starting CBD is appropriate?</td><td>Rarely</td></tr>
</table>

Question from NICE technical team	Company response	ERG comments
Issue 1: Positioning of cannabidiol in the Dravet syndrome treatment pathway		
Is the suggested position of CBD in the treatment pathway in line with how it is likely to be used in the NHS?	Based on discussions with UK specialist clinicians, the company is confident that the proposed positioning of CBD is in line with anticipated practice in the NHS. The company notes that the NICE technical team also supports this, stating in its Technical Report that the clinical trial population generally reflects the company's proposed positioning of CBD in the treatment pathway.	The ERG agrees that the trial populations are likely to be representative of the proposed positioning of CBD in the treatment pathway. As stated in the ERG report: *"The treatment pathway proposed by the company placed CBD as a third-line treatment (i.e. for patients who have inadequate seizure control with first-line and at least one adjunctive anti-epileptic drug (AED)). However, the baseline characteristics for GWPCARE1 and GWPCARE2 indicated that approximately 16% of participants included in these studies had previously tried and discontinued fewer than two prior AED. It should be noted that these patients may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled"*
Issue 2: **Generalisability of the trial results to the NHS**		
Are the characteristics of participants in the GWPCARE trials likely to reflect the characteristics of people with DS seen in practice in the NHS?	The company notes from the NHS England statement in the NICE Technical Papers that "The view of NHS England is that the clinical trial data is generalisable to the UK population". The clinical trials for CBD included UK patients. The diagnostic criteria for DS in the trials were based on international guidelines, which are similar to the NICE guidelines for patients with DS. UK specialist clinicians agree that the participants in the GWPCARE trials reflect the characteristics of people with DS seen	The ERG considers that this issue remains a matter for discussion by the committee, as the company's response does not provide any additional evidence. The ERG notes that, as stated in the ERG report, the total number of UK trial participants was [redacted]. The ERG also notes the response to this question from an adult neurologist representing the Association of British Neurologists: *"I can comment only on adults. In adults, not all Dravet patients have*

	in practice in the NHS (based on e.g. age, gender, seizure types, concomitant anti-epileptic drugs).	*at least 4 convulsive seizures per week. Patients in adulthood are likely to be on polytherapy. Adults were not included in the trials."*
Issue 3: **Transition to adulthood**		
Would patients continue to be treated into adulthood?	The company notes the statement from the Association of British Neurologists (ABN) in its Professional Organisation Submission: "Adults and children are both suitable candidates, neither should be excluded on age grounds alone". CBD will be prescribed by specialist clinicians. The company assumes that these experienced specialist clinicians will decide which patients to treat based on the Summary of Product Characteristics (SmPC), clinical guidelines and the profile of individual patients. The company also notes the following relevant statement from the Patient Organisation Submission (for LGS): "They (the parents) also noted that their son had previously been on the ketogenic diet, funded by the NHS, when he was receiving paediatric care and emphasised their disappointment that similar treatments are not available for adults with the condition on the NHS: 'It is hugely frustrating when it's available for children and not adults'."	The ERG considers that this issue remains a matter for discussion by the committee. The ERG also notes the response to this question from an adult neurologist representing the Association of British Neurologists: *"Dravet Syndrome is a lifelong condition. Its cause does not change with age. If cannabidiol is effective, yes its use should continue into adulthood as long as required, noting that for some individuals with Dravet Syndrome, seizure frequency may fall and control improve in adulthood, but also that this is not universal. It must not be the case that (a) it would have to be stopped at some arbitrary age and (b) that it could not be initiated in adulthood, as there are people in whom the diagnosis is made in adulthood. The latter limitation in the marketing authorisation of stiripentol is unnecessary and wrong."*
Would the efficacy of CBD be expected to be similar in adult patients to paediatric patients?	There is no clinical reason to expect that the efficacy of CBD would be different in adult patients compared with paediatric patients. As noted above, the Association of British Neurologists (ABN) in its Professional Organisation Submission stated that: "Adults and children are both suitable candidates, neither should be excluded on age grounds alone".	The ERG considers that, as do data have been presented for this population, the efficacy of CBD in adults with DS remains unknown.
How is the transition to adult services managed in the NHS?		The ERG considers that this is a question for discussion by clinical experts.

<table>
<tr><td colspan="2">Issue 4: Composition of current clinical management</td><td></td></tr>
<tr><td>Does current clinical management as described in the trial reflect clinical practice in the NHS?</td><td>The company notes that the main concern of the NICE technical team for this issue was that, in the company's base case model, the percentage of people with DS on each of the concurrently used anti-epileptic drugs (AEDs) was not based on the trial data (instead it was based on UK market research conducted by the company).
The company also notes that "the technical team considers the trial data to be the most appropriate to use in the model base case analysis".
For this reason, the company has updated its base case so that the baseline characteristics in the trials have been used to define the mix of AEDs in the CCM basket.
Please see the Company's Updated Base Case in the separate 'Response Addendum' document.</td><td>The ERG notes that the estimates provided in response to this question by an adult neurologist representing the Association of British Neurologists:
<table><tr><th rowspan="3">Anti-epileptic drug</th><th colspan="4">Proportion of patients</th></tr><tr><th colspan="2"><12 years</th><th colspan="2">≥12 years</th></tr><tr><th>Company</th><th>Clinical expert</th><th>Company</th><th>Clinical expert</th></tr><tr><td>Clobazam</td><td>[redacted]</td><td></td><td>[redacted]</td><td>70</td></tr><tr><td>Valproate</td><td>[redacted]</td><td></td><td>[redacted]</td><td>80</td></tr><tr><td>Stiripentol</td><td>[redacted]</td><td></td><td>[redacted]</td><td>15 (growing)</td></tr><tr><td>Levetiracetam</td><td>[redacted]</td><td></td><td>[redacted]</td><td>30</td></tr><tr><td>Topiramate</td><td>[redacted]</td><td></td><td>[redacted]</td><td>30</td></tr></table>differ markedly from the rates of concurrent AED use reported for the trials (see Table 4.3 of the ERG report)</td></tr>
<tr><td>If possible please estimate the percentage of people in the specified age groups eligible for treatment with CBD who would be treated with the anti-epileptic drugs specified in the adjacent table.</td><td><table><tr><th rowspan="3">Anti-epileptic drug</th><th colspan="4">Proportion of patients</th></tr><tr><th colspan="2"><12 years</th><th colspan="2">≥12 years</th></tr><tr><th>Company</th><th>Clinical expert</th><th>Company</th><th>Clinical expert</th></tr><tr><td>Clobazam</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr><tr><td>Valproate</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr><tr><td>Stiripentol</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr><tr><td>Levetiracetam</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr><tr><td>Topiramate</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr></table></td><td></td></tr>
<tr><td colspan="2">Issue 5: Subgroups of patients with additional clinical benefit</td><td></td></tr>
</table>

Are there any subgroups where the efficacy of CBD may be different from the overall trial population?	The company is currently investigating scenarios for clinical and cost effectiveness outcomes in subpopulations on certain AEDs. It has not been possible to complete these analyses in time for the submission deadline for responses to the technical report. The company will aim to provide these scenarios for the Appraisal Committee Meeting.	The ERG considers that this question remains open.
Issue 6: Criteria for stopping treatment		
Would treatment stop if seizure frequency did not improve? How would this be defined, and would this be related to convulsive seizure frequency, total seizure frequency or both? At what time-point(s) would response to treatment be assessed?	In most cases, CBD treatment would be expected to stop if there was no improvement in seizure frequency. In some cases, there may be benefits from CBD that are related to e.g. cognition/behaviour rather than just purely related to seizure reduction. The company assumes that, in those cases, the decision to stop treatment would be based on a discussion between the patient/carer and specialist clinician, especially given the lack of alternative treatment options in this highly refractory population. The company notes that there is now a draft Clinical Commissioning Policy Statement from NHS England, which includes suggested continuation/stopping rules. In response to feedback from the NICE technical team, the Company's Updated Base Case now incorporates the NHSE recommendations for stopping CBD in clinical practice (see Table 3 in the separate 'Response Addendum' document). Specifically, the company has implemented a one-off discontinuation at 6 months in each convulsive-seizure health state. This is equal to the proportion of non-withdrawn patients in each health state at 6 months in the GWPCARE5 study who had a <30% reduction from baseline in GWPCARE1/2. The 6 month timepoint represents the earliest time at which a patient is likely to	It is unclear to the ERG: 1. whether the proposed 6 months stopping rule is clinically plausible; 2. what discontinuation probabilities were used for the proposed 6 months stopping rule and how exactly was this implemented; 3. whether the assumptions for longer-term discontinuation (from cycle 10 onwards), adjusted to [redacted]% per cycle in all 'seizure' health states, are plausible and consistent with the US Early Access Program for CBD (referenced by the company). Moreover, it is unclear why this assumption is more plausible than using the "Subsequent cycle discontinuation" based on GWP-CARE 5 for long-term discontinuation (as preferred by the ERG, see section 5.2.6 of the ERG report).

	be seen in clinical practice (visits are typically every 3-6 months) after the timepoint at which de-escalation of dose for non-responders to >10 mg/kg/day is recommended in the draft Clinical Commissioning Policy Statement from NHSE. Existing discontinuation rate assumptions, as observed in the GWPCARE5 study, continue to be applied for cycles 2-9. The ERG's preferred assumption has been adopted: see Table 3 in the 'Response Addendum' document. The longer-term discontinuation rates (from cycle 10 onwards) have been adjusted to [redacted]% per cycle in all 'seizure' health states, which is in line with those observed in the US Early Access Program for CBD and reflects long-term non-persistence in a real-world setting. For the convulsive-seizure free health state, long-term discontinuation rates remain at [redacted]%.	
Issue 7: Ignoring non-convulsive seizures in the model		
Is excluding non-convulsive seizures from the model appropriate?	Convulsive seizures are the seizure types about which parents/caregivers of patients with DS are most concerned, given the risk of injury and SUDEP associated with convulsive seizures. Reduction in convulsive seizures was the primary endpoint in the CBD DS Phase 3 trials. Non-convulsive seizures include myoclonic, partial and absence seizures. These seizures are often more difficult to count. For example, an absence seizure may cause the person to blank out or stare into space for a few seconds, whilst a partial seizure may involve a person's leg or arm twitching briefly. It should be noted that data from the CBD Phase 3 trials shows that the average number of total seizures is lower in health states with fewer convulsive seizures. Therefore, it is the change in QoL in moving from higher to lower convulsive-seizure health states	The impact of excluding non-convulsive seizures is unclear to the ERG. The main ERG concerns relate to input parameters used for the convulsive-seizure free health state that may reflect the health state where patients are also non convulsive-seizure (which was not the case). Particularly input parameters related to mortality (both SUDEP and non-SUDEP) and utility values (see also ERG report section 5.2). It is unclear how the sensitivity analysis referred to and described in Table 4 was conducted: the company appears to have estimated the size of the disutility associated with the presence of non-convulsive seizures in the >25 convulsive seizures health state only that would be required to reduce the QALYs. However, that does not show the additional effect on utility of non-convulsive seizures

	that is important, and there can only be “hidden upside” in terms of QALY gain which is not captured in the model. The magnitude of this hidden upside is explored in the sensitivity analysis presented by the company. Please see the sensitivity analysis in Table 4 of the separate ‘Response Addendum’ document.	given that there is no estimate of the number of convulsive seizures for each health state (including convulsive -seizure free) nor is there any disutility associated with a convulsive seizure.
How big an impact do non-convulsive seizures have on individuals’ quality of life?	Convulsive seizures are assessed as the primary endpoint in trials for DS because they are clinically identifiable, easy to count, and drive the morbidity. Convulsive seizures were chosen as the basis for the model structure for these reasons, and because it is appropriate that a cost utility study is based on the primary endpoint of the trials. However, as mentioned in the NICE technical report, CBD also showed a treatment effect on total seizures and non-convulsive seizures in the trials. As described in the company’s response to question B1a of the ERG’s Clarification Questions, the average number of non-convulsive seizures strongly tracks convulsive-seizure health states. As such, there is unrealised patient benefit associated with non-convulsive seizures that is not captured in the model. Providing a deterministic quantification of this benefit is challenging. Non-convulsive seizures are not a homogenous category: both the treatment effect on, and QoL contribution of, each type is distinct. Incorporating their contribution to the model would require a very complex structure with multiple health sub states, and a utility elicitation study that would be unfeasible in such a rare condition due to the number of health state descriptions needed. To account for the uncertainty in this unrealised benefit, the company has performed a sensitivity analysis in which the	See response to previous issue.

	additional disutility from these seizures required to increase the QALY gain in the updated base case by 5%-20% is estimated (see Table 4 in the separate 'Response Addendum' document). The disutility is assumed to be additive and assigned only in the highest convulsive-seizure health state (i.e. >25 convulsive seizures per month). It is further assumed to apply uniformly across the patient and caregivers. As can be seen in Table 4 of the 'Response Addendum' document, even a 20% increase in QALY gain would require an average disutility of only [redacted], or about a 15% QoL reduction on UK norms. This is within the ranges that might be expected from utility estimates for partial and focal seizures in other forms of epilepsy (see, for example, Kang H, et al. *Epilepsy Res* 2014;108(5):963-971 and Villanueva V, et al. *Neurologia* 2012:28(4):195-204).	
Issue 8: Number of days without convulsive seizures		
Is CBD likely to increase the number of convulsive seizure-free days, in addition to reducing convulsive seizure frequency?	CBD showed a statistically and clinically significant treatment effect on the change in seizure frequency from baseline (see Document B, Section B.2.6). CBD also showed a similar effect on the number of seizure-free days per month (see Table 1 in Appendix 1 below). These outcomes were chosen to delineate health states and sub states respectively in the model because they each contribute independently to QoL. This principle was supported by the outcomes of the vignette utility elicitation study. In the NICE technical report, it is noted that the ERG's preferred assumption was to make transition probabilities flat between treatment arms because "it is unclear whether in the model patients maintain any benefit in health state sub-category after	Based on this response it is still unclear to the ERG what exactly is assumed in the economic model once CBD patients discontinue. Does the "number of seizure-free days" for these patients remain the same after CBD discontinuation or does the "number of seizure-free days" change to be identical to those receiving CCM only (see "# DAYS" worksheet in the economic model). If the "number of seizure-free days" remains the same after CBD discontinuation, then the ERG believes patients maintain a benefit after stopping CBD and hence would prefer the "number of seizure-free days" to be treatment independent.

	stopping CBD, which would bias the results in favour of CBD because patients in the current clinical management arm return to baseline seizure frequency". The model does not treat discontinuing CBD patients differently from CCM patients in this regard. CCM patients are reassigned to the baseline distribution of health states and sub states from cycle 3 onwards (in cycles 1 and 2 they are assigned distributions derived from the placebo arms in the trials - see the company's response to Issue 9 below). Discontinuing CBD patients are assigned to the same distributions at the same timepoints. Therefore, there is no bias in the model structure on the parameter of convulsive-seizure free days, and this assumption has been retained in the Company's Updated Base Case.	
Issue 9: Relative treatment effect		
Is it appropriate to only capture placebo response in current clinical management arm for 1 cycle only (the length of the trial), or should the relative efficacy of CBD compared with current clinical management remain constant over time?	The ERG acknowledged in its report that the placebo effect in the GWPCARE trials for CBD was high. The placebo effect seen in clinical trials for both DS and LGS is very variable. In the CBD studies, it was up to 27%. A recent study in DS showed a placebo effect of <2% In LGS trials, it has varied from a 5% worsening to 12% improvement (Ostendorf AP, *et al*. *Neuropsychiatr Dis Treat*. 2017;13:1131-40). The absolute impact of CBD in DS on convulsive seizures from baseline is very consistent across studies at 40-50%, which is also seen on drop seizures in LGS. This magnitude of effect was observed in the open-label GWPCARE5 study for patients entering from the placebo arms of GWPCARE1 and 2 and re-baselined at study entry (see Tables 2 and 3 in Appendix 1 below), as well as in a real world setting in the	The ERG disagrees that maintaining the placebo effect for CCM is unduly penalising CBD. The placebo effect is likely present in both trial arms. Indeed, it is fundamental to the motivation of the RCT that only the treatment outcome difference, sometimes referred to as 'treatment effect', can be assumed to be unbiased. Indeed, the only way of avoiding any bias due to the so-called 'placebo effect' is to estimate the treatment difference from an RCT. This is because the 'placebo effect' is the effect on the absolute outcome that might not be due to the treatment itself of any treatment, including both CCM and CBD. Indeed, if patients appear to do surprisingly well in the CCM arm then, although we cannot know its precise nature, there appears to be a mechanism that confers a positive effect on outcome aside from that due to CCM. What follows is that this mechanism is likely to be having an effect also on those patients treated with CBD and therefore it can only be cancelled out by

	US Early Access Program (Laux LC, *et al*. Epilepsy Research 2019;154:13-20 - see Figures 1 and 2 in Appendix 1 below). These observations suggest that the absolute effect on seizure frequency as observed in the clinical trials would be replicated in practice. For these reasons, it is important that CBD is not unduly penalised by virtue of the unusually high placebo effect seen in its trials. This would occur if the relative treatment effect were maintained throughout the time horizon (as preferred by the ERG). The company notes that the NICE technical team considered that "assuming the placebo effect is maintained in subsequent cycles may overestimate the treatment effect of current clinical management". The Company's Updated Base Case has applied outcomes from GWPCARE1 and GWPCARE2 to 6 months (2 cycles) for both the CBD and CCM arms in the model (see Table 3 in the separate 'Response Addendum' document). After this point, CCM patients return to baseline, and outcomes from the GWPCARE5 study are applied to CBD patients. To avoid bias, discontinuing CBD patients are treated identically to CCM patients throughout the model. In a scenario analysis (see Table 4 in the 'Response Addendum' document), the company has extended the Phase 3 outcomes for both arms to cycle 8 in the model (up to 2 years). The ICER remains very stable.	estimating the difference between CCM and CBD. Hence, as reported in section 5.2.2 of the ERG report, only removing the placebo effect for CCM while not removing it for CBD would likely overestimate the CBD treatment benefit. The scenario analysis referred to by the company, without further explanation, is not very helpful as it is unclear to the ERG why the incremental QALYs would substantially increase in this scenario.
Issue 10: Use of data from open label extension study		
Are the results from the open label extension study (GWPCARE 5), generalisable to the	No dose response was seen in the GWPCARE2 trial in DS or in the GWPCARE3 trial in LGS.	The ERG notes that the company's response does not include any substantive additional data to support their assertion that there is no dose response for CBD in DS. The CS did not include any

expected maintenance dose?	This lack of dose response is supported by a *post hoc* sub-group analysis of the GWPCARE5 data. There was no statistically significant difference on the primary and secondary endpoints between patients who were on a low dose (≥[redacted] to <[redacted] mg/kg/day) and those who were on a high dose (≥[redacted] to <[redacted] mg/kg/day), and the ITT population. As such, the Company believes that GWPCARE5 represents a good surrogate for outcomes on the expected maintenance dose of 10 mg/kg/day. The company believes that it is preferable to use long-term data from a clinical trial (i.e. the GWPCARE5 data) rather than extrapolating the 3-month outcomes from the Phase 3 trials (as suggested by the ERG). The Company's Updated Base Case extends the Phase 3 GWPCARE1/2 data to 2 cycles (6 months) in both the CBD+CCM and CCM arms, and then applies the GWPCARE5 data up to 2 years for CBD patients (with CCM and discontinued CBD patients returning to baseline). A scenario analysis (see Table 4 in the 'Response Addendum' document) extends the Phase 3 data in both arms to 2 years. The ICER is very stable.	comparison between the 10 mg/kg/day and 20 mg/kg/day arms of GWPCARE2, and the company's response to clarification on this subject stated: *"No formal pre-specified test for significance between the CBD groups was included in the SAPs."* "No results for any between arm comparison have subsequently been provided. The "*post hoc* sub-group analysis of the GWPCARE5 data" mentioned in the company's response was reported only in terms of tests for statistically significant difference (no outcome results provided for the subgroups. In addition, the <16 mg/kg/day and the ≥[redacted] to <[redacted] mg/kg/day subgroups included only [redacted] and [redacted] patients respectively, i.e. the majority of patients in GWPCARE5 ([redacted]) were on doses >[redacted] mg/kg day and were not considered in this analysis. The ERG therefore considers that the presence or absence of a dose response remains uncertain. See also ERG comments in ERG report sections 4.2.5, 4.2.9 and 5.2.6.
Issue 11: Extrapolating the effects of treatment beyond the follow up period in the clinical trials		
Should the model account for a potential decrease in treatment effect on convulsive seizure- and total seizure frequency over time? If so, how should this be estimated? For example,	As noted by the NICE technical team, the treatment effect of CBD is unlikely to stop abruptly at any given time point. The GWPCARE5 study shows a very consistent effect for CBD from baseline, both in the as-observed and LOCF analyses, over more than 2 years (Thiele E, et al. *Epilepsia* 2019;60(3):419-428, and Devinsky O, et al. *Epilepsia* 2019;60(2):294-302).	The ERG believes that waning of treatment effect and treatment discontinuation are two separate (though potentially related) issues. The ERG would consider waning of treatment to be a reduction in relative treatment effect over time for those on CBD treatment. After 3 months there is no comparative effectiveness evidence. This issue has been discussed in depth in the ERG report. See ERG report for more details. Please note that the "no treatment effect

are seizures likely to return to baseline levels, and over what period – 2 years, 4 years or something else?	Any assumption on cut-off or waning of transition probabilities within the model would be arbitrary. The company considers that it is more appropriate to account for any evolution in the drug's efficacy over time through discontinuation assumptions. This reflects clinical practice, and is evidence-led. Any attenuations in treatment effect are already accounted for in cycles 2-9 of the model through the application of the discontinuation rates as observed in the GWPCARE5 study, as well as stopping criteria (see Issue 5 above). Long-term discontinuations are captured by applying 3-month discontinuation rates as observed in the US Early Access Program ([redacted]%), which is the best long-term real-world data set currently available (Laux LC, et al. *Epilepsy Research* 2019;154:13-20). In the Company's Updated Base Case, [redacted]% of patients are on treatment by 3 years, and [redacted]% by 5 years. Increasing discontinuation rate assumptions in the model, which would account for any potential underestimation of treatment waning, reduces the ICER (see scenarios in Table 4 the separate 'Response Addendum' document).	after 27 months" scenario (used to inform the ICER range) assumes no treatment waning (for patients receiving CBD) in the period between month 3 and 27 (for which no comparative effectiveness evidence is available).
If the dose of other anti-epileptic drugs had been reduced (see issue 18) would the dose be increased back to standard levels if the efficacy of CBD was reduced?	To reduce uncertainty about how the dose of concomitant AEDs would vary when taking CBD, the company has removed the assumption that there would be a dose reduction of certain concomitant AEDs with CBD from its Updated Base Case (see response to Issue 18 below).	No AED dose reduction is consistent with the ERG preferred assumptions (see ERG report).
Issue 12: Increasing the dose of cannabidiol		
Would a higher dose of CBD (eg the maximum	CBD will be prescribed by specialist clinicians. The company assumes that these specialist clinicians will decide, in conjunction	The ERG notes that the company's response does not address the question of whether an increase in CBD dose may be considered in

recommended dose of 20 mg/kg/day) be considered for any of the following: • people who did not respond to a 10 mg/kg/day dose? • people whose response to a 10 mg/kg/day dose had lessened over time (see issue 11)? • people who responded to a 10 mg/kg/day dose to try and further reduce seizure frequency? If so, which patients would be considered for this dose and what proportion of responders/non-responders would this be?	with the patient/carer, when/if to escalate the dose based on the Summary of Product Characteristics (SmPC), clinical guidelines and the risk profile of individual patients. Clinicians who treat epilepsy are experienced in doing this for AEDs. The SmPC defines 10mg/kg/day as the preferred maintenance dose for CBD. The company anticipates that the majority of patients will be on this dose in clinical practice. With regard to the groups described here in Issue 11: • People who did not respond to a 10 mg/kg/day dose of CBD should not be considered for a higher dose. (There was no dose response in the CBD clinical trials). • People who are not responding to a 10 mg/kg/day dose of CBD should not be considered for a higher dose. • People who responded to a 10 mg/kg/day dose have the option of being considered for a higher dose of CBD in order to try to further reduce seizure frequency or possibly achieve seizure freedom. The company notes that the draft Clinical Commissioning Policy Statement from NHS England supports this principle, i.e. it recommends escalation only where there is a response to a 10 mg/kg/day dose. The company acknowledges the NICE technical team's comment that scenario analyses relating to dose escalation should consider both the costs and benefits of dose escalation. The company has implemented scenario analyses in a population that includes some patients who receive a dose above 10 mg/kg/day, including both the costs and benefits. Please see the scenario analyses in Table 4 of the separate 'Response Addendum' document	people whose response to 10 mg/kg/day had lessened over time. This is an issue for discussion by clinical experts (note the Association of British Neurologists response).

<table>
<tr><td>At which timepoint(s) would people be assessed to determine if an increased dose could be of benefit?</td><td>The company notes that the draft Clinical Commissioning Policy Statement from NHS England states that the CBD dose should be reviewed at a minimum of 3 months or maximum of 6 months after initiation.</td><td>The ERG considers that this is a question for discussion by clinical experts.</td></tr>
<tr><td colspan="2">Issue 13: Time horizon</td><td></td></tr>
<tr><td>Are all differences in costs and effects attributable to CBD likely to be captured in a 15-year time horizon?</td><td>In line with the recommendations in the NICE technical report, the Company’s Updated Base Case extends the time horizon to 50 years.
The company considers that a lifetime horizon in this therapy area should be based on the time required for most patients to discontinue therapy.
In the Company’s Updated Base Case, only [redacted]% of patients are still on therapy at 50 years. As such, this is considered to be a reasonable lifetime horizon. Scenario analyses are also provided on time horizons between 15 and 40 years.</td><td>The ERG prefers a lifetime time horizon (see also ERG report).</td></tr>
<tr><td colspan="2">Issue 14: Relationship between mortality rates and number of seizures</td><td></td></tr>
<tr><td>Is an association between number of convulsive seizures and increased epilepsy-related mortality rates plausible? If possible, please estimate the increased (value greater than 1) or reduced risk (value less than 1) compared with the >8 and ≤ 25 seizures category in the adjacent table:</td><td>In the original economic model submitted to NICE, the company attempted to consider the impact on mortality of improved seizure control, as this is cited as an important area of unmet need. However, the company has accepted the ERG’s assumption that mortality should be the same in all health states except in seizure-free patients and has updated the company base case to reflect this.
<table>
<tr><td></td><td colspan="4">Risk ratio</td></tr>
<tr><td></td><td>Seizure free</td><td>≤ 8 seizures</td><td>>8 to ≤ 25 seizures (reference)</td><td>> 25 seizures</td></tr>
</table></td><td>The reported risk ratios reflect the risk ratio for being seizure-free: presumably this is not restricted to convulsive-seizures only. Hence, it is unclear to what degree this evidence supports the association between number of convulsive seizures and increased epilepsy-related mortality.</td></tr>
</table>

		Company	0.42	[redacted]	1.0	[redacted]	
		ERG	0.42	1.0	1.0	1.0	
		Clinical expert estimate			1.0		
What proportion of patients with Dravet syndrome treated with current clinical management would be expected to be alive: • 15 years after starting treatment, • 20 years after starting treatment, • 50 years after starting treatment.							
Issue 15: Health-related quality of life of people with Dravet syndrome							
Are the quality of life values presented by the company plausible?	The company considers the quality of life values presented to be plausible. See response below.						See ERG report. The ERG's main reservations relate to the methodology used to elicit utility values as well as the resulting utility estimates.
Are there any sources of evidence from the literature which could be used to validate the proposed quality of life values?	The systematic literature review for both DS and LGS performed by the company identified a single study that provided utility analogues broken out by health state (Verdian *et al*, 2008). This study was done in a UK setting for LGS patients. All other identified cost-utility studies in both DS and LGS used these analogues.						No comments

	The health states investigated in Verdian *et al* were not close surrogates for the CBD model, as they assessed HRQoL associated with relative changes in seizure frequency over time and not absolute seizure frequency. In the company's model, using absolute seizure frequency was a deliberate choice, since QoL is more likely to be determined by absolute and not relative seizure status. In addition, the literature does not report on the contribution of seizure-free days to utilities, which is another key parameter affecting QoL. For these reasons, the company conducted a bespoke vignette study to elicit utility estimates for its model. Utility scores for patients with a high response in Verdian (≥75% reduction) align to the convulsive seizure-free health state in the CBD model. Furthermore, average utility scores for DS populations reported in the large DISCUSS survey showed similar values to the company's health states, both at a European level (Lagae L, et al. Developmental Medicine & Child Neurology 2018;60:63-72) and in the UK (Pagano K, et al. Developmental Medicine and Child Neurology 2019;61: 62). A scenario analysis using the utility estimates from Verdian *et al* applied as closely as possible to the health states in the company's model shows a similar ICER to the Company's Updated Base Case. (See the scenario in Table 4 the separate 'Response Addendum' document).	
Issue 16: Health-related quality of life of carers of people with Dravet syndrome		
Should carer quality of life be included in the model?	The company notes that the technical team concluded that carer quality of life should be included in the model. From the Technical	As described in the ERG report, the inclusion of carer QALYs was not done in accordance with the NICE reference case and the

	Report: "The technical team agrees that it is important to capture the impact of caring for someone with DS in the model in line with the NICE methods guide." In the "Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)" for this appraisal, NICE also commented that "Caregiver related quality could be considered under health-related quality of life".	validity of the methods used is questionable. Potentially, as a result of the latter, the plausibility of the estimated disutilities for care givers can be questioned. For instance, is it plausible that the decrements for caregivers are [redacted] as large than the decrements for patients?
Are the quality of life values presented by the company for carer quality of life plausible?	The quality of life values presented by the company for carer quality of life are in line with those found in the literature (see response below).	See response above.
Are there any sources of evidence from the literature which could be used to validate the proposed quality of life values?	In DS, a survey (Campbell JD, et al. *Epilepsy & Behavior* 2018;80:152-156) assessed caregiver utilities. The disutility (0.22 +/- 0.17) is closely aligned to those measured in the company's vignette study ([redacted] and [redacted] for the two health states with the highest numbers of seizures), validating the plausibility of the company's disutility estimates.	The ERG concerns regarding the plausibility of the carer disutilities used in the company base-case are still present (see above). The decrements provided by the company are based on the difference between the average EuroQol-5D utility and perfect health (i.e., utility of 1). As the average utility in the population is evidently lower than 1, the disutility for proving care as extracted by the company from Campbell et al. 2018 is likely to be overestimated.
How many carers would a child with Dravet syndrome be expected to have? Would this be expected to remain the same after the person reaches adulthood?	The literature suggests that ≥1 carer for patients with DS is usual. For example, in the large pan-European DISCUSS survey of DS patients (Lagae, L. et al. *Developmental Medicine & Child Neurology* 2017), almost 80% of households had more than one adult caregiver. For the majority of children with DS, this remains the same after they reach adulthood. DS is a severe, lifelong, treatment-resistant form of epilepsy affecting children from 2 years of age. It is associated with many consequences/co-morbidities that can result in lifelong intellectual	The ERG concerns regarding the plausibility of the carer disutilities used in the company base-case are still present (see above). Moreover, if multiple carers are involved, the ERG is not convinced that utility decrements are on an additive scale (e.g., if you would consider the whole family, not everyone will have the same disutility)?

	and physical impairment, and complete dependence upon caregivers for daily activities. The company notes from the NICE technical report that "the technical team considers that the company may have underestimated the number of carers". (In the Revised Base Case, March 2019, the company included only 1 caregiver per patient). Therefore, in the Company's Updated Base Case, in line with Lagae et al, 2017, it has been assumed that each patient with DS has 1.8 carers.	
Issue 17: Impact of adverse events on quality of life		
Would the adverse events (AEs) associated with CBD be expected to have a substantial negative impact on health-related quality of life?	The majority of adverse events (AEs) associated with CBD reported in the clinical trials were mild to moderate in severity. The ERG noted that "Safety data appeared to indicate a pattern of gastrointestinal and 'tiredness'-related adverse events". Any negative impact on health-related quality of life is likely to be very small compared to the loss of quality of life associated with the severe seizures experienced by patients with DS. In addition, any AEs are occurring against a background of AEs from the other anti-epileptic drugs in the CCM mix. Therefore, the costs associated with AEs have been included in the model, but the disutilities that may be associated with any AEs have not.	The ERG considers that this is a question for discussion by clinical experts, and notes the response to this question given by the adult neurologist representing the Association of British Neurologists: *"We are still learning about this in adult patients. Loss of appetite may be an important issue, as some adults with Dravet may have lack of appetite (possibly aggravated by stiripentol or topiramate treatment) and some develop dysphagia (Catarino et al. Brain 2012)."*
Issue 18: Reduction in the concomitant use of anti-epileptic drugs		
Is using CBD likely to reduce concomitantly used anti-epileptic drugs? Is a 33% reduction plausible?	Clinically, a reduction in concomitant AEDs is relevant to patients and their carers, as there may be benefits associated with dose reductions through an improvement in side effects. Nonetheless, based on the comments from the ERG and the NICE technical team, in the Company's Updated Base Case, the	No AED dose reduction is consistent with the ERG preferred assumptions (see ERG report).

<table>
<tr><td></td><td>company assumed that there are no reductions in concomitant AEDs.
The dose reduction of concomitant AEDs is included as a scenario in the economic analysis. Please see the scenario analyses in Table 4 of the separate ‘Response Addendum’ document.</td><td></td></tr>
<tr><td>If dose reductions are likely please estimate the percentage of patients who would have a dose reduction and the size of this reduction in the adjacent table:</td><td><table>
<tr><th>Drug</th><th>% of patients</th><th>% dose reduction</th></tr>
<tr><td>Clobazam</td><td></td><td></td></tr>
<tr><td>Stiripentol</td><td></td><td></td></tr>
<tr><td>Valproate</td><td></td><td></td></tr>
<tr><td>Levetiracetam</td><td></td><td></td></tr>
<tr><td>Topiramate</td><td></td><td></td></tr>
</table></td><td></td></tr>
<tr><td>Are there situations where increasing the dose of a concomitant anti-epileptic drug after starting CBD is appropriate?</td><td></td><td></td></tr>
</table>

ERG critique of company's validity checks (18 July)

Changes compared to the original company submission

The new base-case submitted by the company is already the 4th base-case. The various changes that have been made by the company in the various resubmissions are not clear for the ERG. To illustrate this point, as described in our ERG report, the adjustments made in the revised assessment submitted during the clarification phase were not clearly described nor justified ("Most of these additional adjustments were not requested by the ERG (e.g. structural adjustments regarding duration of adverse events and adjusting long-term CBD discontinuation probabilities) nor were all adjustments clearly described"). For instance, the exact changes to the model that were made to ensure that the total QALYs did not exceed the time horizon are unclear. This is for instance also applicable to the technical response addendum submitted by the company. Although the changes are listed in Table 3, it is unclear how these are exactly implemented (i.e. what cell values / parts of the codes are adjusted). Therefore, it would likely be helpful to have an overview of all adjustments the company has made (including details related to the implementation), using the initial submission described in the original CS as starting point. Ideally the adjustments should be accompanied with appropriate justification and reference to evidence /sources where applicable.

Explanations of the symmetry issue provided by the company:

The company stated that the 'Company response to validity issues' document is in response to "…NICE…requesting further clarification on model symmetry". They then cite their response to Issue 32 in the FAC as addressing evidence that the ERG discovered of lack of model symmetry. They state that this is related to how the model "…manages the effect of aging (moving from 2-11 years to ≥12 years) on the distribution of drop seizure health states for patients not on CBD (i.e. either on CCM, or having discontinued CBD)." However, in their response to Issue 32, there is no mention of different assumptions for CCM and CBD related to the effect of aging: instead, in Appendix 1 they stated: "The model moves all patients in the CCM group back baseline after cycle 1, where upon they are re-allocated health states and substates in each cycle based on baseline probability assignments (i.e. those at model entry)" Therefore, there appears to be a discrepancy in their explanations.

Solution proposed by the company to fix the symmetry issue:

In the Company response to validity issues (July 18th), the company removes "aging" as a feature of the model. However, if the company believes that the aging function is clinically plausible then the ERG would have preferred to incorporate "aging" as a symmetric feature in the model (e.g. equal assumptions for all treatments) instead of removing it. Moreover, although the ERG was able to produce equal QALYs for both CCM and CBD based on the instructions in Table 4, this is still not convincing evidence that the model structure is symmetric. In order to produce zero QALYs, symmetry in inputs is not sufficient, but in fact a subset of symmetric values i.e.:

1) 100% in the diagonals for all transition matrices, rather than just matrices that are identical for both CBD and CCM
2) Baseline values for seizure free days, rather than ones that are just identical for both CBD and CCM

If different parameter values than those described in Table 4 (but identical for CCM and CBD) are implemented for the transition probabilities (tab “# SEIZURES”) or seizure free days (tab “# DAYS”) this produces different QALYs for CCM and CBD. This would imply that the symmetry assumption is only applicable under very specific conditions and will not extend to the base-case and scenario analyses provided by the company.

Furthermore, it is still not clear why, even when the “aging function” has been removed that setting the diagonals of the transition matrix in cycle 1 to 100% that future transition probabilities make a difference. The way the model should work if is that the cohort remains in the initial state for the whole of the time horizon.

In conclusion, the symmetry issue still persists, its cause is not clearly described and removal of the “aging function” does not solve the problem.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Cannabidiol for treating Dravet syndrome

The technical report addresses the company's initial submission to NICE, where the population in the decision problem was *people with Dravet syndrome whose seizures are inadequately controlled by established clinical management.*

On 26th July 2019 the Committee for Medicinal Products for Human Use adopted a positive opinion recommending cannabidiol for "*use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.*"

This company's initial submission did not examine cannabidiol used only in conjunction with clobazam. The company has subsequently submitted additional clinical and cost-effectiveness evidence relating to this sub-population. This new evidence was not examined as part of the technical report. However, as the company uses the same economic model the issues discussed in the technical report and the technical team's preliminary judgements remain relevant.

The reader should be aware that technical team judgements, and comments from the company, ERG, and experts are subject to change because the population being considered in the appraisal is different.

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements of the evidence by the technical team
- reflections on NICE's structured decision-making framework.

Technical report template 2 – AFTER technical engagement

This report is based on:

- the key evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Summary of the technical report

After technical engagement the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and rationale. Judgements that have been updated after engagement are highlighted in bold below.

1.1 In summary, the technical team considered the following:

- The company's positioning of cannabidiol (CBD) in the Dravet syndrome (DS) treatment pathway is appropriate (see issue 1).
- **The patients in the GWPCARE trials largely reflect people with DS seen in the NHS** (see issue 2).
- **Adults with DS are likely to benefit from CBD** (see issue 3).
- **The company's updated analyses using the mix of anti-epileptic drugs from the GWPCARE trials is appropriate** (see issue 4).
- There is no evidence to support considering CBD to have equal efficacy regardless of the different combinations of anti-epileptic drugs (see issue 5).
- **The stopping criteria suggested by NHS England are appropriate** (see issue 6).
- **It is appropriate to use convulsive seizures as the main outcome in the model, but there may be benefits of CBD which are not captured in the calculation of the quality-adjusted life years (QALYs)** (see issue 7).
- It is not appropriate to assume in the model that the number of days without convulsive seizures will depend on treatment allocation (see issue 8).
- The relative treatment effect observed in the CBD trials should be maintained for the entire duration of the model (see issue 9).
- **It is appropriate to use the results from the open label extension study in the model, but doing so adds uncertainty to the cost-effectiveness estimates** (see issue 10).
- The treatment effect of CBD may decrease over time (see issue 11).

- The company should take into account both the costs and benefits of dose escalation in its scenario analyses (see issue 12).
- **A 50-year time horizon is suitable for decision-making, but a lifetime time horizon would be more appropriate** (see issue 13).
- **The company's assumptions about epilepsy-related mortality are appropriate** (see issue 14).
- The company should explore the uncertainty around the values used in the model for patient quality of life and use results from the literature to validate these values (see issue 15).
- It is important to capture the impact of caring for someone with DS, however the company should explore the uncertainty around the values used in the model for carer quality of life and use results from the literature to validate these quality of life values (see issue 16).
- The effect of adverse events associated with CBD on quality of life should be included in the model (see issue 17).
- **The company's assumption that there is no reduction in use of anti-epileptic drugs for people who have CBD is appropriate** (see issue 18).

1.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The clinical trial evidence is based on small patient numbers
- Lack of data on the long-term efficacy of CBD

1.3 The cost-effectiveness results include an updated commercial arrangement (patient access scheme) submitted at the technical engagement stage. The company's base case incremental cost-effectiveness ratio (ICER) is £19,347 per quality-adjusted life year (QALY) gained (see table 3).

1.4 The technical team is unable to implement all of its preferred assumptions in the model. Therefore, it cannot calculate an alternative ICER reflecting

the considerations in this report. In addition, some areas of significant uncertainty remain unresolved including issues around model validity (see table 1).

1.5 The company considers the drug to be innovative. However, clinical experts advise that it will be an addition to the currently available anti-epileptic drugs and is unlikely to represent a step change in treatment since no patient in any of the included trials achieved complete freedom from seizures. The technical team noted that the benefits of CBD in reducing non-convulsive seizures are unlikely to be captured in the QALY calculations.

1.6 Comments from stakeholders during scoping noted that there was often difficulty in accessing treatment as an adult, particularly where drugs were not licensed for adults – despite there being no difference in the condition. The expected marketing authorisation for CBD is likely to recommend it for use in people aged 2 years or older. When making recommendations, the committee will consider whether any of them make it more difficult in practice for a specific group to access the technology compared with other groups.

2. Key issues for consideration

Issue 1 – Positioning of cannabidiol in the Dravet syndrome treatment pathway

Questions for engagement	a) Is the suggested position of CBD in the treatment pathway in line with how it is likely to be used in the NHS?
Background/description of issue	The therapeutic indications stated in the submitted summary of product characteristics (SmPC), does not include any limitation based on prior trials of other anti-epileptic drugs: '*Epidyolex is indicated for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.*' **The company** stated in its submission that the position of CBD within the care pathway for treatment of patients with DS will be as an add-on treatment for refractory seizures in people aged two years of age and older, for whom two other appropriate anti-epileptic drugs have failed to achieve seizure freedom (company submission [CS], p24). **The ERG** noted that this positioning does not reflect the marketing authorisation wording, which does not specify any number of prior treatments (ERG report p20–21). It also does not appear to be consistent with the eligibility criteria for GWPCARE1 and 2 where around 15% of patients had stopped taking fewer than 2 anti-epileptic drugs. So, the ERG was concerned that the numbers of prior and concurrent anti-epileptic drugs taken by the trial participants may not be in line with the proposed positioning of CBD in the DS treatment pathway. However, it noted that some patients who had stopped fewer than 2 prior anti-epileptic drugs may still meet the criteria for failure to achieve seizure freedom because anti-epileptic drugs are not always stopped when seizures are not controlled.
Why this issue is important	If CBD use in the trial does not reflect its likely positioning in the treatment pathway in the NHS, this would mean that the results of the trial may not be replicated in practice.
Technical team preliminary judgement and rationale	Most patients stopped taking 2 or more anti-epileptic drugs, therefore the clinical trial population generally reflects the company's proposed positioning of CBD in the DS treatment pathway.
Summary of comments	**Comments received from clinicans** In NHS practice CBD would be offered to patients who have not responded, or not tolerated, other standard treatments. It may be used before stiripentol in people diagnosed as adults as it is

	currently challenging to start treatment with stiripentol in adults because the marketing authorisation indication for stiripentol is for "epilepsy in infancy." **Comments received from company** Based on discussions with UK specialist clinicians, the company is confident that the positioning of CBD is in line with anticipated practice in the NHS.
Technical team judgement after engagement	The company's positioning of CBD in the DS treatment pathway is appropriate.

Issue 2 – Generalisability of the trial results to the NHS

Questions for engagement	a) Are the characteristics of participants in the GWPCARE trials likely to reflect the characteristics of people with DS seen in practice in the NHS?
Background/description of issue	The submission relies, primarily, on two trials of CBD as an add-on treatment to current clinical management (GWPCARE1 and GWPCARE2). Both trials were conducted in people with DS, between the ages of 2 and 18 years, whose seizures were inadequately controlled (at least 4 convulsive seizures per week during the four-week baseline period of the studies) on existing anti-epileptic drugs (CS, p29–30). **The company** reported that one of the two key trials (GWPCARE1) included patients from the UK. The company argues that the trials and the results are generalisable to the NHS practice. **The ERG** was not clear about the extent to which both trials were considered generalisable to the UK population as the company did not provide supporting statements from clinical experts to this effect (ERG report, p40 and 45). The ERG commented that the number recruited from the UK to GWPCARE3 was small (n=16). It also noted that the clinical trials did not include any adults (older than 18 years) with DS (see issue 3). The ERG was also concerned that the numbers of prior and concurrent anti-epileptic drugs taken by trial participants may not be representative of what might be expected in the NHS (see issue 4).
Why this issue is important	If trial participants do not have similar characteristics to those who would have CBD in the NHS, some of these factors may have an influence on how well the treatment works. That may mean that CBD does not work as well in clinical practice as it did in the trials.
Technical team preliminary judgement and rationale	It is not clear whether the trials used in the company submission are generalisable to clinical practice in the NHS. No data are available for people with DS who are older than 18 years.

Summary of comments	**Comments received from clinicans** The characteristics of people in the trials are likely to reflect those seen in the NHS. Adults were not included in the clinical trials, but would be expected to continue having convulsive seizures. Adults may have a lower frequency of convulsive seizures than children. **Comments received from company** The diagnostic criteria for DS in the trials were based on international guidelines, which are similar to the NICE guidelines for patients with DS. UK specialist clinicians agree that the participants in the GWPCARE trials reflect the characteristics of people with DS seen in practice in the NHS (based on characteristics including age, gender, seizure types, concomitant anti-epileptic drug use). NHS England statement in the NICE Technical Papers stated that "The view of NHS England is that the clinical trial data is generalisable to the UK population". **Comments received from ERG** The ERG agrees that the trial populations are likely to be representative of the proposed positioning of CBD in the treatment pathway
Technical team judgement after engagement	The patients in the GWPCARE trials largely reflect people with DS seen in the NHS.

Issue 3 – Transition to adulthood

Questions for engagement	a) Would patients continue to be treated into adulthood? b) Would the efficacy of CBD be expected to be similar in adult patients? c) How is the transition to adult services managed in the NHS?
Background/description of issue	**The ERG** noted that the clinical trials did not include patients over 18 years of age and that the results for the patients in the trials could not necessarily be generalised to adult patients (ERG report, p78). The ERG addresses some of this uncertainty in its exploratory analysis which assumed that clinical benefit did not continue beyond the duration of the trial because in this scenario patients older than 18 years will not derive clinical benefit from CBD.
Why this issue is important	The efficacy of CBD may be over- or underestimated for adults. This may affect the cost-effectiveness results.

Technical team preliminary judgement and rationale	The short time horizon in the company and ERG's base case (15 and 20 years respectively) means that few patients are likely to reach adulthood so any over- or underestimation of clinical effectiveness in these patients is likely to have minimal impact on cost-effectiveness results. Should the assumptions relating to the time horizon (see issue 13) or mortality rates (see issue 14) be changed the level of uncertainty may increase.
Summary of comments	**Comments received from clinicans** People would continue to be treated into adulthood. While there are no data available to assess the efficacy of CBD for adults there is no reason to expect the efficacy to be different than for children. Transition to adult services may be challenging because there are often less support services available for adults than for children. **Comments received from company** The Association of British Neurologists (ABN) stated in its submission to NICE that "Adults and children are both suitable candidates, neither should be excluded on age grounds alone."
Technical team judgement after engagement	Clinicians have stated that the efficacy of CBD for adults is likely to be similar to children, therefore the company's assumption in the cost-effectiveness model that patients over 18 benefit from CBD is appropriate.

Issue 4 – Composition of current clinical management

Questions for engagement

a) Does current clinical management as described in the trial reflect clinical practice in the NHS?

b) If possible please estimate the percentage of people in the specified age groups eligible for treatment with CBD who would be treated with the anti-epileptic drugs specified in the table below:

Anti-epileptic drug	Proportion of patients			
	<12 years		≥12 years	
	Company	Clinical expert	Company	Clinical expert
Clobazam	[redacted]		[redacted]	
Valproate	[redacted]		[redacted]	
Stiripentol	[redacted]		[redacted]	
Levetiracetam	[redacted]		[redacted]	
Topiramate	[redacted]		[redacted]	

Background/description of issue

Clinical management of people with DS consists primarily of anti-epileptic drugs. Polypharmacy is common in this population and people with DS can be on a number of anti-epileptic drugs at any given time. In addition to anti-epileptic drugs, vagus nerve stimulation and ketogenic diet are also used. The composition of current clinical management in the GWPCARE1 and GWPCARE2 trials is described in the company submission (CS, tables 6–7, p30–32). The company did not use these data to populate the economic model and instead used estimates derived based on NICE CG137 recommendations and a market survey conducted in the UK to establish the percentage of the people with DS using each anti-epileptic drug. The data from the trials and the those used in the model (CS, table 59, p44) are presented in the table below.

Anti-epileptic drug use	GWPCARE1		GWPCARE2		Model input <12 years*
	CBD 20 mg	Placebo	CBD 10 mg	Placebo	
N	61	59	[redacted]	[redacted]	
Mean	3.0	2.9	[redacted]	[redacted]	
Prior anti-epileptic drug, n (%)					
Clobazam	40 (66)	38 (64)	[redacted]	[redacted]	[redacted]

	Valprorate	27 (44)	30 (51)	[redacted]	[redacted]	[redacted]
	Stiripentol	30 (49)	21 (35)	[redacted]	[redacted]	[redacted]
	Levetiracetam	22 (36)	23 (40)	[redacted]	[redacted]	[redacted]
	Topiramate	16 (26)	15 (25)	[redacted]	[redacted]	[redacted]
	Vagus nerve stimulation	6 (10)	9 (15)	[redacted]	[redacted]	
	Ketogenic diet	6 (10)	4 (7)	[redacted]	[redacted]	

*Based on company's market research data. See company submission for inputs in the ≥12 years subgroup

The ERG is concerned about how well the trials in the company submission reflect the number and nature of treatments under the umbrella of clinical management in the NHS.

The technical team also noted that the percentage of the trial population using each of the anti-epileptic drugs is not in line with the percentages used in the model, which are based on NICE CG137 recommendations and a UK market survey. Clobazam was the most commonly used anti-epileptic drug in the trials, followed by valproate but, valproate and clobazam were assumed in the model to be used by [redacted]. The latter assumption is based on NICE CG137 recommendations and a UK market survey.

Why this issue is important	It is important to ascertain the percentage of people using each of the anti-epileptic drugs as this affects the cost of current clinical management.
Technical team preliminary judgement and rationale	The technical team considers the trial data to be the most appropriate to use in the model base case analysis. This ensures that any effect of the background therapy composition on CBD efficacy is reflected in the base case analysis. Scenario analysis using data from the UK market survey or clinical expert opinion can be presented to explore a composition of current clinical management that more closely reflects clinical practice, but such analysis will only capture the costs and not the effects of changing the composition of current clinical management.
Summary of comments	**Comments received from clinicans** The trials may not reflect clinical practice because of regional variations in prescribing and the lack of adult patients in the trials. **Comments received from company**

The company has updated its base-case so that the baseline characteristics in the trials have been used to define the mix of anti-epileptic drugs used as current clinical management. The company's updated analysis includes several drugs which are not used in NHS practice; rufinamide, clonazepam and zonisamide.

Anti-epileptic drug	Proportion of patients						
	<12 years			≥12 years			
	Company original values	Company revised values	Clinical expert 1	Company original values	Company revised values	Clinical expert 1	Clinical expert 2
Clobazam	[redacted]	64%	70%	[redacted]	64%	40%	70%
Valproate	[redacted]	14%	90%	[redacted]	14%	50%	80%
Stiripentol	[redacted]	38%	70%	[redacted]	38%	40%	15% (growing)
Topiramate	[redacted]	24%	10%	[redacted]	24%	20%	30%
Levetiracetam	[redacted]	27%	40%	[redacted]	27%	30%	30%

Technical team judgement after engagement

The company's updated analyses using the mix of anti-epileptic drugs from the GWPCARE trials is appropriate because it captures both costs and efficacy of current clinical management. There are some differences between the trials and clinical practice in the NHS, notably lower valproate use and the inclusion of drugs not used in the NHS. The technical team notes that there is only a small difference in the cost effectiveness estimate using the company's original and revised values.

Issue 5 – Subgroups of patients with additional clinical benefit

Questions for engagement

a) Is there a biologically plausible reason that CBD would be more effective in people [redacted]?

b) Do the baseline characteristics of people taking [redacted]?

c) Are the results of the subgroup analysis for convulsive seizure frequency generalisable to other seizure types?

	d) Are there any other subgroups where the efficacy of CBD may be different from the overall trial population?
Background/description of issue	**The company** stated that the subgroup analyses were standard demographic analyses, had small population numbers with low statistical powering and that no clinically relevant trends were seen in the subgroup analysis. **The ERG** noted that subgroup analyses relating to baseline seizure frequency and current/prior anti-epileptic drug use were specific to the clinical area and that subgroup analyses could have been used to examine whether the effectiveness of CBD varies with the use of other anti-epileptic drugs (ERG report p51–53).

	[redacted]
	The technical team noted that a prespecified subgroup analysis of [redacted] showed a statistically significant benefit for [redacted]

Why this issue is important	The company assumes in its modelling that [redacted] of people in the UK take [redacted]. The subgroup analyses suggest that CBD [redacted]. The ICER is therefore likely to decrease [redacted].
Technical team preliminary judgement and rationale	If CBD is not cost-effective in the population identified in the decision problem, it is appropriate to consider scenario analyses based on clinically relevant subgroups where CBD may be cost effective, [redacted]. The technical team acknowledges that due to the small patient numbers in the clinical data informing these analyses the cost-effectiveness results from these scenarios will be subject to uncertainty. The technical team notes that it had not seen the baseline characteristics of any subgroup of patients and could not determine if the subgroups were generalisable to NHS practice, or if any imbalances in characteristics between treatment arms may have influenced efficacy results in particular subgroups.
Summary of comments	**Comments from company** The company is not aware of any biologically plausible reason why taking [redacted] would affect the efficacy of CBD. A recent study has shown no such drug-drug interaction. There were differences in the baseline characteristics between the subgroups which may explain the results. However, the trials were not designed to assess the effect of individual anti-epileptic drug combinations on the efficacy of CBD, and subgroup analyses were based on small numbers. **Comments from clinicians** No subgroups have been identified that may have different efficacy from the overall trial population.
Technical team judgement after engagement	It is possible that the efficacy of CBD may vary within different subgroups but the technical team has not seen robust evidence demonstrating this definitively.

Issue 6 – Criteria for stopping treatment

Questions for engagement	a) Would treatment stop if seizure frequency did not improve? How would this be defined, and would this be related to convulsive seizure frequency, total seizure frequency or both? At what time-point(s) would response to treatment be assessed?
Background/description of issue	**The company** noted that stopping rules may apply in the two most severe health states and that these could be based on a certain percentage reduction in convulsive seizures over time (see company's revised economic assessment [REA] p4–7). The clinical trial did not have a stopping

	rule. To incorporate the effects of a stopping rule, the company proposes that after 2 years of treatment with CBD: • if seizure burden remains high (>25 seizures per month), [redacted]% of people stop treatment • if people continue to experience between 8 and 25 seizures per month, [redacted]% of people stop treatment A submission to NICE from **NHS England** stated that it anticipated that stopping and/or continuation may be part of the recommendations. If not part of the recommendation, then NHS England proposed the following continuation criteria in an application in Blueteq (a system to document high-cost drugs): • If the frequency of all countable seizures has reduced by 25% based on seizure diaries collected by patients, parents or carers OR • If the frequency of target seizure types (convulsive seizures in DS) have reduced by 30% compared to baseline.
Why this issue is important	If a stopping rule is applied this may reduce the health gain, but also the costs associated with CBD. The cost-effectiveness of CBD may improve because people not deriving benefit would not be getting treatment.
Technical team preliminary judgement and rationale	While some stopping rules are likely to be used in clinical practice, the assumptions used by the company to implement a 'stopping rule' in its discontinuation rates are arbitrary and may not reflect the fact that people with a high seizure burden after 2 years may still have experienced a reduction in seizure frequency (of either convulsive seizures or all seizures) compared with baseline. The technical team would prefer to see modelling assumptions which approximate the continuation criteria based on feedback from clinical experts and NHS England.
Summary of comments	**Comments received from clinicians** Convulsive seizures are most reliably documented and affect quality of life and premature mortality risk the most. For adults, outcome for seizures would be measured by convulsive seizure frequency. Reasonable to determine this outcome at a minimum of 3 months on a stable dose, then 6 months, 1 year and with each subsequent follow-up, as with current treatments. In general, treatment would stop if CBD were ineffective, unless it proved better tolerated in which case existing treatments might be withdrawn and CBD continued instead. One clinician specified that treatment should be stopped if a <30% reduction in countable seizures was not observed over a three month period.

	Comments received from company In most cases, CBD treatment would be expected to stop if no improvement in seizure frequency. In some cases, there may be benefits from CBD related to outcomes such as cognition/behaviour rather than seizure reduction. The company assumes in those cases, the decision to stop treatment would be based on a discussion between the patient/carer and specialist clinician, especially given the lack of alternative treatment options for people refractory to 2 or more anti-epileptic drugs. The company's updated base-case analysis incorporates a one-off discontinuation at 6 months in each convulsive-seizure health state. This is equal to the proportion of non-withdrawn patients in each health state at 6 months in the GWPCARE5 study who had a <30% reduction in convulsive seizures from baseline in GWPCARE 1 and 2. The reduction in convulsive seizures criteria is aligned with the NHS England submission for this technology appraisal. 6-months represents the earliest time at which a patient is likely to be seen in clinical practice (visits are typically every 3-6 months).. The **ERG** noted that it was unclear what discontinuation probabilities were used for the proposed 6 months stopping rule and how exactly was this implemented. It also noted that the long-term discontinuation (from cycle 10 onwards), is [redacted]% per cycle in all 'seizure' health states, based on the US Early Access Program for CBD. However, it is unclear why this assumption is more plausible than using the rate from the GWPCARE5 OLE study.
Technical team judgement after engagement	Using the stopping criteria suggested by NHS England in the updated base-case analysis is appropriate. However, the clinicians' stated that review may occur at 3 months rather than 6 months.

Issue 7 – Ignoring non-convulsive seizures in the model

Questions for engagement	a) Is excluding non-convulsive seizures from the model appropriate? b) How big an impact do non-convulsive seizures have on individuals' quality of life?
Background/description of issue	It is likely for people with DS that have a reduction in convulsive-seizures or who have become convulsive seizure-free, to still have **non**-convulsive seizures. Non-convulsive seizures also carry a risk of sudden unexpected death in epilepsy and other epilepsy-related mortality, and adversely affect quality of life. **The company** focused on number of convulsive-seizures and convulsive-seizure free days as the main outcomes in its model and did not provide data on the number of days on which study participants were completely seizure-free (no seizures of any type).

The ERG questioned the omission of non-convulsive seizures from the model and considered the number of seizure-free days (including all seizure types) to be more relevant to the estimation of utility values than the number of convulsive seizure-free days.

The technical team notes that total seizure frequency and non-convulsive seizure frequency were included as secondary outcomes in the GWCARE2 trial. The results showed a significant reduction in total seizure frequency compared with placebo (see below table). The technical team notes that this may represent an uncaptured benefit of CBD on quality of life.

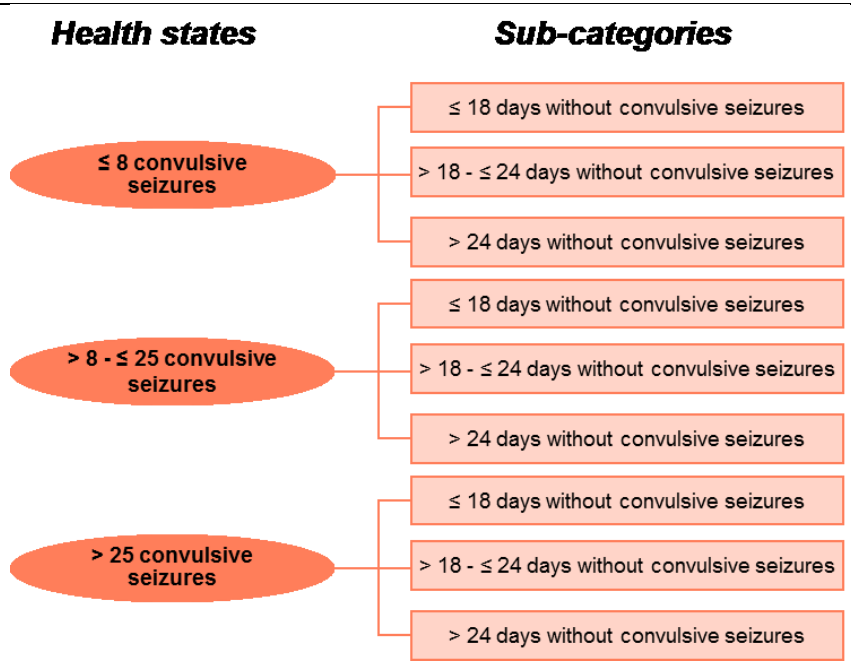
Secondary outcomes – GWPCARE2			
	CBD 10 mg	**CBD 20 mg**	**Placebo**
Total seizure frequency per 28 days			
% change in total seizures during treatment	[redacted]	[redacted]	[redacted]
Comparison to placebo	[redacted]	[redacted]	N/A
Non-convulsive seizure frequency per 28 days			
% change in total seizures during treatment	[redacted]	[redacted]	[redacted]
Comparison to placebo	[redacted]	[redacted]	N/A

Why this issue is important	The exclusion of non-convulsive seizures from the model may result in unrealistically high utility values for the convulsive-seizure free health sub-categories, since patients in this state can still experience non-convulsive seizures which have an adverse effect on quality of life. However, since non-convulsive seizures decreased in the trial, the benefits of this are not captured in the model.
Technical team preliminary judgement and rationale	The exclusion of non-convulsive seizures from the model is not appropriate as it has a non-negligible impact on quality of life.
Summary of comments	**Comments received from clinicans** Ideally non-convulsive seizures should not be ignored, but they are difficult to count, so it is more reliable to use 'countable' seizures. Non-convulsive seizures have a high impact on quality of life, particularly for individuals who have them for prolonged periods. **Comments received from company** Convulsive seizures are the seizure types about which parents/caregivers are most concerned, as they can lead to serious injury/hospitalisation. They are clinically identifiable, easy to count, and drive the morbidity. The number of convulsive seizures were chosen as the basis for the model structure for these reasons, and because it was the primary endpoint of the trials. Non-convulsive seizures include myoclonic, partial and absence seizures. These seizures are often more difficult to count. For example, an absence seizure may cause the person to blank out or stare into space for a few seconds, whilst a partial seizure may involve a person's leg or arm twitching briefly. Non-convulsive seizures are not a homogenous category: both the treatment effect on, and quality of life contribution of, each type is distinct. Incorporating their contribution to the model would require a very complex structure with multiple health sub states, and a utility elicitation study that would be unfeasible in such a rare condition due to the number of health state descriptions needed. Data from the CBD Phase 3 trials shows that the average number of non-convulsive seizures is lower in health states with fewer convulsive seizures. Therefore, there is uncaptured gain in quality of life attributed to the use of CBD. The company explored the magnitude of this uncaptured gain and its possible impact on the ICER in a sensitivity analysis. In this sensitivity analysis, the company estimated the quality of life decrement per person required to increase

	incremental QALY gain, in the base case, by values ranging from 5% to 20%. This showed that it only requires a small uncaptured QALY benefit to increase the incremental QALYs by 5% ([redacted]) and [redacted] uncaptured QALYs would represent a 20% increase in incremental QALYs. The **ERG** noted that the company's scenario analysis does not show the additional effect on utility of non-convulsive seizures because there is no estimate on the number of non-convulsive seizures in each health-state and no disutility associated with a convulsive seizure.
Technical team judgement after engagement	It is appropriate to use convulsive seizures as the main outcome in the model. The benefits of a reduction in non-convulsive seizures are difficult to measure and to include in the model. The potential benefits are unlikely to accurately estimated by the company's scenario analyses. Therefore, there may be benefits of CBD which are not captured in the calculation of the QALYs.

Issue 8 – Number of days without convulsive seizures

Questions for engagement	a) Is CBD likely to increase the number of convulsive seizure-free days, in addition to reducing convulsive seizure frequency?
Background/description of issue	Improvements in quality of life of people with DS is assumed to relate to both the total number of convulsive seizures and number of convulsive seizure-free days **The company** subdivided the convulsive seizure frequency health states into three sub-categories based on the number of convulsive seizure-free days per 28 days. It assumed that the number of days without convulsive seizures depends on treatment, based on evidence from the trials (CS, p53 and 64).

	 **The ERG** does not agree with this assumption as it noted it is unclear whether in the model patients maintain any improvements in health state sub-category after stopping CBD, which would bias the results in favour of CBD because patients in the current clinical management arm return to baseline seizure frequency. It preferred to assume that the number of convulsive-seizure free days was the same for both treatment arms (ERG report, p83).
Why this issue is important	Including treatment-dependent number of days without convulsive seizures might overestimate the treatment effect and bias the results in favour of CBD, because it is unclear whether this benefit persists in the model after CBD discontinuation.
Technical team preliminary judgement and rationale	It is not appropriate to assume that the number of days without convulsive seizures will depend on treatment allocation.
Summary of comments	**Comments received from clinicans**

	It is possible that treatment with CBD will increase the number of convulsive-seizure free days but this will vary between patients and is difficult to predict for adult patients because of a lack of clinical evidence. **Comments received from company** CBD showed a statistically and clinically significant treatment effect on the number of seizure-free days per month. The model does not treat CBD patients who stop treatment differently from CCM patients. Therefore, there is no bias in the model structure because of the parameter of convulsive-seizure free days, and this assumption has been retained in the company's updated base case. The **ERG** noted that the company's assumptions in the model after CBD patients discontinue treatment are unclear and that if their number of seizure-free days remain the same then patients who were treated with CBD would maintain a benefit after stopping CBD.
Technical team judgement after engagement	It is not appropriate to assume that the number of days without convulsive seizures will depend on treatment allocation if patients treated with CBD maintain a benefit after stopping CBD. If it is demonstrated that this is not the case, it may be appropriate to include this assumption.

Issue 9 – Relative treatment effect

Questions for engagement	a) Is it appropriate to only capture placebo response in current clinical management arm for 1 cycle only (the length of the trial), or should the relative efficacy of CBD compared with current clinical management remain constant over time?
Background/description of issue	A relatively large placebo response was observed across the trials included in the company submission. **The company** explained that large placebo effect is common in epilepsy trials and has been observed in DS studies since the 1990s. According to the company, the exact reason is unknown but could be attributed to a number of reasons including the psychological expectation of improvement and regression to the mean. To account for this background effect, the company implemented a treatment response for current clinical management in the first cycle of the model and assumed that this effect will be lost, with return to baseline occurring after the first cycle. **The ERG** agreed that the large placebo effect was in line with that observed in trials of other anti-epileptic drugs. However, it was concerned that the placebo effect was assumed to affect the

	current clinical management cohort for only the first cycle and that the clinical effectiveness of CBD in subsequent cycles may be overestimated. **The technical team** notes that there is no comparative data beyond 14 weeks (i.e. the first cycle of the model) and that assuming the placebo effect is maintained in subsequent cycles may overestimate the treatment effect of current clinical management.
Why this issue is important	Assuming the placebo effect for current clinical management persists only for 1 cycle might result in an overestimated relative treatment effect for CBD.
Technical team preliminary judgement and rationale	The technical team considers that assuming the relative efficacy of CBD compared with current clinical management is constant over time may more closely reflect the benefits of CBD in clinical practice.
Summary of comments	**Comments received from company** The placebo effect seen in clinical trials for both LGS and DS is variable. The CBD studies demonstrated up to 27% improvement from baseline. Another study in DS showed a placebo effect to less than 2%. The absolute impact of CBD in DS on convulsive seizures from baseline is consistent across studies at 40-50%. This magnitude of effect was observed in the open-label GWPCARE5 study and in the US Early Access Program. These observations suggest that the absolute reduction in seizure frequency in the clinical trials would be replicated in clinical practice. If the relative treatment effect were maintained throughout the time horizon (as preferred by the ERG), CBD will be unduly penalised by virtue of the unusually high placebo effect. The company's provided 2 analyses: 1. Applying the outcomes from GWPCARE1 and GWPCARE2 for 6 months (2 cycles) for both the CBD and current clinical management arms in the model. After this point, patients in the current clinical management arm return to baseline, and outcomes from the GWPCARE5 study are applied to CBD patients. 2. The outcomes from GWPCARE1 and GWPCARE2 are applied to both arms to cycle 9 in the model (up to 2 years).

	The **ERG** notes that CBD would not be penalised by continuing to use the relative treatment effect for the duration of the model as this is the principal by which effect sizes are measured in randomised controlled trials.
Technical team judgement after engagement	The technical team understands that Analysis 2 represents the company's updated base case. Although the relative treatment effect is maintained for longer in this analysis, it is still only for 2 years. The technical team considers that assuming the relative efficacy of CBD compared with current clinical management is constant over the entire time horizon of the model would more closely reflect the benefits of CBD in clinical practice.

Issue 10 – Use of data from open label extension study

Questions for engagement	a) Are the results from the open label extension study (GWPCARE 5), where patients had an average maintenance dose of CBD of [redacted] generalisable to the expected maintenance dose of [redacted]?
Background/description of issue	**The company** used efficacy inputs from GWPCARE 5 for months 3 to 27 in the model (CS, p59–63). Treatment benefit was maintained for CBD from 27 months (see issue 11). **The ERG** noted that the clinical inputs were based on evidence from a different dose of CBD than included in the model and that the clinical benefit of CBD may therefore have been overestimated. It therefore explored scenarios (ERG report, p102–104) where: • The costs of CBD were set to the 20 mg/kg/day dose after the first cycle, or • The clinical effectiveness of CBD was based on the 10 mg/kg/day dose only.
Why this issue is important	If the results from the open label study are not generalisable to the dose of CBD used in clinical practice, then the clinical benefit of CBD will be overestimated and the ICER underestimated.
Technical team preliminary judgement and rationale	The results from GWPCARE 5 may not be generalisable to the use of CBD in clinical practice. The ERG's first scenario is likely to overestimate the ICER as increasing the dose of CBD in all patients to 20 mg/kg/day is not likely to reflect clinical practice. The ERG's second scenario is more plausible, but includes the assumption that treatment benefit continues throughout the model (see issue 11) and does not account for dose escalation (see issue 12) or stopping rules (see issue 6).
Summary of comments	**Comments received from clinicians**

	One clinician stated the results would be generalisable, another stated that this may not necessarily be the case. **Comments received from company** No dose response was seen in the GWPCARE2 trial in DS (GWPCARE1 did not study multiple doses). This lack of dose response is supported by a post hoc sub-group analysis of the GWPCARE5 data. There was no statistically significant difference on the primary and secondary endpoints between patients who were on a low dose (≥[redacted] to <[redacted] mg/kg/day) and those who were on a high dose (≥[redacted] to <[redacted] mg/kg/day), and the ITT population. Therefore, GWPCARE5 represents a good surrogate for clinical outcomes on the expected maintenance dose of 10 mg/kg/day. It is preferable to use long-term data from GWPCARE 5 rather than extrapolating the 3-month outcomes from the Phase 3 trials (as suggested by the ERG). The **ERG** considers the absence of presence of a dose response to be uncertain because the company's post-hoc analysis did not include outcome results and did not consider the subgroup of patients on >20 mg/kg/day, which included the majority of patients in GWPCARE5.
Technical team judgement after engagement	The company has not provided robust evidence that there is no dose response relationship so using this data in the model adds uncertainty to the cost-effectiveness estimates. However, in the absence of any alternative data, the technical team considers it acceptable to use data from the open label extension in the base-case analysis.

Issue 11 – Extrapolating the effects of treatment beyond the follow up period in the clinical trials

Questions for engagement	a) Should the model account for a potential decrease in treatment effect on convulsive seizure- and total seizure frequency over time? If so, how should this be estimated? For example, are seizures likely to return to baseline levels, and over what period – 2 years, 4 years or something else? b) If the dose of other anti-epileptic drugs had been reduced (see issue 18) would the dose be increased back to standard levels if the efficacy of CBD was reduced?

Technical report template 2 – AFTER technical engagement

Background/description of issue	**The company** assumed in their model that after 27 months (maximum follow-up period of the open-label extension study GWEPCARE 5) patients would remain in the same health state until discontinuation or death (CS, p53–55). **The ERG** noted that there was no evidence to support this assumption and presented two base-case analyses, one using the company's assumption and one assuming no treatment effect after 27 months (ERG report, p102–104).
Why this issue is important	If the treatment effect is not maintained over time, then the health gains associated with CBD would be lower. In addition, there may be a need to increase the dose of other anti-epileptic drugs (if such discontinuations have occurred), increasing the costs associated with the CBD plus current clinical management treatment strategy. Both of these would worsen the cost-effectiveness estimates.
Technical team preliminary judgement and rationale	The treatment effect of CBD may decrease over time. The company's assumption therefore may underestimate the ICER. The ERG's assumption may overestimate the ICER as the ERG assume people continue to take CBD, which would be unlikely because if there is no clinical benefit people would stop CBD and costs would be expected to decrease. In addition, the treatment effect is more likely to gradually diminish over time than abruptly stop at 2 years.
Summary of comments	**Comments received from clinicians** The possibility of a reduction in treatment effect of CBD should be taken into account in the model. One clinician stated there is no evidence of a decreased effect over time, Another stated that return to baseline levels on the same drug (combination) should be apparent within a year. If the dose of any other anti-epileptic drugs had been decreased it would likely be increased back to standard levels if a reduction in treatment effect of CBD was observed but this depends on the specific combination of treatments **Comments received from company** The treatment effect of CBD is unlikely to stop abruptly at any given time point. The GWPCARE5 study shows that people taking CBD have a very consistent reduction in convulsive seizures from baseline over more than 2 years. Any assumption on cut-off or waning of transition probabilities within the model would be arbitrary. The company considers that it is more appropriate to account for any evolution in the drug's efficacy over time through discontinuation assumptions, which are already included in the model. This reflects clinical practice, and is evidence-led. In the company's updated base case, [redacted]% of patients are on treatment by 3 years, and [redacted]% by 5 years.

	A scenario analysis increasing the long-term discontinuation rate from [redacted]% to [redacted]% shows that if the waning of the CBD treatment effect has been underestimated, the ICER would decrease, as more people stop ineffective treatment. The **ERG** considers waning of treatment effect to be a reduction in relative treatment effect over time and that this is a separate (though potentially related) issue to discontinuation rate.
Technical team judgement after engagement	There is no evidence of the efficacy of CBD after 2 years, this is a source of uncertainty in the model. The company's scenario analysis to address this uncertainty is unlikely to be appropriate.

Issue 12 – Increasing the dose of cannabidiol

Questions for engagement	a) Would a higher dose of CBD (eg the maximum recommended dose of 20 mg/kg/day) be considered for any of the following: • people who did not respond to a 10 mg/kg/day dose? • people whose response to a 10 mg/kg/day dose had lessened over time (see issue 11)? • people who responded to a 10 mg/kg/day dose to try and further reduce seizure frequency? If so, which patients would be considered for this dose and what proportion of responders/non-responders would this be? b) At which timepoint(s) would people be assessed to determine if an increased dose could be of benefit?
Background/description of issue	In its base case, the company assumes that all patients remain on 10 mg/kg/day. **The company** states that dose escalation would most likely to be received only by a small proportion of patients who have the potential to achieve further seizure reductions and/or seizure-freedom. The company's base case did not include dose escalation. The company did a scenario analysis using a mean dose of [redacted] based on the assumption that patients [redacted] would receive the 20 mg/kg/day dose of CBD. **The technical team** noted that because the effectiveness data beyond the first cycle is based on the open label extension where the average dose was around [redacted] the company's scenario analysis changes only the costs and not the effectiveness of CBD.

Why this issue is important	Increasing the dose of CBD for some patients may increase both the health gains and costs associated with CBD. The effect of this on the ICER is unknown and will depend on which categories of patients have dose increases.
Technical team preliminary judgement and rationale	Scenario analyses relating to dose escalation should take into account both the costs and benefits of dose escalation. The company's scenario analysis is limited, because as in the base case, all patients receive the benefit of the 20 mg/kg/day dose beyond the first cycle because this is the only source of efficacy data. However, it is unclear if it would be possible to adequately model a dose escalation scenario because of the limited efficacy data.
Summary of comments	**Comments received from clinicians** It is unlikely that a higher dose would routinely be tried if the 10 mg/kg/day dose had no effect. Both the clinical experts stated that the dose would be increased if there was a partial response to cannabidiol, if this dose increase is tolerated. One expert stated it is likely the dose would be increased if the effect of CBD lessened overtime, whereas another stated this would be unlikely. Dosage should be assessed routinely; at 3, 6, 12 months after starting CBD and at each subsequent follow-up. **Comments received from company** The summary of product characteristics defines 10 mg/kg/day as the preferred maintenance dose for CBD. The company anticipates that most patients will be on this dose in clinical practice. Of the groups described in Issue 11: • People who did not respond to a 10 mg/kg/day dose of CBD should not be considered for a higher dose because there was no dose response in the CBD clinical trials. • People who are not responding to a 10 mg/kg/day dose of CBD should not be considered for a higher dose. • People who responded to a 10 mg/kg/day dose have the option of being considered for a higher dose of CBD in order to try to further reduce seizure frequency or possibly achieve seizure freedom. The company acknowledges that scenario analyses relating to dose escalation should consider both the costs and benefits of dose escalation. The company has implemented scenario analyses in a population that includes some patients who receive a dose above 10 mg/kg/day, including both the costs and benefits.

Technical team judgement after engagement	The company and clinical experts both indicated that some people who respond to 10 mg/kg/day of CBD may have an increase in dose. The clinical benefits of this are likely to be captured in the model if data from the open label extension study are used because some people in the extension study had a dose increase. The technical team prefers that the cost of this is captured but notes that the method used to calculate the average dose in the company's scenario analysis may not reflect the population who would have a dose increase in clinical practice.

Issue 13 – Time horizon

Questions for engagement	a) Are all differences in costs and effects attributable to CBD likely to be captured in a 15-year time horizon?
Background/description of issue	The NICE guide to the methods of technology appraisal stipulates that a lifetime time horizon is required when alternative technologies lead to differences in survival, health benefits or costs that persist for the remainder of a person's life. **The company** used a time horizon of 15 years in its analysis and stated that this has been chosen given the lack of long-term data. **The ERG** considers this to be inconsistent with NICE methods, given the survival differences in mortality that were attributed to CBD treatment. A 20-year time horizon was used by the ERG in their base case analysis as this is the maximum allowed in the company's model (ERG report, p71).
Why this issue is important	People with DS are at risk of higher mortality depending on their seizure frequency. Given the potential effect of CBD on survival, the NICE methods guide suggests that a lifetime time horizon should be used to accurately capture all the differences in costs and effects.
Technical team preliminary judgement and rationale	A lifetime time horizon is required to accurately capture the incremental costs and benefits. This is due to the survival benefit attributed to CBD in the model.
Summary of comments	**Comments received from clinicians** A 15 year time horizon is insufficient to capture all costs and benefits. If effective, CBD is likely to be continued, which may increase actual costs. **Comments received from company** In line with the recommendations in the NICE technical report, the company's updated base-case extends the time horizon to 50 years.

	The company considers that a lifetime horizon in this therapy area should be based on the time required for most patients to discontinue therapy. In the updated base-case, only [redacted]% of patients are still on therapy at 50 years. This is considered to be a reasonable lifetime horizon. Scenario analyses with time horizons of 15, 20, 30 and 40 years are provided. The **ERG** prefers a lifetime time horizon.
Technical team judgement after engagement	The technical team notes that around [redacted]% of patients are still alive in each arm after 50 years and therefore would have preferred a lifetime time horizon to fully capture costs and benefits. Because changing the time horizon from 40 to 50 years did not substantially change the ICER the technical team considers a 50-year time horizon reasonable for decision making, although a lifetime time horizon would be more appropriate.

Issue 14 – Relationship between mortality rates and number of seizures

Questions for engagement

a) Is an association between number of **convulsive** seizures and increased epilepsy-related mortality rates plausible? If possible, please estimate the increased (value greater than 1) or reduced risk (value less than 1) compared with the >8 and ≤ 25 seizures category in the following table:

	Risk ratio			
	Seizure free	≤ 8 seizures	>8 to ≤ 25 seizures (**reference**)	> 25 seizures
Company	0.42	[redacted]	1.0	[redacted]
ERG	0.42	1.0	1.0	1.0
Clinical expert estimate			1.0	

b) What proportion of patients with Dravet syndrome treated with current clinical management would be expected to be alive:

- 15 years after starting treatment,
- 20 years after starting treatment,

	• 50 years after starting treatment.
Background/description of issue	The **company** estimates the mortality of people with DS by adjusting data from the >8 to ≤ 25 subgroup (derived from Cooper *et al.* 2016) to estimate the mortality in each seizure state in the model (revised economic assessment, p8–9). The **ERG** noted that the company's adjustment was not based on evidence and presented alternative analysis where unadjusted values were used in all seizure states except for the seizure free state (see above table). It also noted that these values may be underestimated in the seizure free state as the literature values are linked to all seizures, whereas patients in the model are only free of convulsive seizures (ERG report, P75–76).
Why this issue is important	If mortality rates in the health states with lower seizure frequency are underestimated, then the clinical benefit of CBD will be overestimated because the number of patients in the model treated with CBD who die will be too low.
Technical team preliminary judgement and rationale	The company did not present evidence to support their adjustments to epilepsy-mortality rates, therefore the technical team preferred the ERG's approach of using unadjusted values.
Summary of comments	**Comments received from company** In the original economic model submitted to NICE, the company attempted to consider the impact on mortality of improved seizure control, as this is cited as an important area of unmet need. However, the company has accepted the ERG's assumption that mortality should be the same in all health states except in seizure-free patients and has updated the company base-case to reflect this.
Technical team judgement after engagement	The company's updated assumption that mortality is the same in all health states except for the seizure-free health state is appropriate.

Issue 15 – Health-related quality of life of people with Dravet syndrome

Questions for engagement	a) Are the quality of life values presented by the company plausible? b) Are there any sources of evidence from the literature which could be used to validate the proposed quality of life values?
Background/description of issue	The **company** derived EQ-5D quality of life values for each health state from a survey of people with Dravet syndrome and their carers (CS, p70–79). The company did this because there are limited literature data available for quality of life values for Dravet syndrome and those available are

not defined based on the number of convulsive seizures or number of convulsive seizure-free days. The quality of life values derived from the survey are summarised below.

Health state (number of convulsive seizures)	Sub-state (number of seizure free days)	Mean quality of life scores
No seizures	No seizures	[redacted]
≤ 8 seizures	≤ 18 seizure-free days	[redacted]
	> 18 - ≤ 24 seizure-free days	[redacted]
	> 24 seizure-free days	[redacted]
>8 - ≤ 25 seizures	≤ 18 seizure-free days	[redacted]
	> 18 - ≤ 24 seizure-free days	[redacted]
	> 24 seizure-free days	[redacted]
> 25 seizures	≤ 18 seizure-free days	[redacted]
	> 18 - ≤ 24 seizure-free days	[redacted]
	> 24 seizure-free days	[redacted]

The **ERG** noted that the valuation of public preferences from a representative sample of the UK population using a choice-based method and that use of a vignette study was suboptimal compared to multi-attribute utility instruments and public preferences (ERG report, p81–82). The ERG suggested exploring a scenario where utilities were based on the Quality of Life in Childhood Epilepsy (QOLCE) instrument which was used in the GWPCARE2 study. The company noted in response to clarification that the results from the QOLCE instrument were not used because of low response rates and lack of an appropriate mapping algorithm to EQ-5D values.

Why this issue is important

There is uncertainty around the values used to represent the quality of life of patients with Dravet syndrome. These may be either over- or underestimated. The effect of this on the ICER is unclear.

Technical team preliminary judgement and rationale

The technical team acknowledges that the orphan nature of Dravet syndrome presents challenges for assessing the quality of life of people with Dravet syndrome. Therefore, it considers that the company's approach to assessing quality of life may be justified, however it is associated with several limitations. The uncertainty around the evidence should be fully explored. Therefore, the

<table>
<tr><td></td><td>technical team does not consider it useful to exclude evidence from the literature based simply on the fact it is not defined based on number of convulsive seizures or number of convulsive seizure-free days. The technical team would have preferred that the company presented data from their systematic review which could be useful in validating the quality of life values from the vignette study or exploring scenario analyses. It also considers that data collected by the company using alternative scales may be useful for validation purposes but would not expect these values to be included in the model.</td></tr>
<tr><td>Summary of comments</td><td>Comments received from clinicians
One clinician identified Brunklaus, et al 2011, and Nabbout et al 2018 as potential sources to validate the quality of life values used in the model.
Comments received from company
The company considered the quality of life values presented to be plausible. The systematic review conducted by the company identified one study that provided utility values by health state (Verdian et al. 2008). This study reports values in 4 seizure frequency health states for LGS and has been used by other identified cost-utility studies in both LGS and DS. However, the health states investigated in Verdian et al were not close surrogates for the CBD model, as they assessed HRQoL associated with relative changes in seizure frequency over time and not absolute seizure frequency. It also does not report on the contribution of seizure free days to utilities. Hence, the company preferred to undertake a bespoke vignette study to elicit utilities. The utility values reported in Verdian et al closely aligns with those in the company's model where seizure frequency is comparable. Average utility scores for DS populations reported in the large DISCUSS survey showed similar scores to the company's own health states, both at a European level (Lagae, et al, 2017) and in the UK (Pagano, et al. 2019). A scenario analysis using the utility estimates from Verdian et al applied as closely as possible to the health states in the company's model shows a similar ICER to the company's updated base case.

The quality of life values from the sources identified by the company and clinicians are summarised below (Brunklaus et al and Nabbout et al were not included as they did not report EQ-5D scores):

<table>
<tr><th>Source</th><th>Verdian (2008)</th><th>Lagae (2019)</th><th>Pagano (2019)</th></tr>
</table>
</td></tr>
</table>

	Condition	LGS	DS	DS
	Study type	Elicitation from general public (48% were caregivers or patients)	Caregiver survey	Caregiver survey (UK specific cohort of Lagae 2017)
	Number surveyed	119	584	72
	Method of measurement	EQ-5D-VAS[a]	EQ-5D-5L (without VAS)	EQ-5D-5L (without VAS)
	Quality of life values	21-28 seizures per week: 0.02 <50% reduction: 0.100 ≥50% and <75% reduction: 0.500 ≥75% reduction: 0.596	Mean for patients ≥2 years old 0.42	Mean for patients ≥2 years old: 0.382 (range, -0.17 to 0.88)
	a) TTO values also measured but not included in table – results slightly higher for all groups			
Technical team judgement after engagement	Scenario analysis using the published utility values would be required to assess the impact of using these alternative values on the model results.			

Issue 16 – Health-related quality of life of carers of people with Dravet syndrome

Questions for engagement	a) Should carer quality of life be included in the model? b) Are the quality of life values presented by the company for carer quality of life plausible? c) Are there any sources of evidence from the literature which could be used to validate the proposed quality of life values? d) How many carers would a child with Dravet syndrome be expected to have? Would this be expected to remain the same after the person reaches adulthood?
Background/description of issue	The **company** included the quality of life of carers of people with Dravet syndrome in its base case. It based estimates of carers quality of life values from a vignette study (see issue 14). The company assumed that each person with Dravet syndrome has one carer and that care continues into

<table>
<tr><td></td><td>adulthood. The increasing impact of caring for someone with Dravet syndrome as their number of seizures increases is captured by subtracting the quality of life values in the following table from the patient's quality of life score (revised economic assessment, p10-11). The quality of life value decrements compared with the seizure free health state derived by the company are presented in the table below.

<table>
<tr><th colspan="2">Mean quality of life decrements</th></tr>
<tr><td>No seizures</td><td>-</td></tr>
<tr><td>≤8 seizures</td><td>-</td></tr>
<tr><td>>8 - ≤25 seizures</td><td>[redacted]</td></tr>
<tr><td>>25 seizures</td><td>[redacted]</td></tr>
</table>

The ERG has similar concerns as with patient quality of life data (see issue 14) and further noted that the methods of deriving utility methods may be unsuitable because caregivers were only asked to evaluate three vignette tasks in total, therefore the results lack granularity. For these reasons the ERG did not consider carer quality of life in its base case but explored including it in a scenario analysis.
The technical team noted that the company's systematic review had identified studies relating to carer quality of life but had not discussed these further in its revised economic assessment or considered using values from these studies as scenario analyses.</td></tr>
<tr><td>Why this issue is important</td><td>There is uncertainty around the values used to represent the quality of life of carers of people with Dravet syndrome. These may be either over- or underestimated. Also, the company's estimate of the number of carers may be conservative. The combined effect of these uncertainties on the ICER is unclear. Whether or not carer QALYs are included has a large effect on the ICER, with their exclusion resulting in a large increase in the ICER.</td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>The technical team agrees that it is important to capture the impact of caring for someone with DS in the model in line with the NICE methods guide. However, there is substantial uncertainty associated</td></tr>
</table>

	with the quality of life values presented by the company. The technical team would have preferred to have seen scenario analyses based on quality of life values reported in the literature for DS (or other epilepsy-related conditions if not available) to attempt to quantify the extent of the uncertainty around these values. The technical team considers that the company may have underestimated the number of carers.
Summary of comments	**Comments received from clinicians** The clinicians identified Lagae et al (2019) and Nabbout et al (2018) as potential sources to validate the quality of life values used in the model. Both studies report on outcomes related to carers, but neither report EQ-5D values which could be used to validate the model. Children with Dravet would likely have at least 2, possibly 4 carers, 1-2 parents and 1-2 grandparents. Most children would have the same carers in adulthood, though some may be in residential care. **Comments received from company** The company's literature review identified a survey assessing caregiver utilities using EQ-5D-VAS (Campbell et al 2018) provided disutility values The disutility (0.22 +/- 0.17) is closely aligned to those measured in the company's vignette study ([redacted] and [redacted] for the two health states with the highest numbers of seizures), validating the plausibility of the company's disutility values. A scenario using the disutility score from Campbell et al shows a similar ICER to the company's updated base case. The literature indicates that people with severe epilepsy usually have more than 1 carer. In the large pan-European DISCUSS survey of DS patients (Lagae et al, 2017), almost 80% of households had more than one adult caregiver. For many children with LGS, the need for multiple carers remains the same after they reach adulthood because of cognitive and functional impairment. The company's updated base case, in line with Lagae et al, has assumed that each patient with DS has 1.8 carers. The **ERG** notes that the carer quality of life values may not be plausible, as decrements for caregivers are [redacted] as large than the decrements for patients. Also, the scenario analysis using the values from Campbell et al overestimates the reduction in quality of life because it is calculated by subtracting the average carer quality of life from perfect health (a value of 1) rather than the general population average, which would be lower than 1. Also, if multiple carers are

	involved, the ERG is uncertain whether utility decrements should be on an additive scale (e.g., if you would consider the whole family, not everyone will have the same disutility).
Technical team judgement after engagement	The scenario analysis provided by the company using alternative utility values from the literature overestimates the quality of life reduction for carers. Assuming that people with DS requires 1.8 carers is plausible and in line with evidence.

Issue 17 – Impact of adverse events on quality of life

Questions for engagement	a) Would the adverse events (AEs) associated with CBD be expected to have a substantial negative impact on health-related quality of life?
Background/description of issue	Data from the included phase III trials of CBD, GWPCARE1 and GWPCARE2, show a pattern of gastrointestinal and 'tiredness'-related AEs in patients taking CBD, as well as some detrimental effects on markers of liver function. **The company** included costs related to these AEs in its model but did not account for its possible negative impact on health-related quality of life. **The ERG** questions this and considers including this negative impact on the quality of life of people treated with CBD to be important. Given that the costs of these AEs were included in the model, it is appropriate to also include the loss in quality of life that is likely to be associated with these events. The ERG noted it was not feasible to implement these values in the model due to time constraints (ERG report, p83).
Why this issue is important	Ignoring the negative impact of treatment-related AEs on quality of life could result in overestimating the QALY gain achieved for the CBD cohort. This might bias the results of the cost effectiveness analysis in favour of CBD.
Technical team preliminary judgement and rationale	The AEs associated with CBD are likely to have a negative impact on quality of life. This should be accounted for in the model by including disutilities for these events.
Summary of comments	**Comments received from clinicians** AEs potentially have a substantial negative impact on health-related quality of life, in the context of multiple therapies and comorbidities. **Comments received from company**

	Most AEs associated with CBD reported in the clinical trials were mild to moderate in severity. Therefore, any negative impact on health-related quality of life is likely to be very small compared to the loss of quality of life associated with the severe seizures experienced by patients with DS. In addition, any AEs are occurring against a background of AEs from the other anti-epileptic drugs in the current clinical management mix. Therefore, the costs associated with AEs have been included in the model, but the disutilities that may be associated with any AEs have not.
Technical team judgement after engagement	It is preferable to account for disutilities associated with AEs in the model, but the impact of including these on the cost-effectiveness results is likely to be small.

Issue 18 – Reduction in the concomitant use of anti-epileptic drugs

Questions for engagement	a) Is using CBD likely to reduce concomitantly used anti-epileptic drugs? Is a 33% reduction plausible? b) If dose reductions are likely please estimate the percentage of patients who would have a dose reduction and the size of this reduction in the table below: **Drug** / **% of patients** / **% dose reduction** Clobazam Stiripentol Valproate Levetiracetam Topiramate c) Are there situations where increasing the dose of a concomitant anti-epileptic drug after starting CBD is appropriate?
Background/description of issue	**The company** positions CBD as an add-on therapy to other anti-epileptic drugs. It assumed that using CBD will reduce the dose of some concomitantly used anti-epileptic drugs for some people. (CS, p82).

<table>
<tr><td></td><td>The ERG questions this assumption as it is not consistent with the evidence presented by the company. The results from the company's expanded access program that supported this assumption also indicated that some individuals receiving CBD required an increase rather than reduction in anti-epileptic drug dose, and it is unclear from the evidence what percentage of dose reduction/increase occurred in those who had a dose reduction (ERG report, p87).</td></tr>
<tr><td>Why this issue is important</td><td>Assuming a reduction in concomitantly used anti-epileptic drugs in the CBD arm results in reduction in costs for people receiving CBD in the economic model. If no reduction in concomitantly used anti-epileptic drugs is likely, then this may bias the model results in favour of CBD.</td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>It is not clear whether the use of CBD would result in reduction in concomitantly used anti-epileptic drugs. Assuming 33% reduction in the use of some anti-epileptic drugs for those receiving CBD is likely to be an overestimate.</td></tr>
<tr><td>Summary of comments</td><td>Comments received from clinicians
One clinician stated that eaningful estimates of dose reductions for adults are not possible given the lack of available data. It is unlikely that the dose of other anti-epileptic drugs will be increased after starting CBD.
One clinician stated that the following dose reductions would be plausible:
<table>
<tr><th>Drug</th><th>% of patients</th><th>% dose reduction</th></tr>
<tr><td>Clobazam</td><td>50%</td><td>30%</td></tr>
<tr><td>Stiripentol</td><td>50%</td><td>wean</td></tr>
<tr><td>Valproate</td><td>20%</td><td>30%</td></tr>
<tr><td>Levetiracetam</td><td>40%</td><td>wean</td></tr>
<tr><td>Topiramate</td><td>50%</td><td>wean</td></tr>
</table>
Comments received from company
Clinically, a reduction in concomitant anti-epileptic drugs is relevant to patients and their carers, as there may be benefits associated with dose reductions through an improvement in side effects.
The company has assumed in its updated base-case that there are no reductions in concomitant anti-epileptic drugs.</td></tr>
</table>

	The dose reduction of concomitant anti-epileptic drugs is included as a scenario analysis and does not substantially change the ICER.
Technical team judgement after engagement	The company's base case assumption that the dose of concomitant anti-epileptic drugs is stable is appropriate.

3. Other issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate	Responses
Model validity	The model lacks symmetry. That is, when inputs are set equal, there is a QALY gain for CBD, whereas none would be expected.	Unknown	The company has made a number of changes to the model to address the issue of lack of symmetry including removing "ageing function". The ERG did not consider these changes to address the issue and concluded that lack of symmetry is still an issue, leading to a bias in favour of CBD in the base case.
Small patient numbers	The GWPCARE2 trial only included [redacted] patients in the 10 mg/kg/day dose arm. The effectiveness estimates for this dose are highly uncertain.	Unknown	The company considers that [redacted] patients is a clinically meaningful sample size, especially given the orphan nature of DS. All arms in the GWPCARE2 trial were balanced, and the study was adequately powered. The 10 mg/kg arm showed a clinically meaningful treatment effect vs placebo on the primary and key secondary endpoints that had strong statistical significance.

Table 2: Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	Inc costs	Inc QALYs	ICER
Company revised base case	**–**	**£27,262**	**1.41**	**£19,347**
Mean rather than median body weight (see table 3) ***Source: company scenario analysis***	Mean body weight is the appropriate parameter to use in the model	£28,495	1.41	£20,222
Equal number of days without convulsive seizures (see issue 8) ***Source: calculated by technical team***	Including differential number of days without convulsive seizures depending on treatment allocation may introduce bias in the model	£27,262	1.40	£19,467
Relative treatment effect maintained for the whole model time horizon (see issue 9)	Assuming constant relative treatment benefit for CBD compared with current clinical management	-	-	unknown [a]
Decrease in treatment effect over time (see issue 11)	The efficacy of CBD is likely to decrease over time	-	-	unknown [a]
Use the average dose of 12.88 mg/kg/day (see issue 12) ***Source: company scenario analysis***	To reflect the fact that a proportion of people will increase to 20 mg/kg/day dose	£39,821	1.41	£28,384
Lifetime horizon (see issue 13)	More appropriate as mortality benefit expected			unknown [a]
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate cannot be calculated because it cannot implement all of its preferred assumptions in the model. In addition, there are unresolved uncertainties about the validity of the outputs (see table 1)				

[a] Where the ICER is unknown the technical team was unable to implement their preferred assumption within the current model structure

Table 3: Other issues for information

Issue	Comments
Literature review	The ERG identified errors in the company's search strategy but the company did not include the revised search strategy in the clarification response. The ERG is concerned about the company missing potentially relevant evidence and questioned the rationale for limiting conference proceedings to the last two years. The company also did not include trials of vagus nerve stimulation and ketogenic diet as they considered them part of clinical management. However, the ERG advises that these should have been included. The technical team considers that these omissions are unlikely to have an impact on the modelling approach or cost-effectiveness estimates.
Cost of current clinical management	The ERG highlighted that the cost of ketogenic diet and vagus nerve stimulation were not included in the model. Underestimation of these costs may bias the results, given the longer survival of people treated with CBD. The technical team considers that these omissions are not likely to substantially change the cost-effectiveness estimates.
Cost of health states	Resource use, and hence costs, for the "seizure-free" health state were considered to be underestimated as it is not completely seizure-free. Additionally, the cost associated with monitoring was not included. However, this is not anticipated to have substantial impact on the model results.
Institutionalisation rates	Based on comments from the ERG the company updated institutionalisation rates in the model to assume that people in the convulsive seizure-free state could be institutionalised. The proportion was set to 2% based on clinical expert opinion.
Weight of patients in the 18–55 years age group in the model	The mean weights for the age category "18-55 years" in the original submission were deemed implausible as this category was based on a small number of patients (1.89%) and lacked face validity ([redacted]). Hence, for the category aged 18-55 years, the mean weight in the ERG base-case was based on the LGS submission.
Dose titration period	The titration period in the the clinical trials is not included in the model, which uses the maintenance dose of CBD day 1. However, the ERG agreed with company that this is likely to slightly overestimate treatment costs and have little effect on cost-effectiveness results.
Discontinuation rates	The ERG considered that the discontinuation rates used by the company after cycle 1 were not informed by evidence and lacked face validity (ERG report, p77). The technical team preferred the discontinuation rates used by the ERG. These were subsequently included in the company's updated base-case analysis.
Parameter uncertainty	Not all parameters have been included in the probabilistic sensitivity analysis (e.g. non-sudden unexpected death in epilepsy costs). Following response to clarifications, the ERG believes that the probabilistic sensitivity analysis still does

Issue	Comments
	not include all relevant parameters (e.g. excluding discontinuation probabilities up to cycle 9, which are potentially influential). The company reported that the PSA included all parameters that had a significant impact on the ICER in the Deterministic Sensitivity Analysis (DSA). The PSA for the Company's Updated Base Case now includes the parameters of "Subsequent discontinuation rates" (i.e. for cycles 2-9), non-SUDEP probability, and the updated continuation/stopping criteria from NHS England (see Table 3).
Innovation	The company considers the drug to be innovative. However, clinical experts advise that it will be an addition to the currently available anti-epileptic drugs and is unlikely to represent a step change in treatment since no patient in any of the included trials achieved complete freedom from seizures. The technical team noted that the benefits of CBD in reducing non-convulsive are unlikely to be captured in the QALY calculations.
Equality considerations	Comments from stakeholders during scoping noted that there was often difficulty in accessing treatment as an adult, particularly where drugs were not licensed for adults – despite there being no difference in the condition. The expected marketing authorisation for CBD is likely to recommend it for use in people aged 2 years or older. When making recommendations, the committee will consider whether any of them make it more difficult in practice for a specific group to access the technology compared with other groups.

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