NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome [ID1308]

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 Lennox-Gastaut syndrome [ID1308]

Contents:

The following documents are made available to consultees and commentators:

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

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 Lennox-Gastaut syndrome [ID1308]

Document A

Company evidence submission summary for committee

GW Research Ltd confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

May 2019

File name	Version	Contains confidential information	Date
ID1308 LGS Summary for Committee 15May2019	**Final**	**Yes**	**15 May 2019**

Contents

Tables and figures

Submission summary

A.1 Health condition

Lennox-Gastaut syndrome (LGS) is a rare (orphan), severely debilitating, lifelong and treatment-resistant form of epilepsy affecting children from 2 years of age.

LGS is characterised by multiple and frequent seizure types. Atonic and tonic seizures result in a temporary loss of muscle tone or stiffening of muscles, respectively. These sudden ‘drop seizures’ result in severe injuries: patients need to wear helmets or use wheelchairs to minimise injuries.

Up to 95% of patients with LGS have cognitive impairment. Developmental delays and behavioural disturbances are common. Cognitive functioning decline over time correlates with seizure severity/frequency in early life.

LGS is life-threatening, with the all-cause mortality rate for patients with LGS 14 times higher than for the general population. Patients are at high risk of Sudden Death in Epilepsy (SUDEP). Risk of death from neurological causes (e.g. prolonged seizures, status epilepticus) is 179 times greater than in the general population. High seizure frequency is a significant independent predictor of early death. Clinical opinion recommends that the most effective prevention strategy for death related to epilepsy is to reduce the frequency of seizures.

LGS has a severe impact on the patient but also on the family/caregivers. The extremely demanding nature of caring for a child with LGS requires adjustments in virtually all aspects of daily life. Many parents focus on the child with LGS, while siblings get less attention. Cognitive/functional impairments render many patients with LGS unable to live independently. Parents report feeling anxiety about the potential for injury, cognitive decline, or death of the child, as well as the financial burden on the family.

A.2 Clinical pathway of care

NICE Clinical guideline 137 (CG137) recommends sodium valproate as a first-line treatment option for LGS and, if seizures are inadequately controlled, lamotrigine as an adjunctive treatment. Further anti-epileptic drugs (AEDs), including felbamate, rufinamide and topiramate may be considered by epilepsy specialists. According to CG137, a number of anti-epileptic drugs (including carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine and vigabatrin) should *not* be given to patients with LGS as they may worsen seizures. Non-pharmacological treatment options include ketogenic diet, vagus nerve stimulation and neurosurgery.

Despite the availability of a broad range of AEDs, non-pharmacological interventions and invasive surgery such as corpus callosotomy, seizure control in LGS remains inadequate, with the majority of patients unresponsive to treatment or unable to tolerate current AEDs: more than 90% of children with LGS have drug-resistant epilepsy and less than 10% achieve seizure-freedom as adults.

There is a substantial unmet need in LGS for an intervention that can effectively reduce seizures in the long term (without markedly increasing adverse events), improve the overall condition of patients with LGS and reduce carer burden.

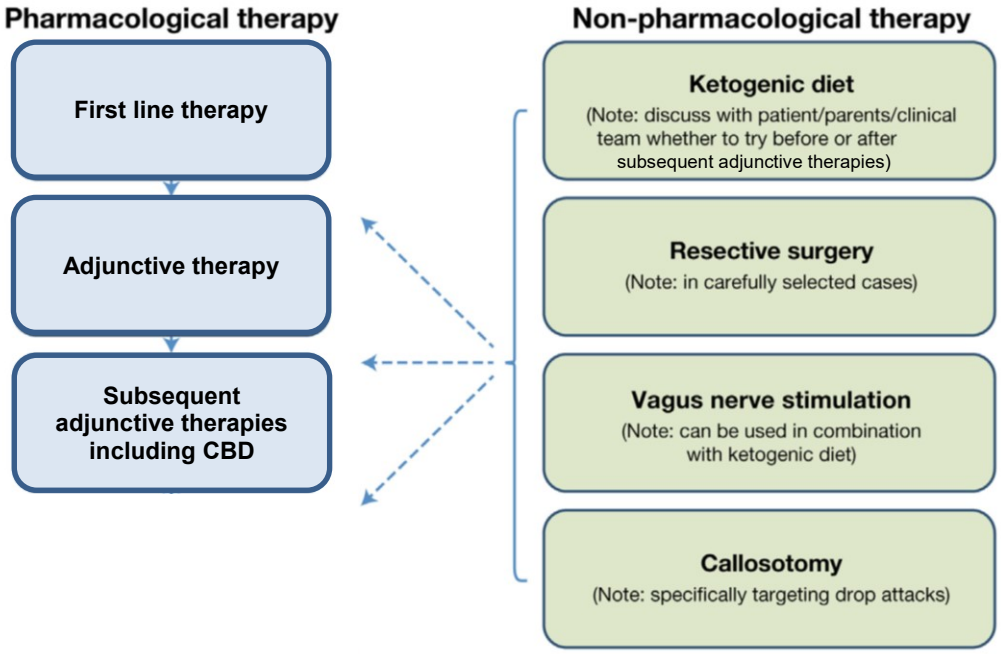
Refractory epilepsy has been defined by the International League Against Epilepsy (ILAE) as failure of adequate trial of two tolerated and appropriately chosen and used AED regimens (as monotherapies or in combination) to achieve sustained freedom from seizures.

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

For patients with LGS 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 *1*).

Figure 1: Clinical pathway for LGS including CBD - B.1.3 (page 25)



Cannabidiol offers patients with LGS 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 LGS treatment pathway aligns with current clinical management.

No service redesign will be required.

A.3 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.

A.4 The technology

Table 1: Technology being appraised - B.1.2 (page 16)

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	Awaiting marketing authorisation in the UK for Lennox-Gastaut syndrome (and Dravet 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	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 oral solution 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.

A.5 Decision problem and NICE reference case

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

Table 2: The decision problem - B.1.1 (page 13)

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with Lennox-Gastaut syndrome whose seizures are inadequately controlled by established clinical management.	People with Lennox-Gastaut syndrome (LGS) whose seizures are inadequately controlled by current or prior established clinical management. People with LGS where current clinical management is unsuitable or not tolerated.	This is in line with recommendations in NICE Clinical guideline 137 (CG137).
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 • lamotrigine • rufinamide • topiramate • felbamate • clobazam • levetiracetam • ketogenic diet • vagus nerve stimulation	Established clinical management without cannabidiol, which may include combinations of: • sodium valproate • lamotrigine • rufinamide • topiramate • felbamate • clobazam • levetiracetam • ketogenic diet • vagus nerve stimulation	Not applicable
Outcomes	The outcome measures to be considered include: • seizure frequency (overall and by seizure type) • response rate (overall and by	The outcome measures to be considered include: • seizure frequency (drop seizures and overall) • proportion of people drop seizure-	The primary endpoint of the pivotal clinical trials was change in drop seizure frequency. A seizure severity proxy (duration of seizures) was measured through the

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	seizure type) • seizure severity • incidence of status epilepticus • mortality • adverse effects of treatment • health-related quality of life	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)	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.
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
Perspective for outcomes	All direct health effects, whether for patients or, when relevant, carers	As per reference case	Not applicable
Perspective for costs	NHS and personal social services (PSS)	NHS and PSS	Not applicable
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	15 years - long enough to reflect all expected consequences in costs and health effects between cannabidiol and current clinical management	Not applicable

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Synthesis of evidence on health effects	Based on systematic review	Systematic review	Not applicable
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects expressed in QALYs. Health states: utilities based on VAS from online survey	VAS data collection in line with guidance in NICE reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Reported directly by patients and/or carers	Not applicable
Source of preference data for valuation of changes in health-related QoL	Representative sample of the UK population	Representative sample of UK epilepsy patients and/or carers of epilepsy patients	Epilepsy patients and caregivers have a better understanding of the impact of seizures and seizure-free days on QoL and wellbeing
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As per reference case	Not applicable
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	As per reference case. Sources: NHS reference costs; PSSRU; British National Formulary; published literature; expert opinion	Not applicable
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per reference case	Not applicable

A.6 Clinical effectiveness evidence

Cannabidiol (CBD) has been rigorously evaluated in the largest global clinical trial programme in patients with LGS, which includes two blinded, randomised, controlled Phase 3 studies, GWPCARE3 (GWEP1414) and GWPCARE4 (GWEP1423), and an ongoing open label extension study (GWPCARE5).

Table 3: Clinical effectiveness evidence

Study title	**GWPCARE3/GWEP1414**	**GWPCARE4/GWEP1423**
Study design	Phase 3 double-blind, placebo-controlled, multicentre, multinational RCT	Phase 3 double-blind, placebo-controlled, multicentre, multinational RCT
Population	Children and adults aged 2 to 55 years with LGS incompletely controlled on existing AEDs, taking 1 or more AEDs, with at least 2 drop seizures/week in initial 28 day baseline period.	Patients aged 2 to 55 years with LGS with at least two drop seizures per week during the 4-week baseline period and had not responded to treatment with at least two AEDs.
Intervention(s)	Cannabidiol 10 mg/kg/day in addition to current clinical management (CCM) Cannabidiol 20 mg/kg/day in addition to CCM	Cannabidiol 20 mg/kg/day in addition to CCM
Comparator(s)	Placebo in addition to CCM	Placebo in addition to CCM
Outcomes specified in the decision problem	• **Percentage reduction in drop seizure frequency/28 days** • Percentage reduction from baseline in frequency of non-drop seizures; • Patient or Caregiver Global Impression of Change from baseline in overall condition; • Patient or Caregiver Global Impression of Change in Seizure Duration from baseline in overall condition; • Frequency of status epilepticus episodes.	• **Percentage reduction in drop seizure frequency/28 days** • Percentage reduction from baseline in frequency of non-drop seizure; • Patient or Caregiver Global Impression of Change from baseline in overall condition; • Patient or Caregiver Global Impression of Change in Seizure Duration from baseline in overall condition • Frequency of status epilepticus episodes.
Reference to section in submission	B.2.2 (page 28)	B.2.2 (page 28)

A.7 Key results of the clinical effectiveness evidence

A.7.1 *Summary*

As part of the largest Phase 3 clinical study programme in LGS, cannabidiol (CBD) met its primary endpoint in both the pivotal Phase 3 LGS studies. CBD demonstrated a clinically and statistically significant median reduction in drop seizure frequency of 40% (at a dose of 10 mg/kg/day) versus 19% with current clinical management (CCM) (p=0.0033). A proportion of patients have the potential to achieve further seizure reduction with a dose of 20 mg/kg/day, and 6% achieved complete drop seizure freedom compared with 0.6% of patients on CCM, thereby offering the potential to transform the lives of those patients and their families.

The ongoing open-label extension study of CBD demonstrates the longer-term consistency and reproducibility of its efficacy: reductions in drop and total seizure frequency were sustained over a 48 week period.

CBD 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.

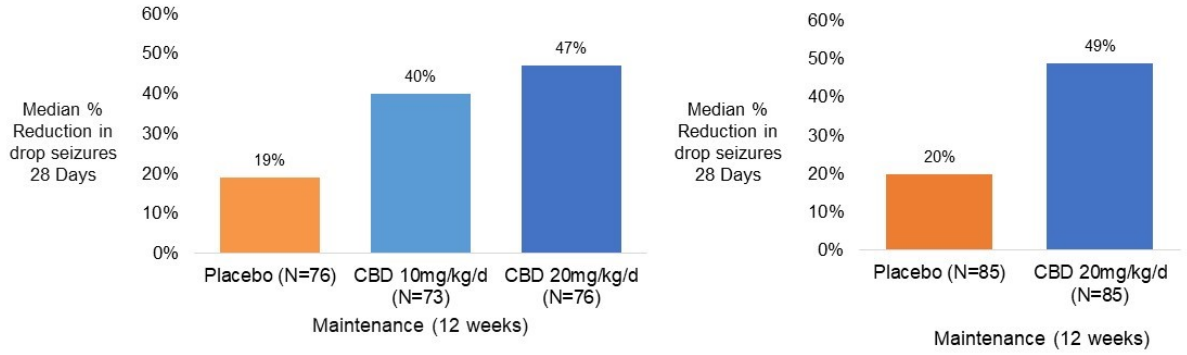
A.7.2 *Percentage reduction in drop seizure frequency/28 days*

The GWPCARE3 and GWPCARE4 studies both met their primary endpoint, demonstrating that CBD in addition to CCM had a statistically significant and clinically meaningful effect compared with CCM alone (i.e. CCM+placebo) in the median percentage change from baseline in drop seizure frequency.

In both studies, treatment lasted 14 weeks: a 2-week initial titration period in which patients started at a dose of 2.5 mg/kg/day and increased by 2.5 to 5.0 mg/kg/day every other day until their target dose was reached, followed by a 12-week maintenance period in which patients continued to take their assigned dose.

The median reductions in drop seizure frequency achieved during the 12-week maintenance period in GWPCARE3 and GWPCARE4 (ITT) are shown in Figure 2.

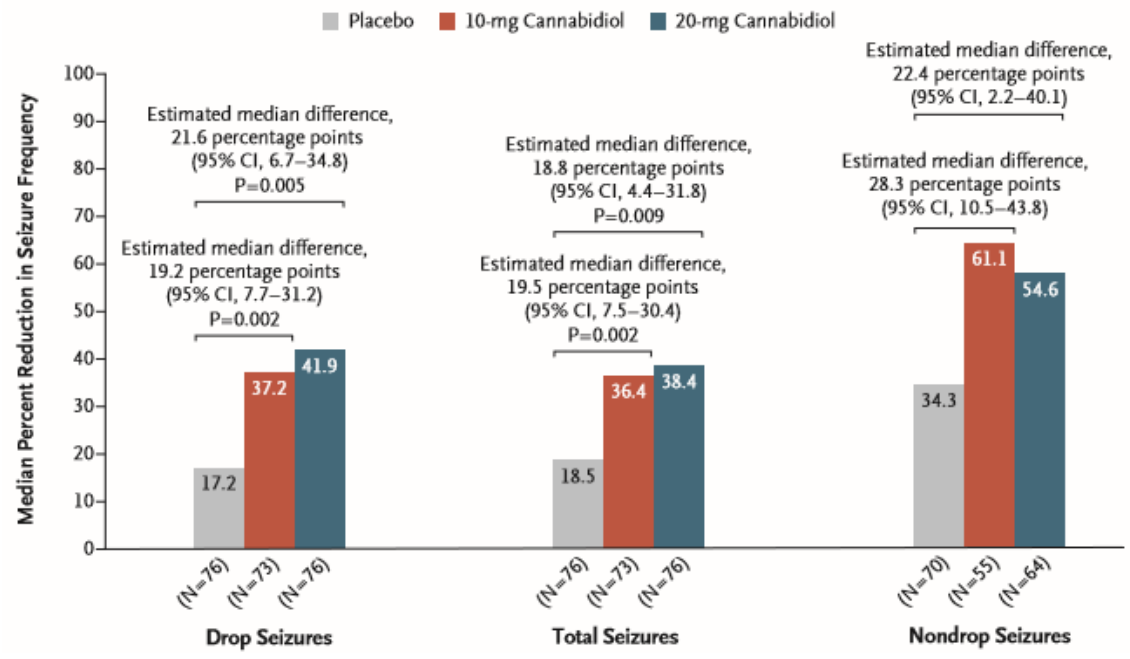
Figure 2: Percentage Change from Baseline in Drop Seizure Frequency in GWPCARE3 and GWPCARE4 - B.2.6 (page 36)



A.7.3 *Percentage reduction in total seizures*

In GWPCARE3, the median percent reduction in total seizures from baseline was 36.4% in the CBD 10 mg group, 38.4% in the CBD 20 mg group and 18.5% in the CCM+placebo group. The median difference in reduction of total seizures between the 10mg cannabidiol group and the placebo group was calculated to be 19.5% (95%CI 7.5 to 30.4%, p = 0.002), and between the 20 mg cannabidiol group and the placebo group it was 18.8% (95%CI 4.4 to 31.8%, p = 0.009).

Figure 3: Median percent reduction in patients' monthly seizure frequency during their treatment period from GWPCARE3 - B.2.6 (page 37)



In GWPCARE4, the frequency of total seizures in the CBD group decreased by a median of 41.2% from baseline during the treatment phase, and in the CCM+placebo group it decreased by a median of 13.7% (estimated median difference = -21.1, 95%CI -33.3 to -9.4, p = 0.0005).

A.7.4 *Caregiver Global Impression of Change*

In the Phase 3 studies, caregivers reported an overall improvement in the condition of patients receiving CBD more often than in CCM (60% versus 39% respectively, as measured on the Caregiver Global Impression of Change (CGIC) scale), an improvement that has been consistently maintained in an open label extension study to 48 weeks in >80% of patients.

A.7.5 *Health-related quality of life*

CBD does not have a detrimental effect on the quality of life of patients with LGS. The GWPCARE4 study assessed patient-reported outcomes and found no significant differences between CBD and current clinical management in Quality of Life in Childhood Epilepsy (QOLCE), Sleep disruption score, Epworth Sleepiness Scale or Vineland II scores between groups (B.3.4, page 75).

A.7.6 *Adverse effects of treatment*

The safety and tolerability profile of CBD shown across the clinical trial programme is consistent, well-defined and manageable. Most AEs were mild or moderate. The majority were transient and resolved within 4 weeks of onset.

The AEs reported across GWPCARE3 and GWPCARE4 with an occurrence in at least 10% of patients, or those leading to withdrawals from treatment, are summarised in the main dossier (B.2.10, page 44).

Common adverse events (occurring in more than 1 in 10 people) with CBD were vomiting, fatigue, pyrexia, upper respiratory tract infection, decreased appetite, convulsion, lethargy, somnolence and diarrhoea. 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.

A.7.7 *Number of people with episodes of 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 LGS studies, status epilepticus was reported as an adverse event in 5 patients receiving cannabidiol 20 mg/kg, 7 patients receiving cannabidiol 10 mg/kg and 4 patients receiving placebo in addition to CCM.

A.8 Evidence synthesis

No meta-analyses or indirect/mixed treatment comparisons were conducted. Refractory 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 LGS 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 (CCM) 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.

A.9 Key clinical issues

Not applicable.

A.10 Overview of the economic analysis

Seizure frequency is known to vary widely among individual patients with LGS. Previous models assessing treatment alternatives for LGS defined the model health states based on the percentage reduction in drop seizures from baseline. However, this approach may not accurately capture the costs and quality of life as patients with similar percentage reductions in drop seizures would be grouped together irrespective of the total number of seizures experienced at baseline. Therefore, the health states in the current analysis were defined based on the total number of drop seizures per month.

The economic analysis is based on a Markov state-transition cohort model (Figure 4). Patients in the treatment and comparator arm can enter the model via any one of the three health states with drop seizures (i.e. ≤45, between >45 - ≤110 and >110 drop seizures).

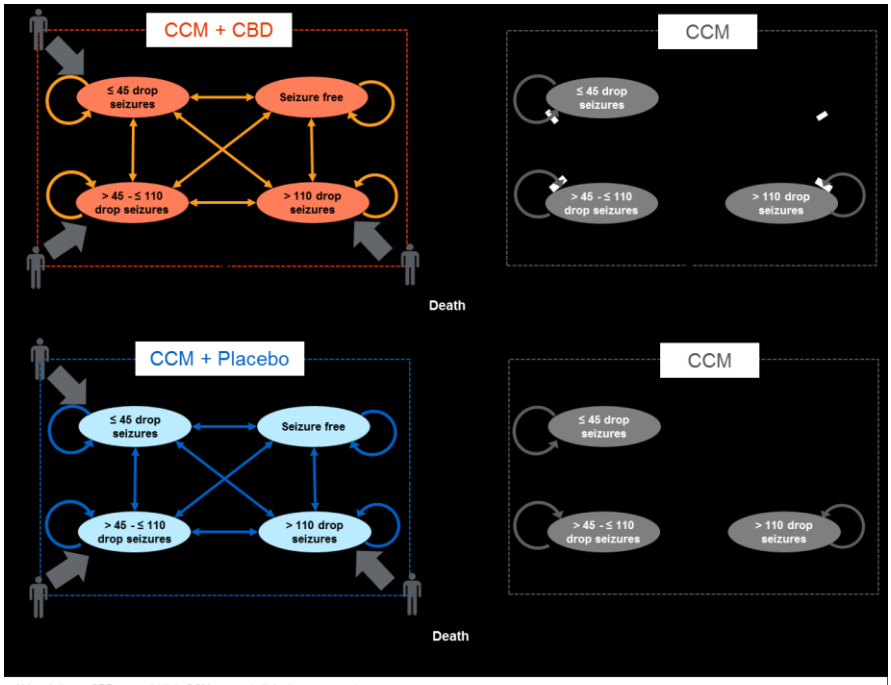
At each cycle (cycle length 3 months), patients in the treatment arm (i.e. CBD in addition to current clinical management (CCM)) can continue to receive treatment, discontinue or die:

- If they continue to receive treatment, patients can move to another health state (better or worse drop seizure group) or stay in the same health state
- Discontinuation rates were applied to only the treatment arm (i.e. CBD+CCM). When patients discontinue their treatment, they go back to baseline efficacy rates and remain in their baseline health state until the end of the analysis
- Once patients have discontinued their treatment, they cannot receive active treatment again (i.e. they only receive 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 (B.3.2, page 55).

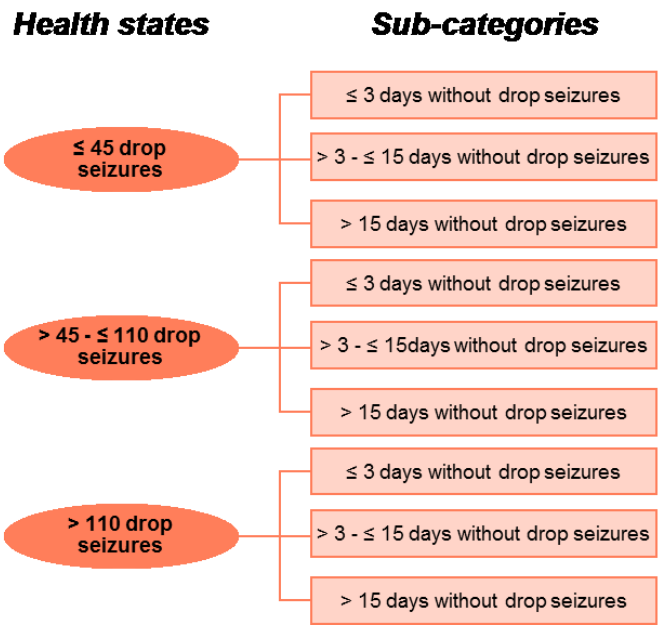
Since improvements in QoL and patient wellbeing can be linked to both reduction in the total number of drop seizures and an increase in the number of seizure-free days, each health state for patients experiencing drop seizures (active treatment and discontinued treatment) was categorised into 3 sub-categories based on the number of seizure-free days experienced in the corresponding health state (Figure 5).

Figure 4: Markov model schematic - B.3.2. (page 58)



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

Figure 5: Heath state sub-categories - B.3.2. (page 59)



A.11 Incorporating clinical evidence into the model

<table>
<tr><th colspan="2">Clinical input and cross reference</th><th>Application in the model</th><th>Validation</th></tr>
<tr><td colspan="4">Cohort definition</td></tr>
<tr><td colspan="2">Age group <12 years:
2-5 years
6-11 years
[B.3.6 (page 94); Revised economic assessment (REA) (page 3)]</td><td rowspan="2">The proportion of patients, mean age and median weight were determined for the four age groups.
Clinical outcomes, costs and resource use were calculated for the <12 years and ≥12 years age groups.</td><td rowspan="2">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.
Demographic characteristics and all clinical efficacy and safety outcomes were obtained from the patient level data (PLD) analysis of the GWEP1414 and GWEP1423 studies and were validated by clinical experts.</td></tr>
<tr><td colspan="2">Age group ≥12 years:
12-17 years
18-55 years
[B.3.6 (page 94); REA (page 3)]</td></tr>
<tr><td colspan="4">Disease severity and health states</td></tr>
<tr><td>Seizure-free</td><td>N/A</td><td rowspan="10">The health states in the current analysis were defined based on the total number of drop seizures per month. The model includes mutually exclusive health states that are based on the following four categories of seizure frequency and an all absorbing health state for death:
1. Seizure-Free
2. ≤ 45 drop seizures per month
3. > 45 - ≤ 110 drop seizures per month
4. > 110 drop seizures per month
As improvements in quality of life and patient wellbeing can be linked to both the reduction in the total number of drop seizures and an increase in the number of seizure-free days, each health state for patients experiencing drop seizures (active treatment and discontinued treatment) was categorised into three sub-categories based on the number of seizure-free days experienced in the corresponding health state.</td><td rowspan="10">The upper and lower bounds of these severity groups were determined in such a way so as to ensure the patients enrolled in GWEP1414 and GWEP1423 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 three distinct severity groups determined for the number of seizures and seizure-free days were also validated by clinical experts.
Based on the patient level data (PLD) analysis of the GWEP1414 and GWEP1423 studies and validated by clinical experts</td></tr>
<tr><td rowspan="3">≤ 45 drop seizures
[B.3.6 (pages 94-95)]</td><td>≤ 3 seizure free days</td></tr>
<tr><td>> 3 - ≤ 15 seizure free days</td></tr>
<tr><td>> 15 seizure free days</td></tr>
<tr><td rowspan="3">> 45 - ≤ 110 drop seizures
[B.3.6 (pages 94-95)]</td><td>≤ 3 seizure free days</td></tr>
<tr><td>> 3 - ≤ 15 seizure free days</td></tr>
<tr><td>> 15 seizure free days</td></tr>
<tr><td rowspan="3">> 110 drop seizures
[B.3.6 (pages 94-95)]</td><td>≤ 3 seizure free days</td></tr>
<tr><td>> 3 - ≤ 15 seizure free days</td></tr>
<tr><td>> 15 seizure free days</td></tr>
</table>

Clinical input and cross reference		Application in the model	Validation
Treatments used			
Cannabidiol dosage: 10 mg/kg/day [B.3.6 (page 95)]		The base case analysis utilises the recommended 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 recommended dose of up to 20 mg/kg/day based on individual clinical response and tolerability.	Based on the recommended dose for cannabidiol in the SmPC
Current Clinical Management [B.3.6 (page 95)]	Valproate Clobazam Lamotrigine Rufinamide Topiramate Levetiracetam	The CCM 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. The NICE scope includes felbamate, ketogenic diet and vagus nerve stimulation as potential comparators. However, these treatments were not considered within this economic analysis. As patients in both the treatment and comparator arms are assumed to receive the same CCM, the exclusion of these interventions from the current analysis will have no impact on the incremental cost-effectiveness ratios (ICERs).	Validated by clinical experts and in line with NICE scope
Transition probabilities			
Transition probabilities for cycle 1 [B.3.6 (page 95)]		Transition probabilities for the first cycle were derived from the GWEP1414 and GWEP1423 Phase 3 trials, for both the treatment and comparator arms. For cycles two to nine, transition probabilities for the treatment arm were estimated using the open label extension study, GWEP1415. After cycle nine, the base case analysis assumed that patients stay in the same health state for the remaining duration of the analysis. After cycle one, patients treated with CCM were assumed to revert to baseline efficacy rates and remain in the same health states for the remaining duration of the analysis.	Based on the patient level data (PLD) analysis of the GWEP1414, GWEP1423 and GWEP1415 studies and validated by clinical experts
Transition probabilities for cycle 2 to cycle 9 [B.3.6 (page 95)]			
Transition probabilities beyond cycle 9 [B.3.6 (page 95)]			
Treatment discontinuation			
Treatment discontinuation rate for cycle 1 [B.3.6 (pages 98-99); REA (pages 4-7)]		A flat discontinuation rate was applied for all health states in the first cycle, using the overall treatment withdrawal rates as observed for each age group (<12	This is a conservative assumption and has been validated by clinical experts

Clinical input and cross reference		Application in the model	Validation
Treatment discontinuation rate for cycle 2 to cycle 9 [B.3.6 (pages 98-99); REA (pages 4-7)]		and ≥12 years old) in the Phase 3 trials. Patients who withdraw from cannabidiol were 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. For cycles two to nine, time-dependent treatment discontinuation probabilities were estimated using the open label extension study, GWEP1415. For seizure-free patients only, a nominal 0.5% discontinuation rate per cycle was assumed as a conservative estimate. Longer term discontinuation rates (cycle 10 onwards) have been applied to account for real-world persistence on treatment.	
Treatment discontinuation rate beyond cycle 9 [B.3.6 (pages 98-99; REA (pages 4-7)]			
Mortality			
All-cause age-dependent mortality rate [B.3.3 (page 71-72)]		The 3-month all-cause age-dependent probability of death was implemented in all health states.	Validated by clinical experts
SUDEP and non-SUDEP deaths [B.3.6 (page 99); REA (pages 8-9)]		Additional risk associated with LGS-specific mortality was applied. The SUDEP and non-SUDEP rates were assumed to be the same as in Dravet syndrome patients (due to a lack of LGS-specific data) and were obtained from the published literature. The 3-month probability was assumed to increase with the number of seizures experienced.	
Adverse events			
Treatment-emergent adverse events of special interest [B.3.6 (page 100); REA (pages 8-9)]	Rash, Somnolence, Fatigue, Lethargy, Sedation, Diarrhoea, Decreased appetite, Aggression, Irritability	Treatment-emergent adverse events of special interest were included in the base case analysis. The incidence rates estimated for the first cycle were assumed to remain the same up to cycle 9.	Based on the patient level data (PLD) analysis of Phase 3 trials for LGS and DS (GWEP1332B, GWEP1424, GWEP1414 and GWEP1423) and validated by clinical experts
Abbreviations: LGS, Lennox-Gastaut syndrome; mg, milligram; PLD, patient level data; SUDEP, sudden unexpected death in epilepsy.			

A.12 Key model assumptions and inputs

Table 4 Key model assumptions and inputs

Parameter	Assumption	Rationale
Time horizon [B.3.6 (page 104)]	15 years	Appropriate timeline to assess costs and benefits associated with the intervention.
Active treatment dosage [B.3.6 (page 104)]	All patients receive 10 mg/kg/day	This is the maintenance dose from the Epidyolex® SmPC
Treatment efficacy [B.3.6 (page 104)]	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 remain in the same health states for the remaining duration of the analysis.	This assumption was considered appropriate as patients in the GWEP1414 and GWEP1423 Phase III 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 [B.3.6 (pages 104-105); REA (pages 4-7)]	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 SOC).	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.
	Longer term discontinuation rates (cycle 10 onwards) were applied to account for real-world persistence on treatment.	Based on conservative 'stopping rule' assumptions' and real-world data from an Early Access Program.
	In the base case analysis, patients discontinuing cannabidiol were assumed to stop benefiting from the treatment effect immediately (they revert to baseline seizure rates and seizure-free day rates).	This is a conservative assumption and has been validated by expert opinion.
CCM basket [B.3.6 (page 105)]	The model assumes the same CCM basket for the treatment and comparator arm (i.e. same drugs).	This is a conservative assumption
	The patients receiving cannabidiol are also assumed to benefit from a reduction in the dose of adjuvant concomitant AEDs.	Published evidence and clinical opinion
Quality of life [B.3.6 (page 105)]	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 the VAS scale was used in the economic model.
Mortality [B.3.6 (page 105)]	Patients with a higher number of seizures were assumed to be at greater risk of death compared to those with fewer seizures.	Published evidence and clinical opinion

Parameter	Assumption	Rationale
Resource use associated with disease management [B.3.6 (page 105)]	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 [B.3.6 (page 105); REA (pages 9-10)]	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 (2% probability), 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

A.13 Base-case ICER (deterministic)

Over a time horizon of 15 years, cannabidiol in addition to CCM was associated with a QALY gain of 2.84 and a total overall cost of £140,706 per patient. In contrast, CCM alone was associated with a total QALY of 1.26 and a total overall cost of £91,799.

Therefore, the resulting Incremental Cost-Effectiveness Ratio (ICER) versus CCM alone is £30,970 per QALY gained.

Table 5 Base-case results (deterministic) – Revised economic assessment (REA) (pages 11-12)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM	£91,799	1.26	-	-	-
CBD + CCM	£140,706	2.84	£48,907	1.58	£30,970

A.14 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). Additionally, the PSA included key parameters such as the transition probabilities, patient characteristics (weight), drug dosage, utilities and disease management costs; 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 Section B.3.8, pages 109-110 and the REA, pages 18-19.

Table 6 PSA results compared to base case - REA (page 20)

	Costs		QALYs		ICERs	
	Base case	**PSA**	**Base case**	**PSA**	**Base case**	**PSA**
CCM + CBD	£140,706	£140,136	2.84	2.83	£30,970	£31,107
CCM	£91,799	£91,822	1.26	1.27	-	-

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

Figure 6 Scatterplot of probabilistic results - REA (page 21)

A.15 Key sensitivity and scenario analyses

A.15.1 *Deterministic sensitivity analysis*

A series of parameters were tested in one-way sensitivity analysis. 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 parameters included in the DSA are presented in the REA (pages 13-15). The Tornado diagram is presented in Figure 7

Figure 6.

Figure 7 Tornado diagram - REA (page 16)

A.15.2 *Scenario analysis*

Uncertainty around the following structural and parametric assumptions has been tested in scenario analyses. The parameters included in the scenario analysis are presented in REA (pages 13-15).

Results for the key scenario analyses are presented in Table 7.

Table 7 Key scenario analyses - REA (pages 25-26)

			CCM + CBD		CCM		
Parameter	**Base case**	**Scenario analyses**	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case	N/A	N/A	£140,706	2.84	£91,799	1.26	£30,970
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	Document B, Table 26	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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the resource use in the management of the disease							
No variation in healthcare resource	Document B, Table 30	No variation across seizure categories	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

			CCM + CBD		CCM		
Parameter	**Base case**	**Scenario analyses**	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
use (number of visits and hospital admissions) across seizure groups		(number of visits for >45 - ≤ 110 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)					
		No variation across seizure categories (number of hospital admissions for >45 - ≤ 110 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]
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)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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]

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

A.16 Innovation

Current guidelines for LGS recommend the use of AEDs developed more than 20 years ago. Seizure control remains inadequate: >90% of children with LGS do not respond to or are intolerant to currently available AEDs.

Epidyolex is the first cannabidiol medicine under review by EMA for the treatment of LGS. It is the first cannabinoid in class, with a novel, multi-modal mechanism of action, different to that of other AEDs.

In addition to demonstrating reductions in seizure frequency, CBD has demonstrated drop seizure-freedom and/or additional seizure-free days. For patients with LGS and their families/caregivers, a period of seizure-free time 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, patients and families can undertake ‘everyday’ activities previously considered unthinkable, such as playing outside, learning new skills, visiting relatives or going on holiday.

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

For further information, see B.2.12 (page 48-50).

A.17 Budget impact

The budget impact analysis (BIA) evaluated a world where patients receive cannabidiol as an adjunctive treatment to current clinical management (CCM) and a world without cannabidiol, where patients only receive CCM.

The inputs and assumptions implemented are described in sections 3-6 of the Budget Impact Analysis and in the revised Budget Impact Analysis. The base case results are presented in Table 8.

Table 8: Budget impact – updated BIM report (page 13)

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population for treatment with cannabidiol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population expected to receive cannabidiol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway without cannabidiol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway with cannabidiol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A.18 Interpretation and conclusions of the evidence

LGS is a rare, devastating and life-threatening form of epilepsy associated with refractory seizures and poor outcomes. In addition to the high seizure burden and high risk of mortality, it results 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.

Even with current clinical management, there remains a significant unmet need for treatments that reduce seizure frequency, improve the overall condition of patients with LGS and reduce carer burden, without further increasing adverse events.

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

Cannabidiol offers patients with LGS 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.

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

The base case results of the *de novo* cost-utility model show that cannabidiol plus CCM is associated with an incremental cost per QALY gained of £30,970.

The core strength of the 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 clinical experts in order to ensure that all assumptions and parameters were clinically relevant to the UK setting. Furthermore, uncertainty in the model inputs and assumptions have been explored in sensitivity analyses to test the robustness of the base case results.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome [ID1308]

Revised economic assessment

May 2019

File name	Version	Contains confidential information	Date
ID1308 Revised economic assessment CBD in LGS 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 Lennox-Gastaut Syndrome (LGS).

This document is intended to be read in conjunction with Document B "Company evidence submission: Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome [ID1308]". 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 (p62) Table 16 (p64)	COHORT DEFINITION	B5a/b.	Data on file: Patient level data GWPCARE3 and GWPCARE4	Section 7

Due to outliers, patient weights at baseline in the GWPCARE3 and GWPCARE4 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 drop seizures per 28 days				
≤45 drop seizures per 28 days	[redacted]		[redacted]	
>45 - ≤110 drop seizures per 28 days	[redacted]		[redacted]	
>110 drop seizures per 28 days	[redacted]		[redacted]	
Health state allocation at baseline: Number of days without drop seizures per 28 days				
≤45 drop seizures				
≤3 days	[redacted]		[redacted]	
>3 - ≤15 days	[redacted]		[redacted]	
>15 days	[redacted]		[redacted]	
>45 - ≤110 drop seizures				
≤3 days	[redacted]		[redacted]	
>3 - ≤15 days	[redacted]		[redacted]	
>15 days	[redacted]		[redacted]	
>110 drop seizures				
≤3 days	[redacted]		[redacted]	
>3 - ≤15 days	[redacted]		[redacted]	
>15 days	[redacted]		[redacted]	

Treatment discontinuation

Document B	Excel Tab	ERG Questions	Source
B.3.3 Clinical parameters and variables (p70)	DISCONTINUATION	A20, B10c, B12a, B12d, B26a	Data on file: Patient level data GWPCARE3 and GWPCARE4 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 GWPCARE3 and GWPCARE4 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 GWPCARE3 and GWPCARE4 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 GWPCARE3, 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 no discontinuations observed in the patients who were seizure-free throughout the study. This 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 ">110 drop 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 drop 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 110 drop seizures per month after 2 years would continue, whilst all those experiencing 111 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 “>45 - ≤110 drop 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 very 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 “≤45 drop seizures”:

- A discontinuation rate of [redacted] per cycle has been implemented, as measured from patient level data for patients with LGS from the April 2017 readout of the US Early Access Program for cannabidiol. This dataset reports treatment withdrawals over up to 34 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 "drop 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]
	≤45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>45 - ≤110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 mg	Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>45 - ≤110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events

Document B	Excel Tab	ERG Questions	Source
B.3.3 Clinical parameters and variables (p72) Table 22 (p73) B.3.5 Cost and healthcare resource use identification, measurement and valuation (p93)	SAFETY	B15a/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

Document B	Excel Tab	ERG Questions	Sources
NA	BASE CASE RESULTS	B27	N/A

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 (p71)	MORTALITY	B1b. B14.	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 drop seizure-free patients may still be at risk of death due to epilepsy. Mortality rate assumptions in the updated model are shown in Table 3.

The mortality rate in the drop 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 (>45 - ≤110 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†
≤45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>45 - ≤110 seizures	0.23%**	0.16%**	0.23%**	0.16%**	[redacted]
>110 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 (p90). Table 30 (p91)	COSTS	B19a/b.	Assumption

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

The original assumption was that 10% of adult patients in health states with drop seizures would be institutionalised. For drop 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%
≤45 seizures	0%	10%
>45 - ≤110 seizures	0%	10%
>110 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 (p74). Appendix H	UTILITIES	B17d	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: 130 drop seizures per month and 3 seizure-free days
- A moderately severe health state: 80 drop seizures per month and 15 seizure-free days
- A drop 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 (>110 drop seizures) and “middle” (>45 - ≤110 drop 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	-
≤45 seizures	≤3 seizure-free days	-
	>3-≤15 seizure-free days	-
	>15 seizure free days	-
>45 - ≤110 seizures	≤3 seizure-free days	[redacted]
	>3-≤15 seizure-free days	[redacted]
	>15 seizure free days	[redacted]
>110 seizures	≤3 seizure-free days	[redacted]
	>3-≤15 seizure-free days	[redacted]
	>15 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 a total QALY of 2.84 and a total overall cost of £140,706 per patient. In contrast, CCM alone was associated with a total QALY of 1.26 and a total overall cost of £91,799.

Cannabidiol in addition to CCM is therefore associated with an incremental QALY gain of 1.58 and an incremental cost of £48,907 per patient.

This is an Incremental Cost-Effectiveness Ratio (ICER) versus CCM alone of £30,970 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 + placebo	£91,799	1.26	-	-	-
CCM + CBD	£140,706	2.84	£48,907	1.58	£30,970

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	£140,706	£91,799	£48,907
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 (p113) Table 39 (p113)	DSA	B26a.	Various	SAS 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 GWPCARE3 & 4 studies, using 40th and 60th percentiles Section 7 Appendix
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 3,4,5	-10%	+10%	Assumption applied to base case rates for all cycles
Management Unit Costs				
Visits Costs	Between £106 and £2344	-20%	+20%	Assumption
Hospitalisation Costs	Between £0 and £969	-20%	+20%	Assumption
Rescue Med Costs	Between £0 and £54	-20%	+20%	Assumption

Parameter	Base Case	Lower Bound	Upper Bound	References
Institutionalisation Costs	Between £0 and £1604	-20%	+20%	Assumption
Daily Cost ICU				
Adults	£1,299	£643	£4,482	Tables 33 & 39 of Document B
Paediatric	£1,583	£784	£5,867	
Daily Cost General Ward				
Adults	£460	£402	£807	Tables 33 & 39 of Document B
Paediatric	£597	£560	£760	
Phone Call Follow-up				
Neurologist	£107	£57	£153	Tables 33 & 39 of Document B
Paediatric neurologist	£258	£55	£234	
Emergency Department Visit				
Per episode	£237	£56	£838	Tables 33 & 39 of Document B
Non-SUDEP costs, days in ICU				
2 - 11 years	7.00	-20%	+20%	Tables 33 & 39 of Document B
12 - 55 years	7.00	-20%	+20%	
% of institutionalisation				
Seizure-Free	2.00%	0.00%	10.00%	Tables 33 & 39 of Document B
≤45 seizures	10.00%	0.00%	20.00%	
>45 - ≤110 seizures	10.00%	0.00%	20.00%	
>110 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%	
≤45 seizures				
2 - 11 years	0.60	-10%	+10%	Assumption
12 - 55 years	0.60	-10%	+10%	
>110 seizures				
2 - 11 years	1.40	-10%	+10%	Assumption
12 - 55 years	1.40	-10%	+10%	
SUDEP – Probabilities				
>45 - ≤110 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%	
≤45 seizures				
2 - 11 years	0.60	-10%	+10%	Assumption

Parameter	Base Case	Lower Bound	Upper Bound	References
12 - 55 years	0.60	-10%	+10%	
>110 seizures				
2 - 11 years	1.40	-10%	+10%	Assumption
12 - 55 years	1.40	-10%	+10%	
Non-SUDEP – Probabilities				
>45 - ≤110 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; >15 days	[redacted]	[redacted]	[redacted]	Based on standard errors from vignette study Table 26 of Document B
≤45 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
≤45 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	
≤45 seizures; >15 days	[redacted]	[redacted]	[redacted]	
>45 - ≤110 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
>45 - ≤ 110 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	
>45 - ≤110 seizures; >15 days	[redacted]	[redacted]	[redacted]	
>110 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
>110 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	
>110 seizures; >15 days	[redacted]	[redacted]	[redacted]	
Caregiver utility decrements				
Seizure-Free; >15 days	[redacted]	[redacted]	[redacted]	Based on standard errors from vignette study
≤45 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
≤45 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	
≤45 seizures; >15 days	[redacted]	[redacted]	[redacted]	
>45 - ≤110 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
>45 - ≤110 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	
>45 - ≤110 seizures; >15 days	[redacted]	[redacted]	[redacted]	
>110 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
>110 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	
>110 seizures; >15 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
≤45 seizures		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
>45 - ≤110 seizures		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
>110 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
	≤45 seizures	£675	£337	£1,012	172.13	15.37	43.91	Gamma
	>45 - ≤110 seizures	£1,380	£690	£2,070	352.08	15.37	89.82	Gamma
	>110 seizures	£2,344	£1,172	£3,515	597.84	15.37	152.51	Gamma
12 - 55 years	Seizure-Free	£106	£53	£160	27.14	15.37	6.92	Gamma
	≤45 seizures	£235	£118	£353	60.01	15.37	15.31	Gamma
	>45 - ≤110 seizures	£381	£191	£572	97.30	15.37	24.82	Gamma
	>110 seizures	£718	£359	£1,077	183.23	15.37	46.74	Gamma
Hospitalisation Costs								
2 - 11 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤45 seizures	£242	£121	£364	61.83	15.37	15.77	Gamma
	>45 - ≤110 seizures	£606	£303	£909	154.58	15.37	39.43	Gamma
	>110 seizures	£969	£485	£1,454	247.32	15.37	63.09	Gamma
12 - 55 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤45 seizures	£63	£31	£94	16.01	15.37	4.08	Gamma
	>45 - ≤110 seizures	£157	£78	£235	40.02	15.37	10.21	Gamma
	>110 seizures	£251	£125	£376	64.03	15.37	16.33	Gamma
Rescue Med Costs								
2 - 11 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤45 seizures	£14	£7	£20	3.47	15.37	0.89	Gamma
	>45 - ≤110 seizures	£34	£17	£51	8.67	15.37	2.21	Gamma
	>110 seizures	£54	£27	£82	13.88	15.37	3.54	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
	≤45 seizures	£14	£7	£20	3.47	15.37	0.89	Gamma
	>45 - ≤110 seizures	£34	£17	£51	8.67	15.37	2.21	Gamma
	>110 seizures	£54	£27	£82	13.88	15.37	3.54	Gamma
Institutionalisation Costs								
18 - 55 years	Seizure-Free	£321	£160	£481	81.86	15.37	20.88	Gamma
	≤45 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
	>45 - ≤110 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
	>110 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
12 – 55 years	>45 - ≤110 seizures	0.23%	0.11%	0.49%	0.00	5.80	0.00	Gamma
Utilities								
Patient utilities - Values estimated based on SE								
No seizures	>15 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
≤45 seizures	≤3 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>3 - ≤15 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>15 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
>45 - ≤110 seizures	≤3 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>3 - ≤15 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>15 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
>110 seizures	≤3 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>3 - ≤15 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
	>15 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Beta
Caregiver utility decrements – values based on SE								
>45 - ≤110 seizures	≤3 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Gamma
	>3 - ≤15 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Gamma
	>15 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Gamma
>110 seizures	≤3 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Gamma
	>3 - ≤15 days	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	Gamma
	>15 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 GWPCARE3, GWPCARE4 and GWPCARE5 studies.

[redacted] bootstrap samples (the same sample size as the trials) were drawn independently from the GWPCARE3 and GWPCARE4 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.

Table 10 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	£140,706	£140,136	2.84	2.83	£30,970	£31,107
CCM	£91,799	£91,822	1.26	1.27	-	-

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 B22a/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 drop seizure frequency on 10mg/kg/day in GWPCARE3 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 GWPCARE3)	[redacted]	[redacted]
Patients receiving 20 mg/kg/day (≥75% response in GWPCARE3)	[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 25 p83 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		
	≤3 days	>3 - ≤15 days	>15 days	≤3 days	>3 - ≤15 days	>15 days
Seizure-Free	-	-	[redacted]	-	-	[redacted]
≤45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>45 - ≤110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>110 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	£140,706	2.84	£91,799	1.26	£30,970
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 GWPCARE3. 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 26 p84 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 p91 Document B	No variation across seizure categories Visits for >45 - ≤110 seizures applied to all other seizure groups in the corresponding age group. Seizure-free same as the base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

			CCM + CBD		CCM		
Parameter	**Base case**	**Scenario analyses**	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Number of hospital admissions	Table 30 p91 Document B	No variation across seizure categories Hospitalisations for >45 - ≤110 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] ≤45 seizures [redacted] >45 - ≤110 seizures [redacted] >110 seizures [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Both age groups: Seizure-Free [redacted] ≤45 seizures [redacted] >45 - ≤110 seizures [redacted] >110 seizures [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying the approach to modelling mortality risk							
Epilepsy-related mortality	According to clinical opinion	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 drop seizure frequencies and not seizure frequency reductions, we validated outcomes from the model against those from the GWPCARE trials for the endpoints of drop seizure-freedom and mortality.

Proportion of drop seizure-free patients in the cannabidiol arm

The proportion of drop 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 (GWPCARE3 10mg/kg/day arm)	[redacted]	-
Seizure-Free (GWPCARE5)	[redacted]	[redacted]

Mortality

The disease-specific mortality rate in DS (used as an analogue for LGS) 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, >15 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤45 seizures, ≤3 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤45 seizures, >3 - ≤15 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤45 seizures, >15 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>45 - ≤110 seizures, ≤3 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>45 - ≤110 seizures, >3 - ≤15 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>45 - ≤110 seizures, >15 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>110 seizures, ≤3 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>110 seizures, >3 - ≤15 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>110 seizures, >15 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 17: Summary of costs by health state

Health state	Cost comparator (CCM)	Cost intervention (CCM + CBD)	Increment	Absolute Increment	% absolute increment
Seizure-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>45 - ≤110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£91,799**	**£140,706**	**£48,907**	**£48,907**	-

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	£3,299	£3,815	£1,294	£1,523	£117	£138	£1,966	£2,014	£6,676	£7,490
2	£2,844	£3,714	£1,097	£1,488	£101	£134	£1,798	£1,915	£5,839	£7,251
3	£2,440	£3,187	£924	£1,263	£94	£127	£1,696	£1,821	£5,155	£6,399
4	£1,574	£2,065	£555	£775	£85	£121	£2,550	£2,728	£4,764	£5,690
5	£1,553	£1,958	£551	£735	£85	£115	£2,732	£2,913	£4,920	£5,721
6	£1,518	£1,856	£542	£697	£83	£109	£2,605	£2,770	£4,749	£5,432
7	£1,475	£1,760	£530	£660	£82	£103	£2,484	£2,634	£4,571	£5,157
8	£1,150	£1,370	£396	£494	£78	£98	£2,368	£2,505	£3,993	£4,467
9	£1,020	£1,204	£346	£427	£75	£92	£2,573	£2,715	£4,013	£4,438
10	£981	£1,142	£334	£404	£72	£88	£3,360	£3,536	£4,747	£5,169
11	£942	£1,082	£321	£383	£70	£83	£3,202	£3,360	£4,535	£4,909
12	£903	£1,026	£309	£363	£67	£79	£3,051	£3,193	£4,329	£4,661
13	£864	£973	£296	£344	£64	£75	£2,906	£3,034	£4,131	£4,426
14	£826	£922	£284	£326	£61	£71	£3,057	£3,184	£4,229	£4,504
15	£790	£874	£271	£309	£59	£67	£3,004	£3,121	£4,124	£4,372
Total	**£22,177**	**£26,949**	**£8,050**	**£10,194**	**£1,193**	**£1,499**	**£39,354**	**£41,445**	**£70,774**	**£80,087**

Table 21 and Figure 4 below present the impact of cannabidiol on the frequency of seizures when added to CCM. After 15 years, 8.40% of patients who receive cannabidiol in addition to CCM are drop seizure-free compared to 0% when cannabidiol is not added to the treatment.

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%	8.40%	0.00%
≤45 drop seizures	28.79%	28.79%	34.12%	31.66%
>45 - ≤110 drop seizures	34.34%	34.34%	32.15%	34.50%
>110 drop seizures	36.87%	36.87%	25.32%	33.84%

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

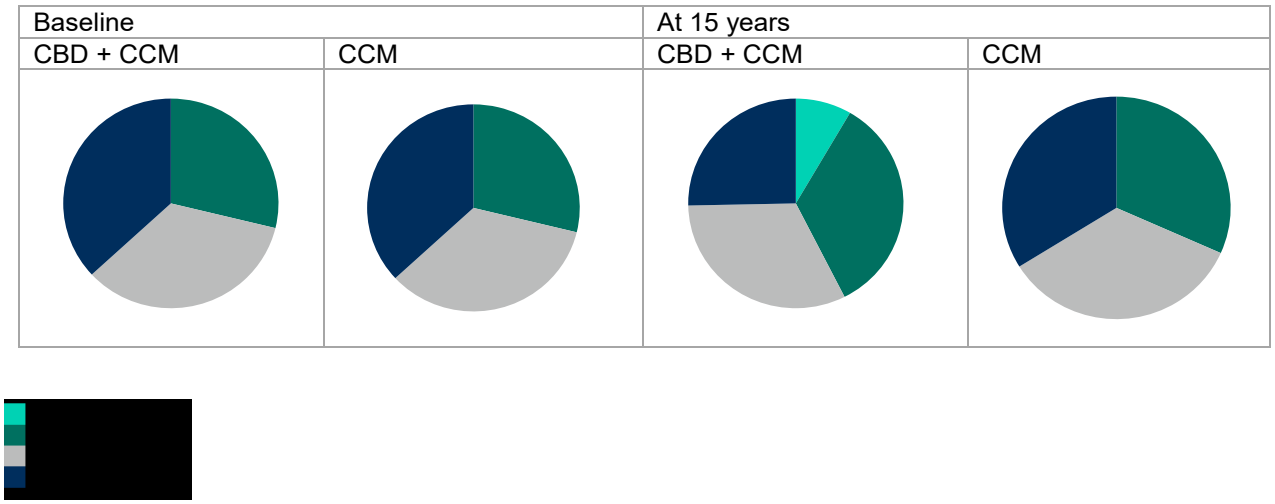


Table 22: Number of deaths after 15 years

	CCM + CBD	CCM	Difference
SUDEP	1,099	1,251	-152
Non-SUDEP	768	874	-106
Background	53	52	1
Total of lives saved	257	-	-

DSA disaggregated results

	CBD + CCM vs. CCM							
Parameter	**Lower limit**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Upper limit**	**Incremental costs**	**Incremental QALYs**	**ICER**
Decrements of utilities (care givers)	[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]
SUDEP mortality (Probability)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emergency Department Visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% of institutionalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visits Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient utilities (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations (all rates)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phone Call Follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily Cost General Ward	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-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]
Institutionalization Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUDEP mortality (RR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-SUDEP mortality (RR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rescue Med Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-SUDEP costs, days in ICU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7 Appendix

SAS tables on weight of patients with LGS

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome [ID1308]

Clarification questions

April 2019

File name	Version	Contains confidential information	Date
ID1308 ERG Clarification Answers LGS 12Apr2019	Final	Yes	12 April 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 in the company submission (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 is anticipated to 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? Is it anticipated that all patients will start with the lower dose? If so, what cut-off for inadequate response to the lower dose would be used?

c. In the long term, are patients expected 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.'

d. Please describe the method and time point of assessment for an increase in maintenance dose.

A1a. It is anticipated that all patients will start with a maintenance dose of 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 in the alternative scenario was estimated by assuming that patients who achieve ≥75% reduction in drop seizures receive 20 mg/kg/day, while patients experiencing <75% reduction in drop seizures receive 10 mg/kg/day. The proportion of responders with ≥75% and <75% reduction in drop seizures was obtained from the Phase 3 clinical trial, GWEP1414 (see Table 41 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.

A1d. See A1b above.

A2. Priority question: The company has added to the population scope 'People with Lennox-Gastaut syndrome (LGS) where current clinical management is unsuitable or not tolerated' (Table 1). 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 LGS patients. For example, NICE CG137 states that carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine and vigabatrin should not be given to patients with LGS as they may worsen seizures.

A3. Priority question: Under 'Placement of CBD within the care pathway' (page 24 of the company submission) and at other points in the document, it is stated that: 'For patients with LGS 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 GWPCARE3 given in Table 5 (taking 1 or more AEDs) and with the prior AED use for GWPCARE3 in table 7 (range across the treatment groups 0 to 22). In addition, the prior use of AEDs in GWPCARE4 ranges from 0 to 28. How many patients had 0 and how many patients had 1 prior AED in each treatment arm of the two trials?

c. The median number of prior AEDs in both trials was 6. 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 GWPCARE3 and GWPCARE4 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 median number of concurrent treatments in the trials was 3 with a range across the trials of 0 to 5. How does this reflect UK clinical practice?

A3a. No.

A3b. The number of patients at baseline in each arm of GWPCARE3 and GWPCARE 4 on 0, 1, and ≥2 prior AEDs is shown in the table below.

Prior AEDs (no longer taking) at baseline GWPCARE3 and GWPCARE4

		Prior AEDs (no longer taking)		
		10 mg/kg/day	20 mg/kg/day	Placebo
	No. AEDs	n=73	n=76	n=76
GWPCARE 3 (1414)	0	1 (1.4%)	0	0
	1	2 (2.7%)	5 (6.6%)	3 (3.9%)
	≥2	70 (96%)	71 (93%)	73 (96%)
			n=86	n=85
GWPCARE 4 (1423)	0		0	1 (1.2%)
	1		4 (4.7%)	3 (3.5%)
	≥2		82 (95%)	81 (95%)

The number of patients in each arm of GWPCARE3 and GWPCARE 4 on 1, 2, and ≥3 current AEDs is shown in the table below.

Concomitant AEDs in GWPCARE3 and GWPCARE4

		Concomitant AEDs		
		10 mg/kg/day	20 mg/kg/day	Placebo
	No. AEDs	n=73	n=76	n=76
GWPCARE 3 (1414)	1	0	1 (1.3%)	0
	2	4 (5.5%)	4 (5.3%)	5 (6.6%)
	≥3	69 (94.5%)	71 (93.4)%	71 (93.4%)
			n=86	n=85
GWPCARE 4 (1423)	1		0	0
	2		5 (5.8%)	5 (5.9%)
	≥3		81 (94.2%)	80 (94.1%)

A3c. No. More than 90% of children with LGS have drug-resistant epilepsy [Ostendorf 2017]. 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.

In the clinical trials, patients were currently treated with a median of 3 AEDs, and had previously been treated with a median of 6 AEDs, at baseline. This is an artefact of the population that could be recruited into clinical trials and does not reflect the inclusion criteria in studies, or where clinical need lies in treatment practice. Patients with LGS are highly drug refractory [Ostendorf 2017, Panayiotopolus 2005]. As such, the standing population in clinical practice, from which trial patients were recruited, has been extensively treated. Recently diagnosed children with LGS 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 LGS GWPCARE trials are shown below.

A3e. Patients were having seizures not controlled by their current AEDs. In GWPCARE3 and GWPCARE4, patients were taking 1 or more AEDs at a dose that had been stable for at least 4 weeks, and were still having at least 2 drop seizures each week during the first 28 days of the baseline period. 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. More than 90% of children with LGS have drug-resistant epilepsy. As a result, physicians use a variety of medical, surgical and dietary approaches in an attempt to control seizures, and polypharmacy 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 LGS and Dravet syndrome submissions. The PRISMA flow chart appears to indicate that 59 studies were included for clinical effectiveness in the LGS population.

a. Please confirm whether this figure refers to LGS only (i.e. does not include Dravet syndrome).

b. Please confirm the correct number of included studies (there appear to be 15 in Table 45) and the number of publications (there appear to be 61 in Table 45).

c. Table 44, 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 45).

A4a. The PRISMA diagram is specific to LGS only; studies that were relevant to DS only are reported as excluded in the PRISMA.

A4b. Two Phase 3 studies of CBD (GWPCARE3/GWEP1414 and GWPCARE4/ GWEP1423) 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 22 publications, which are listed in the first three rows of Table 45 in Document B.

Table 45 also lists other RCTs of drug treatments for LGS, 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 12 clinical trials of other drug treatments in LGS, reported in a total of 39 publications.

A4c. 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 LGS. 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 43 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 clarify why the abbreviation "LGS" was not included in any of the searches.

b. Please check the PubMed strategy reported in Table 43 for errors where truncation (*) has been incorrectly applied within specific phrases ("") e.g. "Dravet* syndrome"

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

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

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

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

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

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

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

j. Please clarify whether Database of Abstracts of Reviews of Effects (DARE) was searched either via the Cochrane Library or CRD. DARE was not reported as a source in Section D1.1, however it was referred to in Table 43. 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 to include the term LGS, as well as correcting the truncation issues identified in point A8b. This search identified 19 new papers (after deduplication) that were not originally 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 06/02/19 to include the term LGS, as well as correcting the truncation issues identified here. 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. The PubMed search was re-run on 06/02/19 to include the term LGS, as well as correcting the truncation issues identified in point A8b. 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.

A8d. This search was re-run on 06/02/2019 with (title) change to (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.

A8e. 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.

A8f. 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.

A8g. 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.

A8h. 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.

A8i. We searched the Reviews and Trials sections of the Cochrane library.

A8j. DARE was searched via 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 the choice of the individual patient / caregiver?

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

c. How is the relatively large placebo response across the trials explained?

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 LGS in the cannabidiol clinical trials were children and young adults with a broad spectrum of abilities, some 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, and have been observed in LGS studies for lamotrigine, topiramate, felbamate, rufinamide and clobazam going back to the early 1990s [Ostendorf 2017].

A comparison of placebo effects between trials is challenging given the high levels of heterogeneity in study designs [Goldenholz 2016]. Nonetheless, a numerical comparison on the primary endpoint (median percent change in drop seizure frequency from baseline) suggests that GWPCARE3 (which studied the maintenance dose of 10mg/kg/day) has a placebo effect that is 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 is 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 LGS.

In GWPCARE3, an 18% median reduction in drop-seizure frequency was assumed in the placebo group for the determination of sample size. The final outcome was 17.17% and, as such, there was sufficient statistical powering. 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 for 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 OLE 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 LGS 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.

Included trials: patient characteristics

A10. Priority question: How similar does the company consider the patients in GWPCARE3, GWPCARE4 and GWPCARE5 to be compared to patients seen in practice in England and Wales? Have any clinical experts commented on this issue?

It is expected that the patients in these studies will be very similar to those seen in practice in England and Wales.

GWPCARE3 included patients from the UK, the USA, Spain and France.

GWPCARE4 included patients from the USA, Netherlands and Poland.

GWPCARE5 is an ongoing, open-label extension of GWPCARE1 (Dravet syndrome), GWPCARE2 (Dravet syndrome), GWPCARE3 (LGS) and GWPCARE4 (LGS).

A11. Priority question: Please provide patient level data showing baseline total seizure frequency and concurrent AEDs at baseline for each patient in each treatment group of GWPCARE 3 and GWPCARE4. An example table using fictional data is given below.

See the separate document provided ("Patient Level Data LGS DS.xlsx").

Included trials: efficacy results

A12. Priority question: Please provide full results, for all outcomes assessed, for GWPCARE3 and GWPCARE4. Results are currently missing for many of the outcomes listed in Table 6 for these studies (e.g. Change from baseline in Quality of Childhood Epilepsy questionnaire score, Frequency of status epilepticus episodes).

Please refer to CSRs and the separate document provided ("Detailed Responses A12, A13, A18, A19 and A20").

A13. Priority question: The results provided in tables 11 and 12 are incomplete. Baseline and endpoint (e.g. 14 weeks) measures are needed for all outcomes. Please ensure that all medians are presented with an associated interquartile range (IQR).

Please refer to CSRs and separate document provided (Detailed Responses A12, A13, A18, A19 and A20").

A14. Priority question: Please ensure that all outcomes are reported clearly indicating whether differences between treatment groups are statistically significant. For example it is not sufficient to state that 'A higher proportion of patients in the 20 mg CBD group achieved at least a 75% reduction in drop seizures (25%) compared with the 10 mg group (11%) and the placebo group (3%)' (Page 37). Please provide full statistical measures (e.g. median/mean difference or odds ratio with 95% confidence intervals).

No formal pre-specified test for significance between the CBD groups was included in the SAPs.

A15. Priority question: For GWPCARE3, 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.

A16. Priority question: On page 43 of the company submission it is stated that 'no subgroup analyses were conducted.' However, on page 56 it is stated that '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).' Please provide these subgroup analyses?

The primary and key secondary endpoints were analysed in the following pre-specified subgroups for both GWPCARE3 and GWPCARE4. The sources are shown in the table below.

- Age group (2-5 years, 6-11 years, 12-17 years and 18-55 years)
- Sex (Male, Female)
- Region (US, Rest of the World)
- Clobazam use (Yes, No)
- Valproate use (Yes, No)
- Lamotrigine use (Yes, No)
- Levetiracetam use (Yes, No)
- Rufinamide use (Yes, No)
- Baseline average drop 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 (< 6, ≥ 6).

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
GWPCARE3	CSR Figure 8.4.1.1.1-1 p140 Figure 8.4.1.5.1-1 p191 Figure 8.4.1.5.1-2 p192 Table 8.4.1.5.2-1 p194 Table 8.4.1.5.2-2 p195 CSR Figures: Figure 9.15 p52
GWPCARE4	CSR Figure 8.4.1.1.1-1 p124 CSR Figure 8.4.1.4.1-1 p164 CSR Table 8.4.1.2.2.16-1 p165 CSR Figures: Figure 9.15 p51

A17. Priority question: In the company submission 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%.' Is there any data on reduction in medication use from GWPCARE 3, GWPCARE 4 or GWPCARE 5? If so, please provide this.

In GWPCARE3 and GWPCARE4, 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 (see Table 28 in Document B).

Included trials: safety results

A18. Priority question: Appendix F provides a full breakdown of adverse events for GWPCARE4. – Please provide the same for GWPCARE3 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 A12, A13, A18, A19 and A20").

A19. Priority question: Please provide a detailed breakdown of the serious adverse events (SAEs) (i.e. any untoward medical occurrence 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 GWPCARE3, GWPCARE4 and GWPCARE5 including their relationship to treatment.

Please refer to CSRs and separate document provided (Detailed Responses A12, A13, A18, A19 and A20").

A20. Figures 13 and 14 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 A12, A13, A18, A19 and A20").

Ongoing studies

A21. 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].

A22. 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 drop seizures and (drop) seizure-free days per 28 days. However,

based on the clinical data (i.e., GWPCARE3, GWPCARE4, and GWPCARE5), a substantial number of non-drop seizures is reported for both CBD and the current clinical management (CCM) group. Non-drop 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-drop seizures are still occurring in patients in the (drop) 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 LGS. Please adjust the model accordingly.

c. Please justify whether the model structure still adequately represents the natural course of the disease. In your response, please focus on, for example, cognitive decline and the likelihood of becoming seizure-free over time.

B1a. Reduction in drop seizures was the primary endpoint of the trial.

The presence of treatment-intractable seizures (tonic, atonic and tonic-clonic) is a salient feature of LGS, and forms part of the diagnostic criteria for the condition [Berg 2010]. The temporary loss or gain of muscle tone associated with atonic, tonic and tonic-clonic seizures leads to sudden falls which often lead to injury [Arzimanoglou 2011]. Such drop attacks drive the physical morbidity and complications of the condition. As such, the GWPCARE studies, as well as those for other AEDs in patients with LGS, were designed to investigate the impact of CBD on drop seizures; the effect on non-drop 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-drop seizures. Cannabidiol showed a statistically significant mean percentage reduction in total seizures, and an improvement in non-drop 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-drop seizures reduces substantially across drop-seizure-based health states (the median is the most relevant measure due to outliers). As patients spend more time in lower drop-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.

Number of non-drop seizures across drop seizure frequency-defined health states (treatment period)

	Non-drop seizures					
Drop seizures	**N**	**Mean**	**SD**	**Median**	**Min**	**Max**
Seizure-Free*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>45 - ≤ 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Drop-seizure free or ≤1 drop seizure

B1b. We acknowledge that patients in the drop 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 very rare indeed.

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-drop seizures:

- Drop-seizures are accepted as the most clinically relevant seizure type in LGS, driving the physical morbidity and complications of the disease over time
- Patients with LGS rarely achieve complete freedom from all seizures, no matter how good their response is to any given treatment; seizure types not associated with falls often persist. However, achieving freedom from drop-

seizures is still a highly meaningful clinical and patient/caregiver relevant outcome

- Reduced exposure to non-drop seizures, and the consequential gain in QALYS, would be likely on CBD; this is “hidden” upside in the cost-utility outcomes

- Longer-term cognitive and behavioural outcomes are linked to seizure control [Hoffmann-Riem 2000]. However, the independent contributions of drop and non-drop seizures 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 “hidden” upside.

Healthcare resource utilisation levels would be similar whether non-drop seizures are considered or not. The non-drop 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 drop-seizures. As such, costs for non-drop 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 then 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.

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 the CCM.

A placebo response was observed in both GWPCARE3 and GWPCARE4. 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 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 GWPCARE3 and GWPCARE4 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 LGS is that treatment with AEDs is unlikely to control seizures completely [Panayiotopolus 2005], and patients retain a 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 LGS 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. LGS 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 significantly increased risk of deaths in children and young adults versus the general population. In addition, previous economic models in epilepsy from the literature (as described in Appendix G of the submission) 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 wane 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 LGS.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. In the model, treatment costs are based on the average weight by age group (Table 33).

a. Please justify whether the weight per age group in the model is representative for the LGS patient population in the UK.

b. Please validate the mean weight for each age category in the model (e.g. using UK specific data).

c. Please provide the starting age of the cohorts for which the results are presented (i.e. <12 years and ≥12 years)

B5a/b. It is not possible to definitively conclude whether the mean weights at baseline in the clinical trials are representative of those for the LGS 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 GWPCARE3 and GWPCARE 4 trials ([redacted] overall) to use only this subgroup in the model.

However, it is recognised that patients with LGS are generally underweight relative to the general population [Verdian 2010]. A cost-utility study in the UK for rufinamide

in LGS [Verdian 2010] used almost the same weight assumption for an adolescent patient population as the cannabidiol model (42.3 kg versus [redacted] respectively).

As only [redacted] patients out of 396 were from UK centres, UK-specific data have not been used in the model. We have included below a table displaying the mean and median weight of UK patients versus all patients. 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.

B5c. 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 (see Table 16 on page 64). Please find them also in the table below.

Mean starting age in the Phase 3 trials

	Mean age
2 - 5 years	[redacted]
6 - 11 years	[redacted]
12 - 17 years	[redacted]
18 - 55 years	[redacted]

Intervention

B6. 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 GWPCARE4 and the open label study, the focus appears to be on substantial 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?

c. In the pivotal trials, 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). Please justify why a one-week escalation period is assumed in the model.

B6a. 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 118 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 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 or 20 mg/kg/day, and are not intended in the model to represent outcomes on doses above 20mg/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 GWPCARE3 (also seen in DS patients in GWPCARE2), and the greater validity of

using real long-term data from a clinical study rather than extrapolating 14 week outcomes (from GWPCARE3 and GWPCARE4) to more than 2 years in the model.

B6b. See A1a and A1b above.

B6c. For simplicity, no escalation period was assumed in the model; patients are considered to enter the model on their maintenance dose. This will provide an over-estimation of drug costs in the model outcomes relative to real world use.

B7. In the scenario analysis varying the CBD dosage (company submission Table 42), 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).

c. It appears that the cost of 20 mg/kg/day is incorporated only in the first cycle. Please include the price of 20 mg/kg/day in subsequent cycles according to the proportion of patients receiving this dose. Otherwise, please justify why only the price of 10 mg/kg/day is incorporated in subsequent cycles.

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 drop-seizure frequency from baseline during the treatment period (measured as the 28-day mean in 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 118 of Document B). Proportions were used as reported for the endpoint in the CSR tables for the maintenance period in the ITT populations from GWPCARE3 and GWPCARE4, in line with the definition above.

Calculation of mean doses for the scenario analysis

	LGS			Weighted mean mg/kg/day
	1414		1423	
	10mg	20mg	20mg	
n	73	76	86	
75%-responders	[redacted]	[redacted]	[redacted]	[redacted]

The average dose was calculated assuming that everyone who achieved the 75% responder outcome in GWPCARE3 ([redacted]) was moved to a maintenance dose of 20 mg/kg/day, and everyone else ([redacted]) was 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.

B7c. The model does not consider the cost of the 20mg/kg/day dose in the first cycle only; the full drug cost is captured across all cycles via different mechanisms in cycle 1 and subsequent cycles.

In the first cycle, the cost of drug is captured based on a split of patients assigned to each dose. In all subsequent cycles, the cost is captured based on an average per patient dose entered manually. The mean dose per patient based on the split in the first cycle must equal that entered manually for all subsequent cycles (for example, if 50% of patients are allocated to each of the 10 and 20 mg/kg/day doses in cycle 1, then the average dose assumption in all subsequent cycles must be 15 mg/kg/day).

The reason for this is that the first cycle is the only one for which there are data to model transition probabilities separately between the 10 and 20 mg/kg/day treatment arms, as it is based on outcomes from the 14 week Phase 3 trials (GWPCARE3 and GWPCARE4). All subsequent cycles utilise data from the GWPCARE5 open label extension study, which did not randomise patients to a fixed dose but instead allowed physicians to titrate each patient up to an individually optimised dose. Transition probabilities derived from this study are considered to apply equally to patients irrespective of their dose allocation in cycle 1. This assumption is considered optimal in order to utilise the totality of the data available from the clinical studies for CBD.

It is anticipated that, in clinical practice, most patients will be maintained on 10 mg/kg/day, with a minority escalated to the higher dose. As clinicians are not choosing between doses for individual patients prior to treatment initiation, it is meaningful to model the cost-utility only in a population on a mix of doses and not on each dose separately.

In line with expected clinical practice, the base case assumes all patients are on 10 mg/kg/day, and therefore 100% of patients are assigned to this dose in cycle 1, with the average dose in all subsequent cycles set at this level. An alternative scenario assumed [redacted] of patients to be on 10 mg/kg/day, and [redacted] to be on 20 mg/kg/day. These proportions were assigned in cycle 1, and the weighted mean ([redacted] mg/kg/day) was assigned for all subsequent cycles.

Comparator

B8. 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 (GWPCARE3 and GWPCARE4) 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. It is stated 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 AEDs proportions, as shown in Table 17 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 41 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 were preferred above the pivotal trials to inform the AEDs proportions (as shown in Table 17 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 LGS, 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 a 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 17 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 98) of the Unblinded Final Tables in the GWPCARE3 (1414) CSR show usage levels of AEDs amongst patients at baseline in the clinical trial. There are differences: in 1414 clobazam, rufinamide and levetiracetam are over-represented, whilst valproate is 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. GWPCARE3 and GWPCARE4 included [redacted] UK patients, whereas this research included findings from [redacted] treating clinicians with a combined caseload of over 450 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.

B9. Priority question: Contrary to the final scope issued by NICE, (combinations including) felbamate, ketogenic diet and vagus nerve stimulation were not considered as comparators in the cost effectiveness model.

Please include felbamate, 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).

Felbamate. Felbamate is only available in Europe on a patient-by-patient basis due to a risk of aplastic anaemia and acute liver failure. In England, only a very small number of patients have access to felbamate (on a named-patient basis): it is not routinely

commissioned. Felbamate was not given to any UK patients in the LGS trials. For these reasons, it was not considered in the model.

Ketogenic diet: As per Figures 1 and 2 in Document B, ketogenic diet (KD) is an established part of the treatment pathway for LGS, 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 8% of patients were on a KD at baseline in both GWPCARE3 and GWPCARE4. 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 LGS, 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 24% of patients had previously received a VNS implant in GWPCARE3. Proportions were similar for GWPCARE4. 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

B10. 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 GWPCARE4 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 GWPCARE3 trial only, using similar assumptions 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). Moreover, the treatment discontinuation from the GWPCARE3 trial should be extrapolated beyond the first cycle.

B10a. The GWPCARE4 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 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 GWPCARE4 are material to this scenario analysis.

B10b. 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 GWPCARE3 and GWPCARE4 to over 2 years.

It is reasonable to assume that GWPCARE5 is a good proxy for long-term outcomes on the labelled dose. In GWPCARE3 (and GWPCARE2 for DS), no broad dose response was observed between the 10 and 20 mg/kg/day treatment arms on efficacy endpoints. As such, the higher average doses used in GWPCARE5 are unlikely to offer a significant gain in effectiveness in clinical practice. In addition, a [redacted] is observed in the transition probabilities between cycle 1 (derived from GWPCARE3 and GWPCARE4) and cycle 2 (GWPCARE5) for the 10 mg/kg/dose, as well as between cycles 2 and 9 (see document “Transition probabilities over cycles LGS.xlsx”). As such, the higher average dose in GWPCARE5 is not likely to be benefiting cost-utility outcomes in the model.

B10c. We have not conducted this scenario analysis. We feel that it is not reasonable to extrapolate outcomes at 14 weeks from GWPCARE3 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 B10b).

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 GWPCARE3 and GWPCARE4 studies. This reflects the fact that early discontinuations would be 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, toxicity 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 from these data. As such, we have not applied discontinuation rates from GWPCARE3 and GWPCARE4 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.

B11. Company submission Table 18 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.

B11. 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 in GWPCARE3 and GWPCARE4 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 on the primary endpoint. 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 [Patel 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.

B12. CBD treatment discontinuation (company submission Table 20) is assumed to be dependent on health state.

a. Please justify the assumption that treatment discontinuation is dependent on health state. Particularly given that the treatment discontinuation probabilities might lack face validity (e.g. given treatment discontinuation does not always increase with higher drop seizure frequencies) and is based on a relatively small sample size.

b. Treatment discontinuation reported in company submission Table 20 seems inconsistent with the 27% (40/147) reported by Laux et al, (2017).[1] Please clarify this inconsistency.

c. Only an abstract is provided for the Laux et al, (2017) reference. Please provide a digital copy of the poster presented at the American Epilepsy Society.

d. Please justify that the 0% CBD treatment discontinuation probabilities provided in Table 20 are clinically plausible.

e. Please provide a scenario analysis using the average treatment discontinuation probability across the health states.

B12a. 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.

B12b/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.

B12e. 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 (and as observed for all withdrawals in the GWPCARE3 and GWPCARE4 trials) 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 B12a, variable discontinuation rates per health state, as observed in the GWPCARE5 study, are retained for cycles 2-9.

B13. The number of days without seizures is provided in company submission Table 19 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 using equal number of days without seizures probabilities across treatment allocation (i.e. assuming the number of days without seizures probabilities are only dependent on health state).

B13a/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 drop seizures and the number of drop 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.

B14. The calculation of epilepsy-related mortality rates provided in company submission Table 21 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 72) 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

B15. 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.

B15a. 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 B18 below, disutilities associated with AEs have been ignored.

B15b. 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

B16. Priority question: In the model, health states are defined based on the number of absolute drop seizures and drop seizure-free days per 28 days. However, based on the clinical data (i.e., GWPCARE3, GWPCARE4, and GWPCARE5), a substantial number of non-drop seizures is reported for both CBD and the CCM group. Please clarify what the number of non-drop seizures is per subgroup based on the classification used for the health states (i.e. seizure-free, ≤45 seizures, >45 - ≤110 seizures and >110 seizures).

The table below displays the mean and median number of non-drop seizures across health states defined by drop-seizure frequencies for the treatment period. As explained previously, the mean number of non-drop seizures is lower in health states with fewer drop-seizures. This can be expected to provide a utility gain not measured in the model.

Summary of non-drop seizures across drop-seizure frequency-defined health states

	Non-drop seizures					
Drop seizures	**N**	**Mean**	**SD**	**Median**	**Min**	**Max**
Seizure-Free*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>45 - ≤ 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Drop-seizure free or ≤1 drop seizure

B17. Priority question: Utility values were determined based on a vignette study which only focused on drop 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 very high for patients with LGS, especially given the likelihood of remaining non-drop seizures. Please justify why utility values are not adjusted for non-drop seizures.

d. In the vignette study, three additional vignettes for carers of patients with LGS were included. Please elaborate on how these vignettes were used in determining utility values for the model.

e. 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.

f. In the GWPCARE4study, quality of life was assessed using the Quality of Life in Childhood Epilepsy (QOLCE) instrument (company submission Table 23).

i. Please provide these data for GWPCARE3, which were missing from company submission Table 23.

ii. Please justify why the QOLCE instrument was not used to estimate utilities for the base-case.

iii. Please add a scenario analysis in which utilities are based on the QOLCE instrument from the phase 3 trials.

g. 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.

h. In absence of quality of life estimates, proxy estimates from previous research can be used.

i. Please justify why this was not considered as a source to calculate utilities (see for example De Kinderen et al[3]).

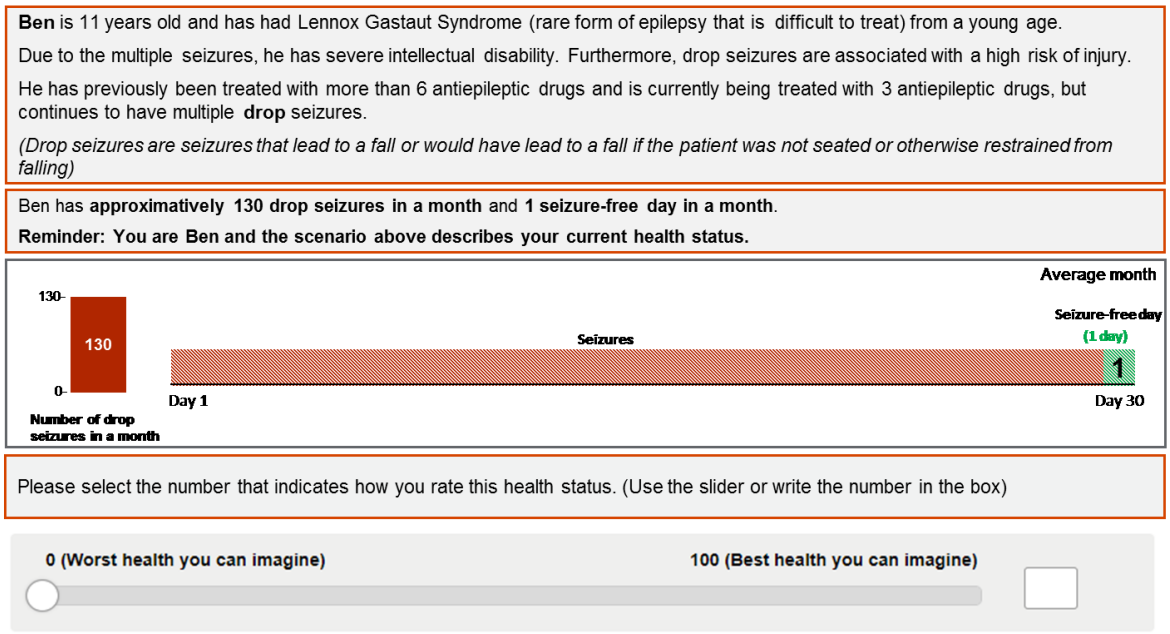
ii. The SLR for utilities was restricted to English language only. Please present the studies that were excluded based on language use in the SLR and elaborate per excluded study on whether it could potentially inform utility values in the economic model.

B17a/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 LGS, 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 drop-seizure frequency and seizure-free days) generated 39 descriptive vignettes in total. An example is given in the table 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 LGS, 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 valuations to a degree.

Main narrative vignette on a patient's current condition



B17c. In Document B, we noted that the VAS score for the drop seizure-free health state from our study ([redacted]) was higher than the utility values reported in a cost-utility study by Clements *et al.* (0.699) [Clements 2013] (refer to HRQoL SLR summary and Appendix H in the Company Evidence Submission). Clements *et al.* obtained QoL estimates from Verdian *et al.* [Verdian 2010], whose study was done in a UK setting. Clements *et al.* assumed that the utility in the seizure-free health state was the same as the lowest health state with seizures (≥75% reduction from baseline) as reported by Verdian *et al.* This was a conservative estimate made by the authors

because the latter did not include a seizure-free health state in the 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. Drop-seizures drive the physical morbidity and complications of the disease. Achieving drop-seizure freedom is a hugely significant and rarely achieved treatment milestone that was attained by some patients in the clinical trials for CBD. As such, it is reasonable to conclude that a high quality-of-life would be assigned to being and remaining drop-seizure free, even if other seizure types persist. Of note, a state of less than full health was still measured in the seizure-free health state, which may account for the latter.

All cost-utility studies in the literature consider only drop seizure-based health states, supporting their clinical validity. Given that utility measured for the drop-seizure free health state in our analysis is broadly in line with those from these other studies (notwithstanding the explainable differences above), it is reasonable to conclude that our estimates are valid, even though they did not consider non-drop seizures.

B17d. 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.

B17e. 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 sometimes distressing nature of LGS 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 B17a/b, the limited sample size facilitate-able in the vignette study meant that we had to focus on measuring the utility impacts of seizure burden alone. By studying a “live” population, we recruited respondents who had an intrinsic understanding of the implications and challenges

of living with LGS, 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.

B17f. Please see responses below for the sub-questions:

i. Please provide these data for GWPCARE3, which were missing from company submission Table 23.

QOLCE. All patients, Overall Quality of Life Score

	Epidyolex 20 mg/kg/day	Epidyolex 10 mg/kg/day	Placebo
Quality of Life in Childhood Epilepsy questionnaire score	[redacted]	[redacted]	[redacted]
Mean change (SD) (all patients)	[redacted]	[redacted]	[redacted]
Difference 95% CI P-value	[redacted]	[redacted]	

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.

B17g. None of the current published studies evaluate how health states based on drop seizure frequency and seizure-free days impact quality of life, and therefore do not report appropriate utility proxy estimates. As such, they could not be considered

for our analysis, and utilities were derived *de novo* using the vignette study as described.

B17h. Please see responses below for each of the sub-questions.

i. The study by De Kinderen *et al*. elicits utility values for epilepsy health states that do not adequately reflect the complications and severity of refractory LGS. The maximum seizure frequency in De Kinderen is two seizures per day, whilst patients with severe refractory LGS in our studies often experience >100 seizures a month. Furthermore, the survey does not consider the impact of seizure-free days. Therefore, it is impossible to derive utility scores that are reflective of our model health states using the algorithm published in this study.

ii. 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 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 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.

B18. In the model, the occurrence of adverse events is not accompanied by 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 the 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 costs captured only.

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

B19. Priority question: The company states that the decline in cognitive functioning in LGS patients is likely to be associated with the symptomatic level of epileptic activity in early age, and patients in the drop 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 LGS, including non-drop seizures.

a. Please justify the assumption that drop-seizure free patients are not being at risk of being institutionalised; is this appropriate.

b. Please include the institutionalisation risk and costs for this patient group in the cost effectiveness model.

B19a/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.

B20. 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.

B20a/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 - LGS”). 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 - LGS") for these findings. These health resource utilisation estimates have been carried through into the model for non-SUDEP deaths.

B21. 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.

B21a. Overall 18 studies were excluded based on language. Citations for these excluded abstracts are provided in the answer to question B17h.ii. None of these studies were relevant to inform utility values or cost and resource use for the economic model. See B17h.ii above for the list of studies.

B21b. The report and questionnaire for UK KOL interviews is provided separately (see ("UK KOL interview reports - LGS"). Unit cost sources are shown on pages 91-93 of Document B.

B22. In the base-case analysis of the cost effectiveness model, <u>patients receiving CBD had a 33% reduction in dose of concomitant AEDs</u>. 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 LGS 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 - LGS"). KOLs reported that physicians strive to use the lowest possible dose in an effort to reduce the drug burden and to reduce 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

B23. 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.

B24. 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.

B24a. The multiple sections represent the 4 age categories.

B24b.

"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 represents 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 cycle, 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.

B25. 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 (e.g. given it is a cohort simulation and the relative 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 37 some parameters (e.g. non-SUDEP costs) are not included in the PSA. Please include all relevant parameters in the PSA.

B25a. 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 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 Dirichlet if only one set of transition probabilities by treatment arm was used.

B25b. The PSA running time has been decreased by setting the Excel calculation mode to manual (instead of automatic) where necessary.

B25c. 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.

B25d. The parameters that had a minor impact on the results were not included in the PSA.

The cost of ICU is included in the current PSA, which directly impacts the non-SUDEP costs.

B26. 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; 0.44% for 2-11 years and 0.74% for 12-55 years). Please add a scenario in which higher discontinuation rates are assumed (e.g. 0.55% for 2-11 years and 1.46% 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 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.

B27. Priority question: The cost effectiveness model has 15-year time horizon. The base-case total QALYs, as reported in company submission Table 35, exceed this time horizon (i.e. are larger than 15). This is not plausible and questions 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 (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.

B27a/b. As per our communication with NICE on 13th February 2019, an updated economic evaluation and model have been provided.

B27c. 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.

B28. The cost effectiveness model has a 3-month cycle time. In the CS 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 LGS (GWEP1414 and GWEP1423) 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 LGS 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.

B28a/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. It 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 CSRs of GWPCARE3 and GWPCARE4.

Full CSRs with all tables and appendices are provided separately.

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.

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 AH, Claxton K, Sculpher MJ. Decision modelling 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 Lennox-Gastaut syndrome [ID1308]

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 around 10,000 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?	A common theme among the five parent carers who responded to this question was the level of care that a person with Lennox-Gastaut Syndrome (LGS) requires. Three of the five respondents highlighted the round-the-clock care needs brought about by the condition. One parent carer noted that seizures happen day and night necessitating continuous one to one care. Two respondents highlighted that LGS prevents people with the condition from being able to look after themselves and denies them their independence. 'My son is 16 with LGS, he is unable to do anything for himself so we have to provide 24 hour care' 'He has no independence and requires continual supervision and support' Another parent carer noted the impact of seizures on their son's heart rate and breathing highlighting that he could not be safely left alone. Two respondents highlighted the quantities of medications that many people with LGS are prescribed in an attempt to control or limit seizures. One parent carer noted that their son is currently taking five antiepileptic drugs (AEDs) without adequate seizure control. Another parent carer has to administer three AEDs, again with limited seizure control, along with other drugs and treatments: 'he needs medicating 6 times a day…he requires supplementary milk feeds through the tube due to weight loss and not willing to eat sufficiently'. A second common theme throughout the responses was the type, frequency and severity of seizures. One parent carer noted that 'We can go for days on end with continuous seizure activity and no rescue meds make any difference'. Another parent carer mentioned that their son continues to have weekly seizures, 'this has been the case for 34 years'. Another parent went on to list the type of seizures their son experiences, including 'atonic seizures…tonic seizures…myoclonic seizures' and noted that these seizures occur day and night. The prevalence of comorbidities in people with LGS was highlighted by three of the five respondents. One parent carer noted that their son also had 'severe learning difficulties' while another noted that their son had other complex health needs as well as his epilepsy. Another parent carer explained that their son was also 'significantly cognitively impaired'. The increased risk of sudden unexplained death in epilepsy (SUDEP) experienced by some people with LGS was noted by one parent carer noting that their son: 'continues to carry five risk factors around SUDEP. His doctor has said he places his risk at 1:100. This causes us untold anxiety and hinders recruiting paid support workers to care for him.'

	Another parent carer noted the wider risk of seizures associated with LGS, their son broke his leg after a drop seizure further exacerbating his care and support needs. They went on to succinctly note: 'LGS and the seizures it causes have major knock on effects on people lives, that severely exacerbate the already huge challenges that affect the individual and their family.' As above, the impact of the condition on parent carers and other family members was made clear by a number of respondents. One parent carer noted 'the impact on our mental health and wellbeing has been significant. Without the respite we have been able to get, I doubt we would have managed at times.' Another parent carer mentioned that they had suffered a recent bought of serious ill health attributable in part to a weakened immune system they link to the exhaustion of caring for their son.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	As above, two respondents noted that their sons are currently taking between three and five AEDs without adequate seizure control. One of these parent carer's highlighted concerns about the effect of these drugs on their son's health: 'I dread to think what the effect of these medications has on his system'. Another noted that despite taking three AEDs daily: 'The drugs available only seem to provide partial benefit and only reduce seizures and improve behaviour and mood to an extent. The condition is still hugely debilitating.' A different parent carer mentioned the availability of new technologies to treat LGS, including implants but they are concerned that these new treatments are not currently available on the NHS. They 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.' Another parent carer highlighted that there are quite a few options for drugs and treatments to treat LGS on the NHS. However another noted that despite the number of available AEDs and treatments the outcomes in term of seizure control are often variable and finding an effective combination of AEDs for specific patient with LGS is often very difficult.

	'It appears to be a guessing game and the only solution is to increase one drug or introduce something else. We might see a difference for a few days until his body gets used to it.' A recurring theme through a number of responses was that despite the prevalence of potential AEDs and treatments, adequate seizure control was often unachievable and the high care and support needs remained. 'Although we are lucky to have provision of supposedly the best drugs for X's condition, the reality is that the negative impacts of the condition are not removed and they are major in consequence.' A parent carer to a daughter with LGS noted problems they have experienced around the provision of care in the NHS and the apparent lack of knowledge and awareness of the condition in primary care settings. 'In the area we have 1 epilepsy/LGS nurse specialist, therefore cannot get help/advice when it's needed. GPs don't know enough about it to be much help. She has 2 appointments a year with a consultant so there is nothing in between.'
8. Is there an unmet need for patients with this condition?	Of the four parent carers who responded to this question, all of them noted that there was some unmet need for patients with LGS. Three of the four parent carers specifically noted that current AEDs used to treat LGS are largely the same as those used to treat other less severe epilepsies. Despite available AEDs and treatments, all three noted that their loved ones seizures remain uncontrolled. 'My son is treated the same as others with epilepsy yet he never gets a day without some type of seizure.' 'Yes there is an unmet need…it's called drug resistant epilepsy and he is continuing to have weekly seizures. This has been the case for 34 years.' 'Existing medications only provide some benefit and only reduce the extent of the very challenging impacts of LGS. The impacts remaining still have major consequences for the individual and their carers' Rescue medications can also be ineffective in the treatment of people with LGS. One parent carer noted that, 'we have just had four days without sleep rescue meds given without response – still continued to seize.' They went on to mention that medications administered in hospitals are similarly ineffective: 'Hospital drugs have little or no effect either. Condition continues to deteriorate.'

	Unmet need was also noted by one parent carer in relation to a lack of LGS specialists and a broader lack of knowledge about the condition, particularly the complexities of LGS. They noted 'The lack of professionals who specialise in LGS, or epilepsy nurses.' One parent carer highlighted how this unmet need contributes to the ongoing high and complex care needs of people with LGS. They noted that despite the number of AEDs and other medications 'The impacts remaining still have major consequences for the individual and their carer's, so any new therapies or treatments that improve situations have to be worth exploring.'.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Of the four parent carer's who responded to this question, all of them believed that cannabidiol could work for some people with LGS. Two of the four respondents specifically noted that they believed cannabibiol could help in reducing seizure frequency. Both also noted that the technology could also bring about improvements in quality of life, while one further noted that they hoped it could reduce the number of drugs their son is currently taking. 'I would hope that should this medication be made available that we might be able to reduce his condition of drugs and reduce his seizures thereby giving him a better quality of life.' 'From what we have recently heard in the media about CBDs affects on a couple of individuals with epilepsy, we consider there may be similar reduction in seizures for those with LGS. We appreciate things aren't that simple and every individual and condition may react differently. We would also expect that behaviour and mood could positively change from CBDs.' Another parent carer echoed the point in the above quote about the potential for cannabidiol to benefit some but not all people with LGS: 'CBD or Cannididiol like any treatment works for some and not others from the information I know (which is limited)'. The complexity of LGS and the individual nature of AED combinations used by each patient is a relevant point here and is explicitly mentioned in the second quote above. While not specifying specific potential benefits of the treatment, a parent carer noted that 'We have been waiting a longtime for the drug Epidiolex'. They went on to express continued concerns about accessing this technology in light of the likely cost to the NHS.

	The potential advantages were put into context by one parent carer in light of the severe unmet needs of many people with LGS. They noted that 'the severity of the condition and scale of impact on the individual and their family should warrant the acceleration and facilitation of testing CBD for the individual.' 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 Lennox-Gastaut syndrome. In light of available clinical evidence, the often uncontrolled and severe nature of seizures associated with Lennox-Gastaut syndrome, the current unmet need for this patient group and associated increased risk of premature mortality, 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?	As mentioned in response to the above question, two respondents highlighted that this technology may not work for all patients with LGS. One parent carer noted that: 'things aren't that simple and every individual and condition may react differently.' Similarly another parent carer noted: 'It seems to work for some and not for others' but went on to add that 'but (I) feel everyone with this condition should be given at least the opportunity to see if it makes a difference.' Potential side effects were also mentioned by two parent carers. Interestingly, both of these respondents noted that these concerns existed in relation to all AEDs and other medicines: 'I worry about Long term affects, which I worry about all the drugs my son takes' 'As with any drug, we would expect there may be side effects or negative effects.' One of these respondents went on to say that they believed there had not yet been enough trials for long term use of this technology.

	'In my opinion I don't think enough trials for long term use has been done' Another parent carer raised the point of knowledge of clinicians about this technology in response to this question. They noted that – 'any of the cannabis based oils should be prescribed by knowledgeable doctors and I don't believe there are any in the UK.' Similarly, a separate parent carer noted the need to clarify the clear differences between recreational and medicinal cannabidiol. 'Just because society has deemed CBDs inappropriate for recreational use should not deny people with life limiting medical conditions and to not evaluate if CBDs can provide some benefit.'
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	**N/A**

considering this condition and the technology?	
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. In light of some responses, 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. One respondent noted the potential benefits of other cannabis-based medicines for the treatment of LGS. This could be an area of consideration for NICE in the longer term.
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: • All of the parent carers who responded in whole or part to our information request (five out of five) noted that there was a clear unmet need for people with LGS. • All of the parent carers also emphasised the high level of care and support that a person with LGS often requires. • A majority of respondents noted that despite taking multiple medications, people with LGS remain unable to achieve seizure control • A majority of respondents believed the technology should be made available if there was a possibility that it could improve seizure control in people with LGS.	

• Necessary consideration should be given to potential side-effects, particularly in the longer term, and should be judged against the side effects of currently prescribed AEDs.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome [ID1308]

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists (ABN)

3. Job title or position	Consultant Neurologist, Professor of Neurology, ABN Epilepsy Advisory Group Chair
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 not 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,	Prevention of seizures and their consequences. There are many other comorbidities in Lennox-Gastaut Syndrome (depending on the exact cause), 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.

or prevent progression or 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 that can be 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. Cessation of drop seizures, typical of this condition, is of definite value. The commonly used measures of a 50% 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 Lennox-Gastuat 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?	There is not a well-defined pathway for care of all aspects.
• Are any clinical guidelines used in the treatment of the	NICE cg137 offers some guidance on drug treatment

condition, and if so, which?	
• 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.)	Not well defined overall
• 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 between the technology and current care?	Should not be different – is another AED, potentially with a different mechanism of action.
• In what clinical setting should the technology be	Specialist clinics

used? (For example, primary or secondary care, 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 RCT data: Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, Greenwood SM, Roberts C, Checketts D, VanLandingham KE, Zuberi SM; GWPCARE3 Study Group. N Engl J Med. 2018 May 17;378(20):1888-1897.
• Do you expect the technology to increase length of life more than current care?	Yes, if seizure freedom is achieved. Stopping drop seizures can also be life-saving.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, if seizure freedom is achieved.

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 Lennox-Gastaut 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 tests or monitoring needed.)	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.

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 Lennox-Gastaut 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, but there is no proof currently that this occurs.
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 cited RCT.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, reasonably.

• 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 drop seizures
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Only drop seizures properly evaluated. Cannot extrapolate to outcomes for other seizure types.
• 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 trial data?	These are too limited/biased for cannabidiol to give a reliable opinion
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Lennox-Gastaut Syndrome affects all populations and ages and treatment availability should not be restricted to any particular subgroup within the population of patients with Lennox-Gastaut 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 Lennox-Gastaut Syndrome
- Freedom from drop 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

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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

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut 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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Dr. Judith Verhoeven, Academic Center for Epileptology Kempenhaeghe/Maastricht University Medical Center, Heeze, The Netherlands.

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.

This report should be referenced as follows:

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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 event
AED	Anti-epileptic drug
AWMSG	All Wales Medicines Strategy Group
CADTH	Canadian Agency for Drugs and Technologies in Health
CBD	Cannabidiol
CBZ	Carbamazepine
CCM	Current clinical management
CE	Cost effectiveness
CGIC	Caregiver global impression of change
CGICSD	Caregiver global impression of change seizure duration
CI	Confidence interval
CLB	Clobazam
CS	Company submission
CSR	Clinical study report
DARE	Database of Abstracts of Reviews of Effects
DS	Dravet syndrome
DSA	Deterministic sensitivity analysis
EEG	Electroencephalogram
EMA	European Medicines Agency
ERG	Evidence Review Group
ESL	Eslicarbazepine acetate
ETX	Ethosuximide
FLB	Felbamate
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
KSR	Kleijnen Systematic Reviews
LEV	Levetiracetam
LGS	Lennox-Gastaut syndrome
LTG	Lamotrigine
MeSH	Medical subject headings
mg	Milligram
NA	Not applicable
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
OLE	Open-label extension
OR	Odds ratio
OXC	Oxcarbazepine
PB	Phenobarbital
PAS	Patient access scheme
P/CGIC	Patient/carer global impression of change
P/CGICSD	Patient/carer global impression of change seizure duration
PER	Perampanel
PHT	Phenytoin
PRESS	Peer review of electronic search strategies

PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PT	Preferred term
QALY(s)	Quality-adjusted life year(s)
QOLCE	Quality of life in childhood epilepsy
QOLIE-31-P	Quality of life in epilepsy version 3
QoL	Quality of life
RCT	Randomised controlled trial
RUF	Rufinamide
SAE	Serious adverse events
SD	Standard deviation
SE	Status epilepticus
SGEs	Symptomatic generalised epilepsies
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SSW	Slow spike-wave
STA	Single technology appraisal
STP	Stiripentol
SUDEP	Sudden unexplained death in epilepsy
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TGB	Tiagabine
TPM	Topiramate
TRAE	Treatment-related adverse event
TRSAE	Treatment-related serious adverse event
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
VNS	Vagus nerve stimulation
VPA	Sodium valproate
WTP	Willingness to pay
ZNS	Zonisamide

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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 Lennox-Gastaut syndrome (LGS) whose seizures are inadequately controlled by established clinical management'. The company extended the scope to include 'people with LGS 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) (GWPCARE3 and GWPCARE4) of cannabidiol (CBD) as an add-on treatment to current clinical management (CCM). The number of previous or current AEDs was not specified in the NICE scope. However, 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 AED). The patients included in the two RCTs were broadly representative of this population; the proportion of participants who had fewer than two prior AEDs was low (<5%).

The description of the comparators is in line with the scope (established clinical management without cannabidiol), which may include combinations of: sodium valproate, lamotrigine, rufinamide, topiramate, felbamate, clobazam, levetiracetam, ketogenic diet and vagus nerve stimulation. The comparator used in the key trials (GWPCARE3 and GWPCARE4) is 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 ERG questions the validity of this assumption.

The CS focused primarily on drop seizures as these were the primary outcome in the two main trials. Although mortality was investigated, the two main RCTs 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 CBD (GWPCARE 3, GWPCARE4) and an ongoing open-label extension study (GWPCARE5) as relevant to the submission. Both RCTs were conducted in patients aged two to 55 years with LGS, whose seizures were incompletely controlled with previous AEDs and who had suffered at least two drop seizures per week in the baseline period. The intervention was CBD in addition to CCM and the comparator was CCM without cannabidiol (i.e. CCM plus placebo). GWPCARE3 was a three-arm study, comparing two doses of CBD (10 mg/kg/day and 20 mg/kg/day) in addition to CCM and CCM plus placebo, and GWPCARE4 compared CBD (20 mg/kg/day) in addition to CCM and CCM plus placebo. Both randomised trials had a dose escalation phase (14 days in GWPCARE3 and 11 days in GWPCARE4) followed by a 12-week treatment period. GWPCARE3 included patients from the UK (three centres and [redacted] patients overall) but GWPCARE4 did not include patients from the UK. GWPCARE3 had a total of 225 patients and GWPCARE4 171. Patients had used on average six or seven prior anti-epileptic drugs (AEDs).

Patients in GWPCARE3, who received 10 mg/kg/day CBD in addition to CCM, achieved better seizure frequency outcomes than those who received CCM + Placebo. Specifically, patients in the 10 mg/kg/day CBD groups experienced fewer drop seizures and fewer seizures overall, during the 14-week treatment period, than those in the placebo group. The median difference in the change in drop seizures per 28 days between the 10 mg/kg/day CBD group and the placebo group was -19.2% (95% CI: -31.2% to -7.7%), and the median difference in the change in total seizures per 28 days was -19.5% (95% CI: -

30.4% to -7.5%). In addition, a higher proportion of patients in the 10 mg/kg/day CBD group achieved at least a 50% reduction in drop seizures, during the treatment period, than in the placebo group, OR 3.27 (95% CI: 1.47 to 7.26). No patient in GWPCARE3 achieved freedom from drop seizures for the whole 14-week treatment period; three patients in the 10 mg/kg/day CBD group and one patient in the placebo group were drop seizure-free for the whole of the maintenance phase (day 15 onwards). 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. The rates of individual, treatment-related AEs were generally higher in the 20 mg/kg CBD groups than in the 10 mg/kg CBD group.

1.3 Summary of the ERG's critique of clinical 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.

Although the CS included two international RCTs and an open-label extension study, there are some limitations in applying this evidence to UK practice. One of the RCTs included [redacted] UK patients, the other had none. This is most likely to be relevant when considering the nature of current clinical management, which may differ between countries and which is the comparator in the trials.

A major limitation of the evidence is the small size of the data set relating to the recommended 10 mg/kg/day CBD dose. Just 73 patients in GWPCARE3 and none in GWPCARE4 received the 10 mg/kg/day dose.

A further important limitation is the short-term nature of the RCTs (14 weeks). There is a lack of long-term efficacy and safety data, particularly for the 10 mg/kg/day dose. Data from GWPCARE5 are for patients taking 20 mg/kg/day CBD or higher (up to 30 mg/kg/day). Any observations of reduction in seizures in the short-term trials may not be sustained in the long-term and the effects on outcomes relating to mortality (especially SUDEP) are unknown.

Current clinical management is considered to be a 'basket' of choices of AED. Although the company conducted a number of subgroup analyses based on the presence or absence of various AEDs, they assumed that the effectiveness of CBD does not vary with the combinations of AEDs to which it is added. This assumption is crucial to the validity of the 'mixed' CCM comparator. The ERG considers that there is currently a lack of evidence to support this assumption.

The innovation section of the CS emphasised the value, to patients and carers, of periods of seizure-free time. The ERG notes that neither the CS nor the CSRs provided any data on the number of days, if any, on which study participants were seizure-free (no seizures of any type) and that no patient, in any of the included studies, achieved complete freedom from seizures.

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 drop seizure frequency and the number of drop 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 LGS 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 (GWPCARE3 and GWPCARE4) and the open label extension study (GWPCARE5). It should be noted that GWPCARE4 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 drop seizures, number of days without drop seizures, discontinuation rates and adverse events for both CCM plus CBD and CCM. GWPCARE3 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 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 drop 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.

[redacted]

Similarly, the company's revised analysis, resulted in an ICER of £31,107.

The company performed face validity, internal validity and external validity checks.

1.5 ERG commentary on the robustness of evidence submitted by the company

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 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.

The main concern of the ERG related to the model structure was the assumption that patients receiving CCM transfer back to their baseline drop seizure frequency after the first cycle. The company clarified that this was done as a placebo effect was observed in both the GWPCARE3 and GWPCARE4 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 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 23 mg/kg/day) 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. The 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. 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 drop seizures, the treatment benefit (compared with CCM) potentially induced by the difference in number of days without drop 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 attempted 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 0.43 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. 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 (£31,107 per QALY gained, including QALYs gained by caregivers) as not credible. In the latter case, adjustments (to the model structure and inputs that were not requested by the ERG) made by the company are also an issue.

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 £80,205 per QALY gained (assuming a constant treatment effect after 27 months) and £176,638 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 (£31,107) should be interpreted with extreme caution given the highlighted validity issues and adjustments (model structure and input) made by the company. The ERG has incorporated various adjustments to the original 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 £80,205 per QALY gained and £176,638 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 section, the Evidence Review Group (ERG) provides a review of the background evidence submitted by GW Research Ltd. in support of cannabidiol (CBD), trade name Epidyolex®, for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS). We outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken mainly from Chapter B.1 of the company's submission (CS) with sections referenced as appropriate.[1]

2.1 Critique of company's description of underlying health problem.

The underlying health problem, addressed by this appraisal, is LGS. LGS is a severely debilitating, lifelong and treatment-resistant form of epilepsy affecting two in 10,000 children from two years of age.[1] Onset of LGS usually occurs before the age of eight years, peaking between three and five years of age.[2]

LGS is characterised by the presence of multiple seizure types and frequent seizures including atonic, tonic, atypical absence seizures and myoclonic jerks, an abnormal electroencephalogram (EEG) pattern of slow spike-wave (SSW) complexes, and moderate to severe cognitive impairment.[1, 3]

Atonic and tonic seizures result in a temporary loss of muscle tone or stiffening of the muscles, respectively. These sudden drop seizures (defined as an attack or spell involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface) often result in severe injuries, so that patients need to wear helmets with full face masks or use wheelchairs to minimise injuries.[2]

Moderate to severe cognitive impairment is a common feature of LGS, with 20 to 60% of LGS patients having clinically apparent cognitive impairment at the point of diagnosis.[2] This usually worsens over time, with 75 to 95% of patients displaying serious intellectual problems within five years of diagnosis.[2] Cognitive impairment in LGS is often accompanied by behavioural problems: hyperactivity, aggression and autistic traits occur in up to 50% of patients.[4] It is thought likely that the extent of cognitive impairment is related to the severity and frequency of seizures in early life and, in particular, to non-convulsive status epilepticus, which occurs in around two-thirds of LGS patients.[3, 5]

The CS noted that risk of death is significantly elevated in patients with drug-resistant forms of epilepsy and patients with LGS are at high risk of sudden unexplained death in epilepsy (SUDEP).[1] The all-cause mortality rate for LGS patients has been reported, in a United States of America (USA) study, to be 14 times higher than for the general population.[6] The same USA study found that children with LGS have a risk of death from neurological causes, such as prolonged seizures and status epilepticus, which is 179 times greater than that for the general population.[6]

LGS has a severe impact not only on the patient but also on their families and caregivers. Survey studies have reported high levels of anxiety in the parents of children with LGS.[7, 8] Parents report feeling anxiety about the potential for injury, cognitive decline, or death of the child, as well as anxiety about the financial burden of the disease on the family.[7] The CS reported that functional impairment renders 87% of LGS patients unable to live independently, with 58% being completely dependent on others for all activities of daily living.[2, 9] However, these data were for all patients in the cohort with symptomatic generalised epilepsies (SGEs), and were not specific to LGS.[9]

Despite the availability of a broad range of anti-epileptic drugs (AEDs) and non-pharmacological interventions, seizure control in LGS remains inadequate; more than 90% of children with LGS have drug-resistant epilepsy and less than 10% achieve seizure-freedom as adults, indicating a substantial

unmet need.[10] Orphan designation (EU/3/17/1855) was granted by the European Commission on the 20th March 2017 for cannabidiol for the treatment of LGS.

ERG comment: The company provided a good overview of the underlying health problem of LGS illustrating the seriousness of the condition and its impact on patients and their families. The ERG checked the references cited by the company to support the statements made in the CS. In general, these were appropriately referenced, with the following exceptions:

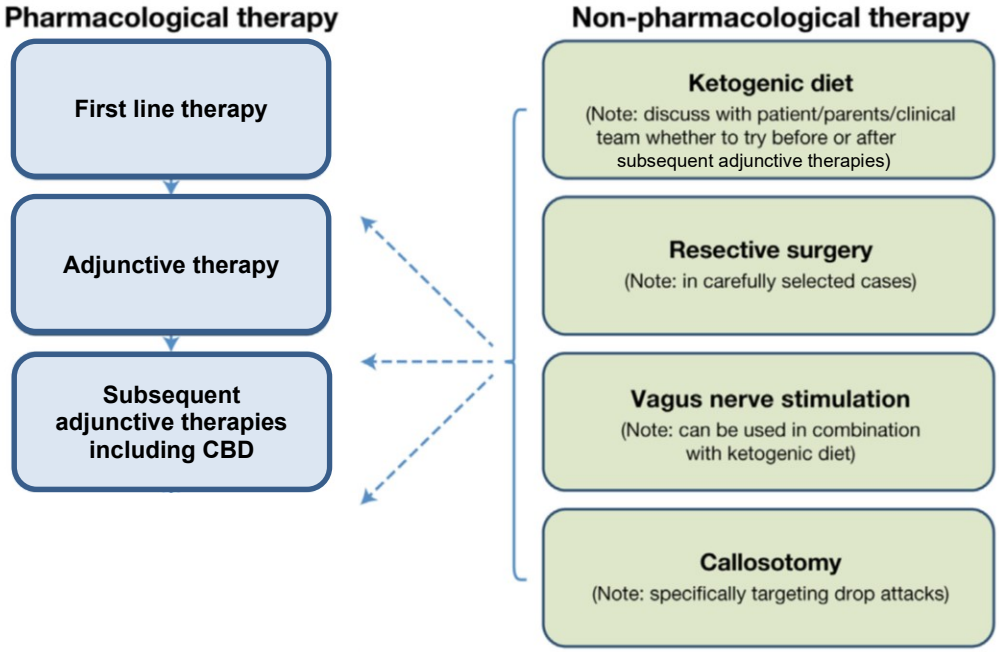
The references relating to the prevalence and aetiology of cognitive impairment were for review articles, rather than primary research. The professional organisation submission, from the Association of British Neurologists (ABN),[11] included the following statement: '*There are many other comorbidities in Lennox-Gastaut Syndrome (depending on the exact cause), 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.*'

The CS stated that patients with LGS are at high risk of SUDEP, but did not quantify this risk or provide a supporting reference. The CS also stated that the mortality risk in LGS is greater at a young age and in the years following onset and that high seizure frequency is a significant independent predictor of early death, with persistent seizures strongly related to excess mortality. However, all of the references cited were about mortality in epilepsy in general and did include specific data or statements about LGS patients. It should also be noted that, a correlation between seizure frequency and mortality does not necessarily mean that reductions in seizure frequency will translate directly into proportionately reduced mortality risk. The professional organisation submission, from the ABN,[11] included the following statement on clinically significant treatment response: '*Cessation of generalised tonic-clonic seizures (one type of seizure that can be 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. Cessation of drop seizures, typical of this condition, is of definite value. The commonly used measures of a 50% 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 (e.g. of sudden death) or improve quality of life.*'

2.2 Critique of company's overview of current service provision

The company stated that the position of CBD within the care pathway for treatment of patients with LGS will be as an add-on treatment for refractory seizures in people aged two years of age and older, once two other appropriate AEDs, trialled to a maximally tolerated dose, have failed to achieve seizure freedom. The proposed care pathway is shown in Figure 2.1

Figure 2.1: Proposed treatment pathway LGS patients with uncontrolled seizures despite treatment with at least two AEDs



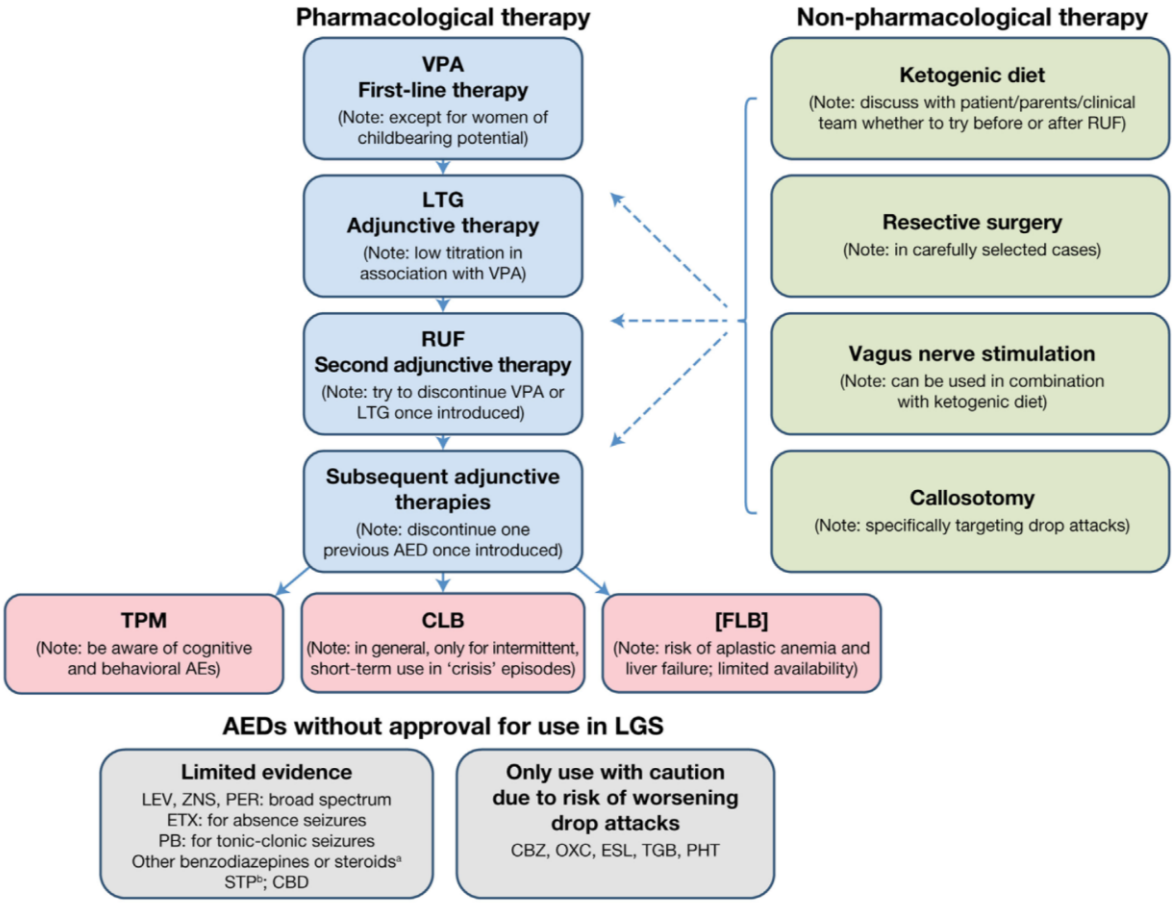
Source: Figure 2 in the CS[1]

This positioning reflects the expected use of CBD in the National Health Service (NHS). The company's specification of the population, in the decision problem (Table 1 in the CS)[1] also included '*people with LGS where current clinical management (CCM) is unsuitable or not tolerated*'; these patients are not included in the pathway shown in Figure 2.1.

Current NICE guidelines (CG137) recommend sodium valproate as a first-line treatment option for LGS and, if seizures are inadequately controlled, lamotrigine as an adjunctive treatment.[12] Further AEDs (rufinamide and topiramate) may be considered by tertiary epilepsy specialists and felbamate should only be offered, in centres providing tertiary epilepsy specialist care, when treatment with other recommended AEDs (valproate, lamotrigine, rufinamide and topiramate) has proved ineffective or not tolerated.[12] A number of AEDs (including carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine and vigabatrin) should not be given to patients with LGS as they may worsen seizures.[12]

The CS also included a treatment algorithm for LGS management in newly diagnosed patients (see Figure 2.2), which was formulated by a panel of European epileptologists, based on the available evidence in 2017 and is based on a literature review and clinical experience.[13] This algorithm is broadly consistent with the recommendations provided in NICE CG137.

Figure 2.2: Example of a treatment algorithm for a newly diagnosed patient with LGS



Source: Figure 1 in the CS[1]

[a] Not in combination and only for intermittent, short-term treatment of "crisis" episodes. [b]In combination with VPA and/or CLB. CBD, cannabidiol; CBZ, carbamazepine; CLB, clobazam; ESL, eslicarbazepine acetate; ETX, ethosuximide; FLB, felbamate; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; RUF, rufinamide; STP, stiripentol; TGB, tiagabine; TPM, topiramate; VPA, sodium valproate; ZNS, zonisamide

ERG comment: The company's overview of the current treatment pathway was appropriate. The ERG asked a number of clarification questions relating to the place of CBD in the pathway.[14] 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 Lennox-Gastaut 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 LGS patients. For example, NICE CG137 states that carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine and vigabatrin should not be given to patients with LGS as they may worsen seizures.'[15]

ERG interpretation: The ERG agrees with the response provided and notes that the additional wording '*People with Lennox-Gastaut syndrome where current clinical management is unsuitable or not tolerated*' is consistent with the wording around recommendations for third line AEDs in CG137.

ERG question A3: Under 'Placement of CBD within the care pathway' (page 24 of the company submission) and at other points in the document, it is stated that: '*For patients with Lennox-Gastaut syndrome (LGS) 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*.'[1, 14]

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. 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 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.*'[16]

b. The above statement does not appear to be consistent with the eligibility criteria for GWPCARE3 given in Table 5 of the CS (taking 1 or more AEDs) and with the prior AED use for GWPCARE3 in Table 7 of the CS (range across the treatment groups 0 to 22). In addition, the prior use of AEDs in GWPCARE4 ranges from 0 to 28. How many patients had 0 and 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 GWPCARE3 and GWPCARE 4 on 0, 1, and ≥2 prior AEDs is shown in the table below.'

Table 2.1: Prior AEDs (no longer taking) at baseline GWPCARE3 and GWPCARE4

		Prior AEDs (no longer taking)		
		10 mg/kg/day	20 mg/kg/day	Placebo
	No. AEDs	n=73	n=76	n=76
GWPCARE3[17]	0	1 (1.4%)	0	0
	1	2 (2.7%)	5 (6.6%)	3 (3.9%)
	≥2	70 (96%)	71 (93%)	73 (96%)
			n=86	n=85
GWPCARE4[18]	0		0	1 (1.2%)
	1		4 (4.7%)	3 (3.5%)
	≥2		82 (95%)	81 (95%)
Source: Clarification response, page 5[15]				

ERG interpretation: The ERG notes that the proportion of participants in the key trials, GWPCARE3[17] and GWPCARE4,[18] who had discontinued fewer than two prior AEDs was low (<5%). 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 ERG 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 section 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	Rationale if different from the final NICE scope	ERG comment
Population	People with Lennox-Gastaut syndrome whose seizures are inadequately controlled by established clinical management.	People with Lennox-Gastaut syndrome (LGS) whose seizures are inadequately controlled by current or prior established clinical management. People with LGS where current clinical management is unsuitable or not tolerated.	This is in line with recommendations in NICE clinical guideline 137 (CG137).	The population addressed, (people aged 2 years and over with Lennox-Gastaut syndrome (LGS) 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 LGS where current clinical management is unsuitable or not tolerated is consistent with the pathway outlined in NICE CG137, where consideration of adjunctive AEDs is recommended where earlier lines are ineffective, not tolerated, or (for sodium valproate) unsuitable. Neither the NICE scope nor NICE clinical guideline (CG137) provide a

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				definition of 'inadequately controlled' seizures.
Intervention	Cannabidiol in addition to current clinical management	Cannabidiol in addition to current clinical management	Not applicable	In line with scope
Comparator(s)	Established clinical management without cannabidiol, which may include combinations of: • sodium valproate • lamotrigine • rufinamide • topiramate • felbamate • clobazam • levetiracetam • ketogenic diet • vagus nerve stimulation	Established clinical management without cannabidiol, which may include combinations of: • sodium valproate • lamotrigine • rufinamide • topiramate • felbamate • clobazam • levetiracetam • ketogenic diet • vagus nerve stimulation	Not applicable	The comparator used in the submission is CCM, which includes various combinations of different AEDs. Different combinations of AEDs are 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. 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.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
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 (drop seizures and overall) • proportion of people drop 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 drop 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.	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 drop 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,[19] did not list either SUDEP or overall mortality in the effectiveness outcomes to be assessed.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed	As per scope	Not applicable	Deviations from the NICE reference case included the restricted time horizon of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	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.			15 years and the method used to estimate utilities.
Subgroups to be considered	Not applicable	Not applicable	Not applicable	Not applicable
Special considerations including issues related to equity or equality	Not applicable	Not applicable	Not applicable	Not applicable

Source: CS, Table 1, page 13[1]
AED: anti-epileptic drug; CBD: cannabidiol; CCM: current clinical management; CGIC: caregiver global impression of change; CGICSD: caregiver global impression of change seizure duration; ERG: evidence review group; LGS: Lennox-Gastaut syndrome

3.1 Population

The population in the submission is consistent with that defined in the scope and with the expected licenced indication for Epidyolex®.

The submission relies, primarily, on two randomised controlled trials (RCTs) of CBD as an add-on treatment to CCM (GWPCARE3[17] and GWPCARE4[18]). Both trials were conducted in people with LGS, between the ages of two and 55 years, whose seizures were inadequately controlled (at least two drop seizures per week during the four-week baseline period of the studies) on existing AEDs (CS, Table 5).[1]

The decision problem, described by the company in the CS, defined the population as: '*People with Lennox-Gastaut syndrome (LGS) whose seizures are inadequately controlled by current or prior established clinical management*' (see Table 3.1). The number of previous or current AEDs was not specified, however, the treatment pathway proposed by the company (see Figure 2.1) places 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 GWPCARE3 and GWPCARE4, reported in the CS (Tables 7 and 8) indicate that some participants included in these studies may have been treatment naïve or have tried only one prior AED.[1]

The CS (Section B.2.3, Table 6), reported that one of the two key trials (GWPCARE3) included patients from the UK. However, it was not clear how many UK patients were included in this trial and the extent to which both trials were considered generalisable to the UK population was not discussed.

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, both of the key trials used in the submission (CWPCARE3 and GWPCARE4) excluded patients over the age of 55 years. It is unclear how well the age distribution of adult patients is represented in these trials (See Table 4.3 in section 4.2 of this report for an overview of all baseline characteristics, for both trials). Examination of the more detailed information about baseline demographic characteristics, provided in the clinical study reports (CSRs), indicates [redacted] of participants in GWPCARE3[17] and [redacted] of participants in GWPCARE4[18] were adults (age 18 to 55 years), however, no indication of the age distributions (within the adult category) was provided.

The CS (Section B.2.7) states that "no subgroup analyses were conducted." [redacted]

ERG comment: The ERG asked a number of questions relating to the population defined in the decision problem,[14] and the populations included in the key trials, GWPCARE3[17] and GWPCARE4.[18] The questions are given below with the company's responses and our interpretation.

ERG question A3: Under 'Placement of CBD within the care pathway' (page 24 of the company submission) and at other points in the document, it is stated that: '*For patients with Lennox-Gastaut syndrome (LGS) 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*.'

c. The median number of prior AEDs in both trials was six. Is this a more severe population than might be expected in clinical practice?

Company response: *'No. More than 90% of children with LGS have drug-resistant epilepsy.[10] 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.'*

'In the clinical trials, patients were currently treated with a median of 3 AEDs, and had previously been treated with a median of 6 AEDs, at baseline. This is an artefact of the population that could be recruited into clinical trials and does not reflect the inclusion criteria in studies, or where clinical need lies in treatment practice. Patients with LGS are highly drug refractory.[10, 20] As such, the standing population in clinical practice, from which trial patients were recruited, has been extensively treated. Recently diagnosed children with LGS 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: The ERG remained unclear as to whether the trial populations were more severe/more clinically treated than might be expected in UK clinical practice and noted that both of the references cited are review articles which do not provide any information about the extent of polypharmacy in the UK LGS population. Further opinion was sought, from the ERG's clinical experts, regarding the extent to which the numbers of prior and concurrent AEDs taken by patients in the GWPCARE trials was representative of what might be expected in clinical practice. The response indicted that:

- Although the range of prior AEDs in the trials was broad (0 to 22), there are LGS patients who are extremely drug resistant and have no positive response to any of the registered AEDs.
- LGS is, per. definition, a drug resistant epilepsy. The company selected on these patients that had, despite the use of regular, registered AED's, still an active, disabling epilepsy.

The ERG considers that the numbers of prior and current AEDs seen in the GWPCARE trial participants are likely to be representative of LGS patients seen in clinical practice, but notes that further confirmation, from UK clinical experts on the committee, may be useful.

d. Please provide a histogram showing the number of patients by number of prior treatments in each arm of the GWPCARE3 and GWPCARE4 trials.

Company response:

Figure 3.1: [redacted] for the number of patients on prior AEDS (no longer taking) at baseline (GWPCARE3)

Source: Clarification response, page 6[15]

Figure 3.2: [redacted] for the number of patients on prior AEDS (no longer taking) at baseline (GWPCARE4)

Source: Clarification response, page 7[15]

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 GWPCARE3 and GWPCARE4, patients were taking 1 or more AEDs at a dose that had been stable for at least 4 weeks, and were still having at least 2 drop seizures each week during the first 28 days of the baseline period. 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. Note that the proportion of participants in GWCARE3[17] and GWPCARE4[18] who had fewer than two prior AEDs was low (<5%), (see Section 2.2).

f. The median number of concurrent treatments in the trials was three with a range across the trials of zero to five. How does this reflect UK clinical practice?

Company response: '*This reflects UK clinical practice. See also A3c above. More than 90% of children with LGS have drug-resistant epilepsy. As a result, physicians use a variety of medical, surgical and dietary approaches in an attempt to control seizures, and polypharmacy 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. The applicability of the included studies to the UK population may be a point for discussion with clinical experts on the appraisal committee. For example, it is unclear whether and to what extent standard care, and hence CCM, would be expected to differ between the UK and the USA (the majority of study participants were recruited in the USA).

ERG question A10: How similar does the company consider the patients in GWPCARE3, GWPCARE4 and GWPCARE5 to be compared to patients seen in practice in England and Wales? Have any clinical experts commented on this issue?

Company response: '*It is expected that the patients in these studies will be very similar to those seen in practice in England and Wales*.

GWPCARE3 included patients from the UK, the USA, Spain and France.

GWPCARE4 included patients from the USA, Netherlands and Poland.

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 ERG notes, from the CSR, that [redacted] of the [redacted] sites which randomised patients in GWPCARE3 were in the UK and that only [redacted] of the [redacted] randomised study participants were from the UK.[17] 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 CS (Section B.2.12) includes the following statements: '*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. 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),*' (un-referenced statement, CS, Table 2).[1]

In line with the NICE scope, the CS considered CBD to be an add-on treatment.

The majority of the clinical effectiveness evidence included in the CS concerned the maximum recommended dose (20 mg/kg/day), (See Table 4.2, section 4.2 of this report for an overview of the methods, for both trials).

ERG comment: The ERG asked a number of questions[14] relating to the dose of CBD used in the key trials, GWPCARE3[17] and GWPCARE4,[18] and how this relates 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.

ERG question A1: The description of the technology being appraised in the company submission (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 is anticipated to receive the 10mg/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 a maintenance dose of 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 in the alternative scenario was estimated by assuming that patients who achieve ≥75% reduction in drop seizures receive 20 mg/kg/day, while patients experiencing <75% reduction in drop seizures receive 10 mg/kg/day. The proportion of responders with ≥75% and <75% reduction in drop seizures was obtained from the Phase 3 clinical trial, GWPCARE3 (see Table 41 in the CS).'

b. How would patients be identified as being suitable for the 20 mg/kg/day dose? Is it anticipated that all patients will start with the lower dose? If so, what cut-off for inadequate response to the lower dose would be used?

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 drop 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, are patients expected 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 open-label extension 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,[19] to UK clinical practice. The interim report for GWPCARE5,[19] provided by the company in their clarification response, stated that, [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/day 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 (GWPCARE3 and GWPCARE4).

d. Please describe the method and time point of assessment for an increase in maintenance dose.

Company response: '*See A1b above.*'

ERG interpretation: The ERG notes that the company's response does not provide any protocol/time frame for assessing patients for potential dose escalation.

3.3 Comparators

The NICE scope describes the comparators(s) as: "Established clinical management without cannabidiol, which may include combinations of sodium valproate, lamotrigine, rufinamide, topiramate, felbamate, clobazam, levetiracetam, ketogenic diet and vagus nerve stimulation. The comparator used in the CS and in the key trials (GWPCARE3[17] and GWPCARE4[18]) is CCM, which includes various combinations of different AEDs. Different combinations of AEDs are 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 (GWPCARE3[17] and GWPCARE4[18]) report a number of subgroup analyses, including for concurrent use of a number of individual AEDs (clobazam, sodium valproate, lamotrigine, levetiracetam and rufinamide).

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.

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 affected by the particular composition of clinical management (e.g. by treatment interactions). 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 lists 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 (Table 1) stated that the outcome measures considered were:

- seizure frequency (drop seizures and overall)
- proportion of people drop seizure-free
- number of people with episodes of status epilepticus
- mortality
- adverse effects of treatment
- health-related quality of life (HRQoL)
- CGIC (Caregiver Global Impression of Change)
- CGICSD (Caregiver Global Impression of Change in Seizure Duration)

and noted that the primary outcome of the key trials was drop seizure frequency.[1] Reporting of clinical effectiveness outcomes, in the CS, was incomplete. The CS (Section B.2.6) reported some results for the following outcomes:

- percentage reduction in total seizures
- percentage reduction in drop seizures
- number with ≥50% reduction in drop seizures
- number with ≥75% reduction in drop seizures
- number with ≥100% reduction in drop seizures
- number with P/CGIC (patient or caregiver global impression of change) improvement from baseline
- adverse events
- withdrawals

Status epilepticus was reported as an adverse event and no mortality or health-related quality of life results were reported. The professional organisation submission, from the ABN,[11] includes the following questions and answers, in relation to mortality and HRQoL:

Q Do you expect the technology to increase length of life more than current care?

A Yes, if seizure freedom is achieved. Stopping drop seizures can also be life-saving.

Q Do you expect the technology to increase health-related quality of life more than current care?

A Yes, if seizure freedom is achieved.

indicating that overall freedom from seizures may be the most clinically relevant outcome.

The reason for the inclusion of the additional outcomes, number with ≥50% reduction in drop seizures and number with ≥75% reduction in drop seizures, is unclear. The professional organisation submission, from the ABN,[11] includes the following statement about clinically significant response: '*The ideal is freedom from seizures, but this is rarely achieved with current treatments. Cessation of generalised tonic-clonic seizures (one type of seizure that can be 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. Cessation of drop seizures, typical of this condition, is of definite value. The commonly used measures of a 50% 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 (e.g. of sudden death) or improve quality of life.*'

A potentially more important issue is that, although mortality was 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 drop 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,[19] did not list either SUDEP or overall mortality in the effectiveness outcomes to be assessed, although SUDEP was reported as a serious treatment-emergent adverse event (TEAE).

ERG comment: The ERG asked a number of questions[14] relating to the outcome measures used in the key trials, GWPCARE3[17] and GWPCARE4,[18] and included in the CS.[1] The questions are given below with the company's responses and our interpretation.

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 the choice of 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 LGS in the cannabidiol clinical trials were children and young adults with a broad spectrum of abilities, some 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 note: The information contained in ("QA9b. Collection of the Seizure Data (Primary Endpoint) on the IVRS") is reproduced in Appendix 2 of this report.

We also asked the company to provide full results for all outcomes assessed in GWPCARE3[17] and GWPCARE4,[18] including listed outcomes that were not reported in the CS,[1] incomplete data (e.g. results reported only as relative (percentage) change, missing baseline and end-point values), and provision of point estimates only (missing IQR, SD or 95% CI). The company provided a separate document with addition results and missing data;[21] 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 CS (Section B.1.4) states that: '*The use of cannabidiol CBD is unlikely to raise any equality issues.*'[1]

No patient access scheme (PAS) is proposed. [redacted]

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify studies reporting the efficacy and safety of drug interventions in LGS and Dravet syndrome (DS). This section of the ERG report critiques the methods of the review including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis of cannabidiol studies.

The population defined by the inclusion criteria for this systematic review (see Table 4.1) was children and/or adults with LGS or DS and studies which included mixed populations with other types of childhood epilepsy were also included. No restrictions, based on age or number of prior AED regimens, were applied. The systematic review was described, in detail, in Appendix D of the CS. Appendix D included an abstract screening algorithm (Table 44), which indicated that randomised controlled trials (RCTs) which did not assess an included intervention (defined as CBD) were excluded, however, the list of included efficacy studies (Table 45, in Appendix D of the CS) included RCTs of other (comparator) AEDs, which did not include a CBD arm; these studies were not used in the submission.

ERG comment: The company were asked to provide clarification on the inclusion of RCTs of comparator AEDs.[14] The following response was provided:

'*Table 45 also lists other RCTs of drug treatments for LGS, 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 12 clinical trials of other drug treatments in LGS, reported in a total of 39 publications. These were listed in the submission for transparency and completeness.*'

The company were also asked to clarify whether ketogenic diet and vagus nerve stimulation were also valid comparators in the systematic review; the following response was provided:

'*Vagus nerve Simulation (VNS) and ketogenic diet were considered to be part of current clinical management (CCM) of LGS. 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.*'

The ERG considers that VNS and ketogenic diet should not be treated differently to pharmacological components of CCM. The inclusion of a summary of any RCTs where other AEDs or non-pharmacological comparators were evaluated as adjunctive treatments (other AED or non-pharmacological comparator + CCM versus CCM) would have been appropriate, and the potential of such studies to inform a network meta-analysis (NMA) should have been considered.

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.[22] The submission was checked against the single technology appraisal (STA) template for company/sponsor submission of evidence.[23]

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 of the CS.[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 43 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.[14] These strategies were not provided in the clarification response.[15]

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 comments:

- 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 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 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, 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

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

Domain	Inclusion criteria
Patient population	• Children and/ or adults with LGS or DS • Include mixed populations with other types of childhood epilepsy
Intervention	• Cannabidiol • No intervention (QoL, costs reviews)
Comparator	• 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
Study design	• 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

Domain	Inclusion criteria
	• 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
Other	• Full text publications, any date • Conference abstracts: last 2 years (2016-18) • Most recent update of systematic reviews • Efficacy reviews, any language • QoL, costs, economic model reviews: full text in English
Source: Inclusion criteria listed in Appendix D of the CS DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome; ICU: intensive care unit; QoL: quality of life; RCT: randomised controlled trial; SLR: systematic literature review	

ERG comment: Recommended methods were used for initial inclusion screening (titles and abstracts): two reviewers independently assessed studies for inclusion in the SLR and any disagreements were resolved through discussion and consensus. The company were asked to clarify whether full papers were also independently screened by two reviewers, and they confirmed that this was the case.

The ERG considers that the inclusion criteria for the SLR were in broadly line with the NICE scope, but questions why non-pharmacological comparators (VNS and ketogenic diet) were treated differently to AEDs and why the submission made no use of the RCTs of comparator AEDs identified.

The ERG was also unclear as to why conference abstracts were limited to the past two years.

With respect to evidence about the safety of CBD, 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. The CS did provide limited information on GWPCARE5, an ongoing open label study, and an interim report on safety outcomes from this study[19] was provided in the company's clarification response. Safety data from the GWPCARE5 interim report are included in sections 4.2.8 of this report.

4.1.3 Critique of data extraction

The CS did not provide any details of how data were extracted from the included studies, or how many reviewers were involved in the process. It is therefore not clear whether the data extraction process was adequately designed to minimise error and bias during data extraction.

4.1.4 Quality assessment

The company assessed the quality of the two main trials GWPCARE 3 and 4 and concluded that both trials were of high quality with a low risk of bias. The ongoing trial, GWPCARE5, was not quality assessed. The 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 usually recommended that two reviewers are involved in the extraction of data and assessment of study quality, in order to minimise the potential for bias and error.

4.1.5 Evidence synthesis

As stated in sections B.2.8 and B.2.9 of the CS, respectively,[1] no meta-analysis was conducted and no indirect treatment comparisons or mixed treatment comparisons were conducted. 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.'

ERG comment: The ERG agrees that, due to the variation in CCM in LGS 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/NMA may have been possible, based on the included trials (GWPCARE3 and GWPCARE4) 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 (Section B.2) identified two RCTs of cannabidiol (GWPCARE3[17] and GWPCARE4[18]) and an ongoing open-label extension study GWPCARE5 as relevant to the submission. An interim CSR for GWCARE5[19] was provided in the company's clarification response and this report included some details of the study methods, however, no information about GWPCARE5 methods was included in the CS.[1] With the exception of section B.2.11 Ongoing studies, the CS[1] did not include any results from GWPCARE5.

4.2.1 Details of included cannabidiol studies

Both RCTs (GWPCARE3[17] and GWPCARE4[18]) were conducted in patients aged two to 55 years with LGS, whose seizures were incompletely controlled with previous AEDs and who had suffered at least two drop seizures per week in the baseline period. Both studies defined patients with LGS as those who had an EEG showing a pattern of slow spike-and-wave complexes and had at least two types of generalised seizures including drop seizures for at least six months.[1] The intervention was CBD in addition to CCM and the comparator was CCM without CBD (i.e. CCM plus placebo). GWPCARE3 was a three-arm study, comparing two doses of CBD (10 mg/kg/day and 20 mg/kg/day) in addition to CMM and CCM plus placebo,[17] and GWPCARE4 compared CBD (20 mg/kg/day) in addition to CCM and CCM plus placebo.[18] A summary of study methodology, for GWPCARE3 and GWPCARE4, is provided in Table 4.2.

Table 4.2: Summary of study methodology for included trials

	GWPCARE3[17]	GWPCARE4[18]
Location	USA, Spain, UK, France	USA, Netherlands, Poland
Trial design	Phase 3, multicentre, randomised, double-blind, placebo-controlled trial.	Phase 3, multicentre, randomised, double-blind, placebo-controlled trial.
Eligibility criteria for participants	Aged between 2 and 55 years, EEG pattern of slow spike-and-wave complexes, with ≥2 types of generalised seizures including drop seizures for ≥ 6 months.	Aged between 2 and 55 years, clinical diagnosis of LGS including EEG pattern of slow spike-and-wave complexes, with ≥2 types of generalised seizures including drop seizures for ≥ 6 months.
Settings and locations where data were collected	Clinic visits at 2, 4, 8 and 14 weeks; interactive voice-response system to record number and types of seizures every day; telephone assessment of adverse events and concomitant medication at 6 and 10 weeks; final safety assessment 4 weeks after end of treatment.	Clinic visits at 15, 29, 57 and 99 days; interactive voice-response system to record number and types of seizures every day; telephone assessment at 43 and 71 days; final safety assessment 4 weeks after end of treatment.
Trial drugs (number in each group)	Cannabidiol 10 mg/kg/day oral solution (n=73); Cannabidiol 20 mg/kg/day oral solution (n=76); Placebo (n=76) 2.5 mg/kg/day to start, titrated up to target dose over 2 weeks then 12-week maintenance period, tapering over up to 10 days before discontinuing or optional open-label phase.	Cannabidiol 20 mg/kg/day oral solution (n=86); Placebo (n=85) 2.5 mg/kg/day to start, titrated up to target dose over 2 weeks then 12-week maintenance period, tapering over up to 10 days before discontinuing or optional open-label phase.
Permitted and disallowed concomitant medication	Other AEDs permitted but had to be stable dose for 4 weeks before screening and during trial; Excluded if other use of cannabis in past 3 months, corticotropins in past 6 months or current use of felbamate for <1yr.	Other AEDs permitted but had to be stable dose for 4 weeks before screening and during trial; Excluded if already taking cannabis, corticotropins in past 6 months or current use of felbamate for <1yr.
Primary outcomes	Percentage reduction in drop seizure* frequency/28 days	Percentage reduction in drop seizure** frequency/28 days
Other outcomes used in the economic model or specified in the scope	Percentage of patients with at least 50% reduction from baseline in drop seizure frequency; Percentage of patients with at least 25% reduction from baseline in drop seizure frequency; Percentage of patients with at least 75% reduction from baseline in drop seizure frequency;	Percentage of patients with at least 50% reduction from baseline in drop seizure frequency; Percentage of patients with at least 25% reduction from baseline in drop seizure frequency; Percentage of patients with at least 75% reduction from baseline in drop seizure frequency;

	GWPCARE3[17]	GWPCARE4[18]
	Percentage of patients with 100% reduction from baseline in drop seizure frequency; Percentage reduction in total seizure frequency from baseline; Percentage of patients with worsening or improvement in drop seizure frequency during treatment period; Percentage reduction from baseline in frequency of non-drop seizure, convulsive seizures (tonic-clonic, tonic, clonic or atonic), nonconvulsive seizures (myoclonic, partial or absence) and individual seizures by type; Patient or Caregiver Global Impression of Change from baseline in overall condition; Patient or Caregiver Global Impression of Change in Seizure Duration from baseline in overall condition; Change from baseline in Epworth Sleepiness Scale; Change from baseline in Quality of Childhood Epilepsy questionnaire score; Change from baseline in Vineland Adaptive Behavior Scale score-II; Frequency of status epilepticus episodes.	Percentage of patients with 100% reduction from baseline in drop seizure frequency; Percentage reduction in total seizure frequency from baseline during treatment period; Percentage of patients with worsening or improvement in drop seizure frequency during treatment period; Percentage reduction from baseline in frequency of non-drop seizure, convulsive seizures (tonic-clonic, tonic, clonic or atonic), nonconvulsive seizures (myoclonic, focal or absence) and individual seizures by type; Patient or Caregiver Global Impression of Change from baseline in overall condition; Patient or Caregiver Global Impression of Change in Seizure Duration from baseline in overall condition; Change from baseline in Epworth Sleepiness Scale; Change from baseline in Quality of Childhood Epilepsy questionnaire score; Change from baseline in Vineland Adaptive Behavior Scale score-II; Hospital admissions due to epilepsy; Cognitive function; Proportion of patients with adverse events using standard severity measures; Columbia Suicide Severity Rating scale scores; Frequency of status epilepticus episodes.
Pre-planned subgroups	None	None

Source: CS table 6
*Drop seizure defined as: Atonic, tonic or myoclonic or absence seizures that would lead to a fall if not supported
**Drop seizure defined as: An attack or spell (atonic, tonic or tonic-clonic) involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface.
AED: Anti-epileptic drug; EEG: Electroencephalogram; LGS: Lennox-Gastaut syndrome

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 shown in Figure 2.1). The company were 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 AEDs made up <5% of the study populations (see Section 2.2 of this report).

It should be noted that both of the key studies included in the CS (GWPCARE3[17] and GWPCARE4[18]) 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 monthly drop seizure frequency. It has been reported that reductions in seizures, in individuals with LGS who are treated with AEDs, tends to diminish over time.[10, 24] The ERG notes that it is 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.

In regard to long-term outcomes, the trials were powered to detect changes from baseline in drop seizures. However, the two main trials were of 14 weeks' duration so cannot provide long-term data on SUDEP and other deaths, or about whether any reductions in seizure frequency are sustained in the long-term. Any link between a reduction in drop seizures and possible reductions in mortality cannot be determined from the two main randomised trials. The interim report for the ongoing open-label extension study, GWPCARE5,[19] provides only 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.

Regarding the extent to which the CBD studies are representative of the UK population with LGS, the company were asked to provide clarification on this issue (see Section 3.1 of this report). The ERG notes that the GWPCARE4 study did not include any UK patients, the CSR for GWPCARE3[17] reports that [redacted] of the [redacted] randomised participants were from UK centres, and it is unclear how many, if any, UK patients entered the ongoing open-label extension study, GWPCARE5.[19] The applicability of the key trials to the UK population may be a point for discussion with clinical experts on the appraisal committee.

Studies evaluated different doses of CBD; GWPCARE3 evaluated 10mg/kg/day and 20mg/kg/day, and GWPCARE4 evaluated only 20mg/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 drop 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 escalation 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 drop 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/day dose of CBD is, limited to data from 73 patients in the GWPCARE3 study.[17]

The CS stated that there were no pre-planned subgroups in either trial (see Table 4.2), however the CSRs for both GWPCARE3[17] and GWPCARE4[18] describe 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 both GWPCARE3 and GWPCARE4:

- Age group (2-5 years, 6-11 years, 12-17 years and 18-55 years)
- Sex (Male, Female)
- Region (US, Rest of the World)
- Clobazam use (Yes, No)
- Valproate use (Yes, No)
- Lamotrigine use (Yes, No)
- Levetiracetam use (Yes, No)
- Rufinamide use (Yes, No)
- Baseline average drop 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 (< 6, ≥ 6).

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 power.

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 4.2.5 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 drop seizure frequency per 28 days. A power calculation for the primary outcome was reported for both of the included trials. For GWPCARE3, a sample of 150 patients (50 patients per treatment group) would provide 80% power to detect a 18% difference in the primary outcome with a two-sided 5% significance level and a standard deviation of 56%.[1] Patients receiving placebo were split into two equal cohorts with 25 patients receiving a matching placebo for the 10 mg/kg/day dosing volume and 25 patients receiving a matching placebo for the 20 mg/kg/day dosing volume, but these two groups were pooled for the efficacy analysis. For GWPCARE4, a sample of 100 patients would provide 80% power to detect a 32% difference in the primary outcome with a two-sided 5% significance level and a standard deviation of 32%.

The study flow charts (Figures 12 & 13, Appendix D of the CS)[1] indicate that all patients in GWPCARE4 received their allocated treatment, whereas in GWPCARE3 six of the 73 patients randomised to 10 mg/kg/day received a dose above the target. These patients were included in the 10 mg/kg/day group for the intention to treat (ITT) analysis but included in the 20 mg/kg/day group for the safety analysis.

The company stated that, in both trials, the primary outcome was analysed using the ITT population. In GWPCARE3 and GWPCARE4 the ITT population 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. Patients were analysed according to their randomised treatment group.

For both trials, the percentage change in frequency of all seizure types was assessed using a Wilcoxon rank-sum test and the median difference and 95% confidence intervals (CI) were estimated using the Hodges-Lehmann approach. For both trials, the percentage of patients who had a response (25%, 50%, 75% and 100% reduction in drop seizures) was assessed using a Cochran-Mantel-Haenszel test stratified by age group and odds ratios with 95% CI were calculated. The patient/Caregiver Global Impression of Change scores were analysed using ordinal logistic regression with trial and age groups as factors.[1]

ERG comment: The statistical analyses used appropriate methods and appear to have been conducted appropriately.

4.2.3 Trial participant characteristics

Table 4.3 shows the baseline characteristics of the participants in GWPCARE3 and GWPCARE4. GWPCARE3 included a total of 225 patients and GWPCARE4 171. The mean age across both trials was approximately 15.5 years. Female and male participants were represented approximately equally in the trials; the overall percentage of women in GWPCARE3 was 43% and in GWPCARE4 was 49%. Both trials included predominantly participants who identified as white (GWPCARE3 88%, GWPCARE4: 90%). More than three quarters of the participants (78%) across the two trials were from the USA. Patients had used on average six or seven prior AEDs, although as discussed in Section 3.1 there was a large range in the number of prior treatments (0 to 28). The median number of concurrent treatments was three, (range 0 to 5).

ERG comment: The ERG notes that trial participants were predominately from the USA and that Black and Asian people appear to be underrepresented across the two trials.

Issues relating to the prior and concurrent AED use and the applicability of the study populations to the UK population with LGS are discussed in detail in section 3.1 of this report.

Table 4.3: Baseline characteristics in GWPCARE3 and GWPCARE4

Baseline characteristics	GWPCARE3			GWPCARE4	
	Cannabidiol 10 mg/kg/day + CCM	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**
Number randomised	73	76	76	86	85
Age in years	Mean 15.4 SD 9.5 Median [redacted] Range 2.6 to 42.6	Mean 16.0 SD 10.8 Median [redacted] Range 2.6 to 48.0	Mean 15.3 SD 9.3 Median [redacted] Range 2.6 to 43.4	Mean 15.5 SD 8.7 Median [redacted] Range 2.7 to 39	Mean 15.3 SD 9.8 Median [redacted] Range 2.8 to 45.1
Gender	40 (54.8%) male	45 (59.2%) male	44 (57.9%) male	45 (52.3%) male	43 (50.6%) male
Ethnicity	White: 62 Black: 4 Asian: 1 Other / NA: 6	White: 67 Black: 4 Asian: 1 Other / NA: 4	White: 69 Black: 3 Asian: 2 Other / NA: 2	White: 75 Black: [redacted] Asian: [redacted] Other/NA: [redacted]	White: 79 Black: [redacted] Asian: [redacted] Other/NA: [redacted]
Location*	USA 60 (82%) Rest of world 13 (17.8%)	USA 59 (77.6%) Rest of world 17 (22.4%)	USA 62 (81.6%) Rest of world 14 (18.4%)	[redacted]	[redacted]
Baseline seizure types: number (%) of patients with seizure type during baseline	Tonic: 56 (76.7%) Atonic: 40 (54.8%) Absence: 28 (38.4%)	Tonic: 59 (77.6%) Atonic: 50 (65.8%) Absence: 40 (52.6%)	Tonic: 57 (75.0%) Atonic: 41 (53.9%) Absence: 37 (48.7%)	Tonic: [redacted] Atonic: [redacted] Absence: [redacted] Generalised tonic-clonic: [redacted] Myoclonic: [redacted] Countable partial: [redacted]	Tonic: [redacted] Atonic: [redacted] Absence: [redacted] Generalised tonic-clonic: [redacted] Myoclonic: [redacted]

Baseline characteristics	GWPCARE3			GWPCARE4	
	Generalised tonic-clonic: 37 (50.7%) Myoclonic: 22 (30.1%) Countable partial: 18 (24.7%)	Generalised tonic-clonic: 41 (53.9%) Myoclonic: 33 (43.4%) Countable partial: 17 (22.4%)	Generalised tonic-clonic: 34 (44.7%) Myoclonic: 30 (39.5%) Countable partial: 19 (25.0%)		Countable partial: [redacted]
Baseline total seizure frequency per 28 days: median (Interquartile range [IQR])	165.0 (81.3 to 359.0)	174.29 (82.7 to 392.4)	180.63 (90.4 to 431.3)	144.6 (72.0 to 385.7)	176.7 (68.6 to 359.5)
Baseline drop seizure frequency per 28 days: median (IQR) (range)	86.9 (40.6 to 190.0) ([redacted])	85.5 (38.3 to 161.5) ([redacted])	80.3 (47.8 to 148.0) ([redacted])	71.4 (27.0 to 156.0) ([redacted])	74.7 (47.3 to 144.0) ([redacted])
Baseline non-drop seizure frequency per 28 days: median (IQR)	95.7 (14.0 to 280.0)	93.7 (22.2 to 278.4)	78.0 (22.0 to 216.0)	94.0 (19.8 to 311.0) [n=77]	85.0 (20.5 to 220.0) [n=79]
Prior treatments	Number of prior AEDs: Mean = 7.01 SD 4.63, median = 6 (range 0 to 21)	Number of prior AEDs: Mean = 6.61 SD 3.68, median = 6 (range 1 to 18)	Number of prior AEDs: Mean = 7.18 SD 4.37, median = 6 (range 1 to 22)	Number of prior AEDs: Mean = [redacted] Median 6 Range 1 to 18 Number receiving each prior treatment: VNS: NR	Number of prior AEDs: Mean = [redacted] Median 6 Range 0 to 28 Number receiving each prior treatment:

Baseline characteristics	GWPCARE3			GWPCARE4	
	Number receiving each prior treatment: Vagal nerve stimulation (VNS): 10 Corpus callosotomy: 7 Gastrostomy: 8	Number receiving each prior treatment: VNS: 16 Corpus callosotomy: 8 Gastrostomy: 3	Number receiving each prior treatment: VNS: 14 Corpus callosotomy: 7 Gastrostomy: 5	Corpus callosotomy: NR Gastrostomy: NR	VNS: NR Corpus callosotomy: NR Gastrostomy: NR
Concurrent AED use	Median 3 AEDs, range 1 to 5 Number taking each medication: Clobazam: 37 Valproate: 27 Levetiracetam: 22 Lamotrigine: 22 Rufinamide: 19 VNS: 15 Ketogenic diet: 6	Median 3 AEDs, range 0 to 5 Number taking each medication: Clobazam: 36 Valproate: 28 Levetiracetam: 24 Lamotrigine: 20 Rufinamide: 26 VNS: 17 Ketogenic diet: 6	Median 3 AEDs, range 1 to 5 Number taking each medication: Clobazam: 37 Valproate: 30 Levetiracetam: 23 Lamotrigine: 25 Rufinamide: 20 VNS: 21 Ketogenic diet: 6	Median 3 AEDs; range 1 to 5 Number taking each medication: Clobazam: 42 Valproate: 36 Levetiracetam: 23 Lamotrigine: 33 Rufinamide: 25 Ketogenic diet: 4 VNS: 26	Median 3 AEDs, range 1 to 4 Number taking each medication: Clobazam: 42 Valproate: 33 Levetiracetam: 35 Lamotrigine: 31 Rufinamide: 21 Ketogenic diet: 10 VNS: 25
Source CS and CSRs: CS'[1] Tables 7 and 8; GWPCARE3 CSR,[17] Tables 3.1.2, and 3.2.2; GWPCARE4,[18] Tables 3.1.2 and 3.2.2					

Baseline characteristics	GWPCARE3	GWPCARE4
AED: anti-epileptic drug; CCM: concurrent clinical management; IQR: interquartile range; NA: not applicable; NR: not reported; VNS: vagus nerve stimulation *Detailed breakdown by country (for 'rest of world') cannot be provided, as the relevant appendices were missing from the CSR provided.		

ERG comment: 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.[17, 18, 25-28] Where there were discrepancies between the CS and the CSRs, data were taken from the CSRs.

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 (see Table 4.4). It was not clear how many reviewers were involved in the quality assessment process. As stated in section 4.1.6 of this report, the quality assessment tool used was not referenced.

Table 4.4: Quality assessment for cannabidiol RCTs

Trial acronym	GWPCARE3[17]	GWPCARE4[18]
Randomisation appropriate?	Yes	Yes
Treatment concealment adequate?	Yes	Yes
Baseline comparability adequate?	Yes	Yes
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 47, Appendix D of the CS		

ERG comment: The ERG has assessed the trials included in this report against the criteria provided, and agrees with the quality assessment and supporting information provided in the CS, with the following exception: The ERG does not agree with the judgement that there were no dropout imbalances in the cannabidiol RCTs. The participant flow chart for GWPCARE3 (Figure 13, Appendix D of the CS) reported a higher discontinuation rate for the 20 mg/kg/day arm (9/76 [11.8%]) than for the 10 mg/kg/day arm (2/73 [2.9%]) and the CCM arm (2/76 [2.6%]). Similarly, the participant flow chart for GWPCARE4 (Figure 14, Appendix D of the CS) reported a higher discontinuation rate for the 20 mg/kg/day arm (14/86 [16.3%]) than the CCM arm (1/85 [1.2%]). The quality assessment did not include an item on the adequacy of participant blinding; based on information about the matched composition of the intervention and placebo, provided in the CSRs, the ERG considers that participant blinding was adequate.

4.2.5 Clinical effectiveness results for included cannabidiol studies

The efficacy results for GWPCARE3 and GWPCARE4 are shown in Table 4.5. This Table includes results for outcomes reported in the CS (Tables 11 and 12),[1] with additional data (e.g. baseline and endpoint values, interquartile range (IQR)) as provided in the company's clarification response.[15] Table 4.5 also includes results for status epilepticus (SE), which is reported as an adverse event in the CS.[1] The number of drop 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 also provided; results for this outcome were taken from the CSR full results tables provided in the company's clarification response.[26, 28]

Table 4.5: Efficacy results of GWPCARE3 and GWPCARE4

	GWPCARE3			GWPCARE4	
	Cannabidiol 10 mg/kg/day + CCM	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**
Number randomised	73	76	76	86	85
Study duration	14 weeks			14 weeks	
Primary outcome - drop seizure frequency per 28 days					
Baseline drop seizure frequency	Median 86.9 (IQR 40.6 to 190.0)	Median 85.5 (IQR 38.3 to161.5)	Median 80.3 (IQR 47.8 to 148.0)	Median 71.4 (IQR 27.0 to 156.0)	Median 74.7 (IQR 47.3 to 144.0)
Treatment period drop seizure frequency	Median 50.0 (IQR 20.5 to 113.2)	Median 44.9 (IQR 14.4 to 117.4)	Median 72.3 (IQR 35.3 to 125.0)	Median 31.4 (IQR 14.4 to 92.0)	Median 56.3 (IQR 29.7 to 129.3)
% Change in drop seizures during treatment	Median -37.2 (IQR -63.8 to -5.6)	Median -41.9 (IQR -72.4 to -1.3)	Median -17.2 (IQR -37.1 to 0.9)	Median -43.9 (IQR -69.6 to -1.9)	Median -21.8 (IQR -45.7 to 1.7)
Comparison to placebo	Median difference in % change -19.2 (95% CI: -31.2 to -7.7)	Median difference in % change -21.6 (95% CI: -34.8 to -6.7)	NA	Median difference in % change -17.21 (95% CI: -30.32 to -4.09)	NA

	GWPCARE3			GWPCARE4	
Secondary outcomes - total seizure frequency per 28 days					
Baseline total seizure frequency	Median 165.0 (IQR 81.3 to 359.0)	Median 174.3 (IQR 82.7 to 392.4)	Median 180.6 (IQR 90.4 to 431.3)	Median 144.6 (IQR 72.0 to 385.7)	Median 176.7 (IQR 68.6 to 359.5)
Treatment period total seizure frequency	Median 76.1 (IQR 38.5 to 188.4)	Median 90.3 (IQR 28.7 to 234.0)	Median 138.9 (IQR 65.2 to 403.4)	Median 83.75 (IQR 27.4 to 255.4)	Median 128.68 (IQR 59.3 to 327.4)
% Change in total seizures during treatment	Median -36.4 (IQR-64.5 to -10.8)	Median -38.4 (IQR -64.6 to -0.7)	Median -18.5 (IQR -39.0 to 0.5)	Median -41.2 (IQR -62.8 to -13.0)	Median -13.7 (IQR -45.0 to 7.3)
Comparison to placebo	Median difference in % change -19.5 (95% CI: -30.4 to -7.5)	Median difference in % change -18.8 (95% CI: -31.8 to -4.4)	NA	Median difference in % change -21.13 (95% CI: -33.26 to -9.37)	NA
Response rate					
Number with ≥50% reduction in drop seizure frequenc	26	30	11	38	20

	GWPCARE3			GWPCARE4	
y from baseline					
Comparison to placebo	OR 3.27 (95% CI: 1.47 to 7.26)	OR 3.85 (95% CI: 1.75 to 8.47)	NA	OR 2.57 (95% CI: 1.33 to 4.97)	NA
Number with ≥75% reduction in drop seizure frequency from baseline	8	19	2	17	7
Comparison to placebo	OR 4.55 (95% CI: 0.93 to 22.22)	OR 12.33 (95% CI: 2.76 to 55.13)	NA	OR 2.75 (95% CI: 1.07 to 7.01)	NA
Number with 100% reduction in drop seizure frequency from baseline	0	0	0	0	0
Comparison to placebo	NA	NA	NA	NA	NA
Global impression of change					

	GWPCARE3			GWPCARE4	
Number with P/CGIC improvement from baseline	48	43	33	49	29
Comparison to placebo	OR 2.57 (95% CI: 1.41 to 4.66)	OR 1.83 (95% CI: 1.02 to 3.30)	NA	OR 2.54 (95% CI: 1.45 to 4.47)	NA
Status epilepticus*					
Number with convulsive status epilepticus at baseline	2	8	3	2	1
Number with convulsive status epilepticus in treatment period	1	2	2	1	1
Number with non-convulsive status epileptic	3	3	6	3	2

	GWPCARE3			GWPCARE4	
us at baseline					
Number with non-convulsive status epilepticus in treatment period	3	2	3	1	1
Drop seizure-free days per 28 days					
Baseline period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison to placebo	[redacted]	[redacted]	NA	[redacted]	NA

Sources: Clarification response[15]; GWPCARE3 CSR[17, 26]; GWPCARE4 CSR[18, 28]

CCM: current clinical management; CI: confidence interval; IQR: interquartile range; NA: not applicable; NR: not reported; OR: odds ratio; P/CGIC: patient/caregiver global impression of change; P/CGICSD: patient/caregiver global impression of change seizure duration; SD: standard deviation

*: Status epilepticus, defined as any seizure lasting ≥30 minutes. Only patients who reported convulsive status epilepticus during baseline reported convulsive status epilepticus during the treatment period. However, in GWPCARE3, 4 patients (1 in the 20 mg/kg/day CBD group, 2 in the 10 mg/kg/day CBD group, and 1 in the placebo group) who did not report non-convulsive status epilepticus during the baseline period had an occurrence of non-convulsive status epilepticus during the treatment period.

ERG comments: The ERG notes that only GWPCARE3 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.[15] Patients in GWPCARE3, who received 10 mg/kg/day CBD in addition to CCM, achieved better seizure frequency outcomes than those who received CCM + Placebo. Specifically, patients in the 10 mg/kg/day CBD groups experienced fewer drop seizures and fewer seizures overall, during the 14-week treatment period, than those in the placebo group. The median difference in the percentage change in drop seizures per 28 days between the 10 mg/kg/day CBD group and the placebo group was -19.2% (95% CI: -31.2% to -7.7%), and the median difference in the percentage change in total seizures per 28 days was -19.5% (95% CI: -30.4% to -7.5%). A higher proportion of patients in the 10 mg/kg/day CBD group achieved at least a 50% reduction in drop seizures, during the treatment period, than in the placebo group, OR 3.27 (95% CI: 1.47 to 7.26). No patient in GWPCARE3 achieved freedom from drop seizures for the whole 14-week treatment period; the CS notes that three patients in the 10 mg/kg/day CBD group and one patient in the placebo group were drop seizure-free for the whole of the maintenance phase (day 15 onwards).[1]

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,[15] 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 was defined as those experiencing ≥75% reduction in drop seizures on the 10 mg/kg/day 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. No evidence has been provided to support the idea that patients who have responded to 10 mg/kg/day CBD (≥75% reduction in drop seizures) are likely to derive additional benefit from increasing the dose to 20 mg/kg/day or, conversely, that patients who have failed to reach the threshold of 75% reduction in seizures on 10 mg/kg/day are not likely to benefit from escalation to 20 mg/kg/day.

The company were asked to provide the results of comparisons between the 20 mg/kg/day and 10 mg/kg/day groups in GWPCARE3, for all outcomes where these were available. The company stated, in their clarification response,[15] 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 drop seizures (25%) compared with the 10 mg group (11%) and the placebo group (3%).*' The ERG questions the validity of the assumption of equivalent effects between these two doses, which is inherent in the company's use of data for the 20 mg/kg/day dose to inform their base-case for 10 mg/kg/day, and the company's statement that: '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.' Without any formal statistical comparison of the 10 and 20 mg/kg/day doses there is no supporting evidence for the claim that the doses have equivalent effects.

The CS does 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 the mean modal dose of CBD during the open-label extension (OLE) treatment phase was 23 mg/kg/day (range 21–25 mg/kg/day across the 12-wk visit windows).

[redacted]

[redacted]

In addition to the above points, the company were asked to comment on the relatively large placebo response observed across the trials included in the CS. The company provided the following detailed response:

'*Large placebo effects are well documented in epilepsy clinical trials, and have been observed in LGS studies for lamotrigine, topiramate, felbamate, rufinamide and clobazam going back to the early 1990s.* [10]

A comparison of placebo effects between trials is challenging given the high levels of heterogeneity in study designs.[29] *Nonetheless, a numerical comparison on the primary endpoint (median percent change in drop seizure frequency from baseline) suggests that GWPCARE3 (which studied the maintenance dose of 10mg/kg/day) has a placebo effect that is at the upper end of, but still in line with, those seen with other agents.*[10] *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.*[10]

The reasons why placebo effects are commonplace in epilepsy trials is unknown. Reasons cited in the literature that may be of particular relevance to cannabidiol include[29]*:*

- *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,[29] *as is true for the cannabidiol studies in LGS.*

In GWPCARE3, an 18% median reduction in drop-seizure frequency was assumed in the placebo group for the determination of sample size. The final outcome was 17.17% and, as such, there was sufficient statistical powering. 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 for 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 OLE 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 LGS 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.'

The ERG agrees with the statement 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 analyses for included cannabidiol studies

The CS stated that there were no pre-planned subgroups in either trial, however the CSRs for both GWPCARE3[17] and GWPCARE4[18] describe a number of potentially relevant subgroup analyses (see Section 4.2.1 of this report) 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. The company stated, in their clarification response,[15] 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 statistical analysis plan. Furthermore, as an orphan indication, these subgroups have small population numbers with low statistical powering.'*

The company referenced the CSRs for results of the subgroup analyses and these results are reproduced in Table 4.6.

ERG comment: 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. Adequately powered subgroup analyses, by type of concurrent AED use, could be used to explore the assumption that the effectiveness of CBD does not vary with the combinations of AEDs to which it is added (i.e. that there are no interaction effects between CBD and any of the other AEDs that may be included in CCM). This assumption is crucial to the validity of the 'mixed' CCM comparator. The ERG considers that there is currently a lack of evidence to support this assumption.

Table 4.6: Subgroup analysis: Patients with a ≥50% reduction in drop seizure frequency from baseline, during the treatment period

	GWPCARE3						GWPCARE4			
	Cannabidiol 10 mg/kg/day + CCM		Cannabidiol 20 mg/kg/day + CCM		Placebo + CCM		Cannabidiol 20 mg/kg/day + CCM		Placebo + CCM	
Study duration	14 weeks						14 weeks			
Number randomised	73		76		76		86		85	
	N[a]	**N[b] (%)**	**N[a]**	**N[b] (%)**	**N[a]**	**N[b] (%)**	**N[a]**	**N[b] (%)**	**N[a]**	**N[b] (%)**
Age group										
2-5 years	[redacted]									
6-11 years										
12-17 years										
18-55 years										
Sex										
Male										
Female										
Region										
USA										
Rest of world										
Clobazam Use										
Yes										
No										
Valproic Acid Use										
Yes										
No										
Lamotrigine Use										
Yes										

	GWPCARE3						GWPCARE4			
No	[redacted]									
Levetiracetam Use										
Yes	[redacted]									
No	[redacted]									
Rufinamide Use										
Yes	[redacted]									
No	[redacted]									
Baseline Drop Seizures per 28 Days										
≤55[c], ≤45[d]	[redacted]									
>55 to ≤125[c], >45 to ≤110[d]	[redacted]									
>125[c], >110[d]	[redacted]									
Number of Current AEDs										
<3	[redacted]									
≥3	[redacted]									
Number of Prior AEDs										
<6	[redacted]									
≥6	[redacted]									

Source: GWPCARE3 CSR,[17] Tables 8.4.1.5.2-2 and 8.4.1.5.2-1, and GWPCARE4 CSR,[18] Table 8.4.1.2.2.16-1.

AEDs: anti-epileptic drugs; CCM: current clinical management; N[a]: Number of patients in the given category; N[b]: Number of patients with a ≥50% reduction in drop seizure frequency from baseline the denominator for the percentage calculation is N[a]);

*: p-value for CBD versus placebo <0.05, calculated using a Fisher's exact test.

[c]: GWPCARE3

[d]: GWPCARE4

4.2.7 Health-related quality of life data for included cannabidiol studies

The CS[1] did not include any results for health-related quality of life outcomes. Overall results for the Quality of Life in Childhood Epilepsy (QOLCE) score were provided in the company's clarification response (detailed responses document)[21] and these are reproduced in Table 4.7 of this report, with additional results taken form the CSRs.

The innovation section of the CS (Section B.2.12) stated that: '*In addition to demonstrating reductions in seizure frequency, CBD has also demonstrated drop seizure-freedom and/or additional seizure-free days. In clinical trials, patients receiving CBD experienced a 2 to 3 times greater number of mean additional drop seizure-free days in a 28-day treatment period than those on CCM.*'[1] The ERG notes that the number of drop seizure-free days was not listed as an outcome in either the final NICE scope[30] or the company's definition of decision problem[1] and results for this outcome were not reported in the clinical effectiveness section of the CS,[1] however, these data were used to inform utility values in the cost effectiveness model; this approach is discussed in detail in section 5.2 of this report. The CS (Section B.2.12) also stated that: '*For patients with LGS 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 LGS patients 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 LGS and more able to focus on their own lives and on the child's siblings.*
- *The LGS 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.*'

ERG comment: The ERG notes that neither the CS nor the CSRs provided any data on the number of days, if any, on which study participants were seizure-free (no seizures of any type). As indicated by the above statements, seizure-free days may be more relevant to the estimation of utility values than drop seizure-free days.

The interpretation of the clinical effectiveness and safety section of the CS (section B.2.13) concludes with the statement that: '*Cannabidiol offers 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.*'

ERG comment: The ERG notes that no patient, in any of the included studies, achieved complete freedom from seizures of any type.

Table 4.7: Health-related quality of life results from GWPCARE3 and GWPCARE4

	GWPCARE3			GWPCARE4	
	Cannabidiol 10 mg/kg/day + CCM	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**
Number randomised	73	76	76	86	85
Study duration	14 weeks			14 weeks	
QOLCE					
Overall score number analysed	36	33	38	26	38
Overall score change from baseline to end of treatment	Mean 7.7 SD 12.85	Mean 1.0 SD 11.49	Mean 6.1 SD 14.85	Mean 7.1 SD 16.90	Mean 3.9 SD 11.54
Overall score adjusted mean treatment difference	1.6 (95% CI: -4.5 to 7.8)	-5.1 (95% CI: -11.4, 1.2)	NA	3.7 (95% CI: -3.3 to 10.7)	NA
QOLIE-31-P					
Number analysed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total score change from baseline to	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

end of treatment					
Adjusted mean treatment difference	[redacted]	[redacted]	NA	[redacted]	NA

Sources: Clarification response[15]; GWPCARE3 CSR[17]; GWPCARE4 CSR[18]

CCM: current clinical management; CI: confidence interval; NA: not applicable; NR: not reported; QOLIE-31-P: quality of life in epilepsy version 2; QOLCE: quality of life in childhood epilepsy; SD: standard deviation

4.2.8 Adverse events data for included cannabidiol studies

This section considers the information about AEs provided in the CS. Adverse events data were taken from the CBD studies included in the CS. A more detailed breakdown of AEs and serious adverse events (SAEs) was provided by the company in their clarification response (detailed responses document),[21] along with interim results from the open-label extension study, GWPCARE5.[19] These results are summarised in Table 4.8. Table 4.9 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 some detrimental effects on markers of liver function. With respect to markers of liver function, the CS[1] also reports that, of the 149 patients in GWPCARE3 taking cannabidiol at any dose, 14 (9%) experienced a serum aminotransferase concentration that was over three times greater than the upper limit of a normal range. 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 (detailed responses document)[21] included the following additional detail on SAEs for the two main included studies:

GWPCARE3

'*Approximately one-third of TEAEs were severe (10/29 events [34.5%] in the 20 mg/kg/day CBD group and 7/22 events [31.8%] in the 10 mg/kg/day CBD group.*

Most of the serious TEAEs reported during the trial involved inpatient hospitalisation/prolongation of existing hospitalisation (36/59 events [61.0%]) or were classed as an "other medically important condition" (21/59 events [35.6%]).

Two events (3.4%) were classed as life-threatening, reported in 1 patient in the 20 mg/kg/day CBD group (preferred terms [PTs]: respiratory syncytial virus infection, adenovirus infection). Neither event was considered treatment-related but both led to discontinuation of CBD and withdrawal from the trial, following which both events resolved.

All treatment-related serious TEAEs were of moderate or severe intensity, and over half led to discontinuation of CBD and withdrawal of the patient from the trial (6/10 events [60.0%], reported in 3 patients in the 20 mg/kg/day CBD group [5 events collectively] and 1 patient in the 10 mg/kg/day CBD group [1 event]).'

GWPCARE4

'*One patient (1.2%) died during GWPCARE4, due to acute respiratory distress syndrome; the death was not considered treatment-related. The patient had several ongoing medical conditions at screening, including global developmental delays, spastic quadriplegia, pain related to feeding, and G-tube use, and had a history of acute respiratory distress syndrome and pneumonia (resolved at screening).*

The majority of serious TEAEs were moderate or severe in intensity (53/59 events [89.8%]). Most of the serious TEAEs reported during the trial involved inpatient hospitalisation/prolongation of existing hospitalisation (30/59 events [50.8%]) or were classed as an "other medically important condition" (25/59 events [42.4%]). Four events (6.8%) were classed as life threatening, reported in 2 CBD patients ([PTs: acute respiratory failure and pneumonia] and [PT: acute hepatic failure]) and 1 placebo patient [PT: status epilepticus; reported term: "status epilepticus/respiratory compromise"]). Most of these events (3/4) were not considered treatment-related and resolved during treatment with no changes to

CBD dose. The event of acute hepatic failure was considered treatment-related and led to withdrawal from the trial, but resolved following discontinuation of CBD.

Most treatment-related serious TEAEs were of moderate or severe intensity (18/20 events [90%]), and over half led to discontinuation of CBD and withdrawal of the patient from the trial (13/20 events [65%], reported in 6 CBD patients).'

No narrative detail was provided for GWPCARE5.

The interim report for GWPCARE5[19] included the following information about SAEs for the overall study population (LGS and Dravet syndrome combined):

[redacted]

As can be seen from Table 4.8, the numbers of withdrawals due to adverse events occurring in LGS patients during the open-label extension study were not reported. [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.[19]

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/day), may indicate a loss of efficacy over time.

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).

Table 4.8: Summary of safety results from GWPCARE3, GWPCARE4 and GWPCARE5

	GWPCARE3			GWPCARE4		GWPCARE5
	Cannabidiol 10 mg/kg/day + CCM	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol (variable dose, up to 30 mg/kg/day), LGS patients**
Number in safety analysis set*	67	82	76	86	85	366
No (%) with TEAEs	56 (83.6)	77 (93.9)	55 (72.4)	74 (86.0)	59 (69.4)	337 (92.1)
No (%) with TESAEs	13 (19.4)	13 (15.9)	8 (10.5)	20 (23.3)	4 (4.7)	NR
No (%) withdrawals due to TEAEs	1 (1.5)	6 (7.3)	1 (1.3)	12 (14.0)	1 (1.2)	NR
No (%) with TRAEs	20 (29.9)	51 (62.2)	15 (19.7)	53 (61.6)	29 (34.1)	211 (57.7)
No (%) with TRSAEs	2 (3.0)	5 (6.1)	0 (0)	9 (10.5)	1 (1.2)	23 (6.3)
No (%) withdrawals due to TRAEs	1 (1.5)	5 (6.1)	1 (1.3)	10 (11.6)	1 (1.2)	NR
No (%) SUDEP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NR
No (%) of deaths	0 (0)	0 (0)	0 (0)	1 (1.2)	0 (0)	NR

Source: Tables 11, 12, 13 and Appendix F of the CS; GWPCARE3 CSR[17]; GWPCARE4 CSR[18] GWPCARE5 interim CSR[19]
AE: adverse event; CCM: current clinical management; NR: not reported; SUDEP: sudden unexplained death in epilepsy; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event; TRAE: treatment-related adverse event; TRSAE: treatment-related serious adverse event

*: All randomised patients who took at least one dose of study medication were included and analysed according to the treatment received

Table 4.9: Treatment-related adverse events occurring in ≥3% of patients in any study GWPCARE3, GWPCARE4 or GWPCARE5

	GWPCARE3			GWPCARE4		GWPCARE5
	Cannabidiol 10 mg/kg/day + CCM	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol (variable dose up to 30 mg/kg/day), LGS patients**
Number in safety analysis set*	67	82	76	86	85	366
No (%) with diarrhoea	2 (3.0)	9 (11.0)	2 (2.6)	11 (12.8)	3 (3.5)	59 (16.1)
No (%) with vomiting	1 (1.5)	1 (1.2)	0 (0)	6 (7.0)	4 (4.7)	9 (2.5)
No (%) with fatigue	1 (1.5)	5 (6.1)	1 (1.3)	5 (5.8)	1 (1.2)	14 (3.8)
No (%) with decreased weight	1 (1.5)	3 (3.7)	0 (0)	2 (2.3)	2 (2.4)	18 (4.9)
No (%) with increased ALT	1 (1.5)	3 (3.7)	1 (1.3)	6 (7.0)	0 (0)	18 (4.9)
No (%) with increased AST	1 (1.5)	3 (3.7)	1 (1.3)	5 (5.8)	0 (0)	12 (3.3)
No (%) with increased GGT	1 (1.5)	3 (3.7)	1 (1.3)	3 (3.5)	1 (1.2)	14 (3.8)
No (%) with decreased appetite	7 (10.4)	13 (15.9)	2 (2.6)	8 (9.3)	1 (1.2)	40 (10.9)
No (%) with somnolence	8 (11.9)	21 (25.6)	2 (2.6)	12 (14.0)	7 (8.2)	50 (13.7)
No (%) with lethargy	2 (3.0)	6 (7.3)	1 (1.3)	3 (3.5)	0 (0)	10 (2.7)
No (%) with sedation	1 (1.2)	1 (1.5)	1 (1.3)	7 (8.1)	1 (1.2)	20 (5.5)

Source: Appendix F of the CS; clarification response (detailed responses document)[21]; GWPCARE3 CSR[17]; GWPCARE4 CSR[18] GWPCARE5 interim CSR[19]

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase

*: All randomised patients who took at least one dose of study medication were included and analysed according to the treatment received

4.2.9 Supporting evidence from the ongoing extension study

GWPCARE5 is an ongoing, open-label extension of GWPCARE3 and GWPCARE4 and also of GWPCARE1 and GWPCARE2 (Dravet syndrome). It aims to investigate the safety of cannabidiol in children and adults with inadequately controlled LGS or DS who had previously participated in one of the RCTs. 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. Efficacy outcomes are also being assessed through comparison with baseline values in the randomised study in which the patient participated.

The CS[1] included interim efficacy results based on 366 patients with LGS followed up for a median of 48 weeks. The mean modal dose of CBD during the OLE treatment phase was 23 mg/kg/day (range 21–25 mg/kg/day across the 12-wk visit windows). The reduction in total seizures with CBD was 48% to 63% from the baseline 168 seizures per 28 days. There was a reduction of 48% to 70% in drop attacks from a baseline of 80 per 28 days.[1, 31]

ERG comment: The ERG does not consider the open-label extension study (GWPCARE5) 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. [redacted] No evidence has been provided to support the long-term effectiveness (beyond 14 weeks) of the recommended CBD dose (10 mg/kg/day); the ERG therefore considers that the long-term effectiveness of CBD, at this dose, remains unknown.

4.3 Critique of the indirect comparison and/or multiple treatment comparison

The CS did not include any indirect comparisons.

4.4 Additional work on clinical effectiveness undertaken by the ERG

No further additional work on clinical effectiveness was undertaken by the ERG.

4.5 Conclusions of the clinical effectiveness section

The CS included a systematic review of the evidence for CBD for LGS. 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.

From the systematic review, the company identified and presented evidence from two RCTs (GWPCARE3[17] and GWPCARE4[18]) and an open-label extension study (GWPCARE5).[19] Both RCTs (GWPCARE3[17] and GWPCARE4[18]) were conducted in patients aged two to 55 years with LGS, whose seizures were incompletely controlled with previous AEDs and who had suffered at least two drop seizures per week in the baseline period. Both studies defined patients with LGS as those who had an EEG showing a pattern of slow spike-and-wave complexes and had at least two types of generalised seizures including drop seizures for at least six months.[1]

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. The patients included in the two RCTs appear to be broadly representative of this population; the proportion of participants in GWCARE3[17] and GWPCARE4[18] who had fewer than two prior AEDs was low (<5%).

One of the RCTs included [redacted] UK patients, the other had none. This is most likely to be relevant when considering the nature of current clinical management, which may differ between countries and which is the comparator in the trials.

Patients in GWPCARE3, who received 10 mg/kg/day CBD in addition to CCM, experienced fewer drop seizures and fewer seizures overall, during the 14-week treatment period, than those in the placebo group. Alongside this, safety data from both RCTs (GWPCARE3 and GWPCARE4) and an interim report of the open-label extension study (GWPCARE5) 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.

A major limitation of the evidence is the small size of patient population receiving the recommended 10 mg/kg/day CBD dose, which is specified as the starting dose for all patients in the company's response to clarification.[15] Just 73 patients in GWPCARE 3 and none in GWPCARE4 received the 10 mg/kg/day dose

A further important limitation is the short-term nature of the RCTs (14 weeks). There is a lack of long-term efficacy and safety data, particularly for the 10 mg/kg/day dose. Data from the GWPCARE5 extension study[19] are for patients taking 20 mg/kg/day CBD or higher (up to 30 mg/kg/day). Any observations of reduction in seizures in the short-term trials may not be sustained in the long-term and the effects on outcomes relating to mortality (especially SUDEP) are unknown. The ERG is also concerned that the apparently high rate of withdrawals from GWPCARE5,[19] 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/day).

Current clinical management is considered to be a 'basket' of choices of AED. Although the company conducted a number of subgroup analyses based on the presence or absence of various AEDs, they assumed that the effectiveness of CBD does not vary with the combinations of AEDs to which it is added (i.e. that there are no interaction effects between CBD and any of the other AEDs that may be included in CCM). This assumption is crucial to the validity of the 'mixed' CCM comparator. The ERG considers that there is currently a lack of evidence to support this assumption.

The innovation section of the CS emphasised the value, to patients and carers, of periods of seizure-free time. The ERG notes that neither the CS nor the CSRs provided any data on the number of days, if any,

on which study participants were seizure-free (no seizures of any type) and that no patient, in any of the included studies, achieved complete freedom from all types of seizures.

5 COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

The company submission reported that a rigorous systematic review was carried out to identify relevant publications for the efficacy, safety, health state utility values, cost and resource use data associated with the conditions and existing economic models in Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS).[1]

5.1.1 Searches performed for cost effectiveness section

The main submission presented one set of searches used to inform both the clinical and cost-effectiveness content for both LGS & 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

The inclusion 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 LGS • Or a caregiver of a patient with LGS (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 • Observational studies • Database studies • Systematic reviews were used for citation chasing only	Other study design

PICOS	Inclusion criteria	Exclusion criteria
	• 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, nine unique cost effectiveness studies met the pre-defined eligibility criteria, of which seven were conducted from a UK perspective. All UK-relevant publications were assessments considering rufinamide for the Wales Medicines Strategy Group or the Scottish Medicines Consortium,[32-38] and reported few details of the model development and structure. No cost effectiveness studies appraising CBD were identified.

The search yielded three utility studies that were relevant to the reference case of patients with LGS. Two were cost utility models[32, 39] and the third[8] was a qualitative research study of parents of children with LGS in the UK, Italy and the USA. None of the studies estimated utilities for health states defined by number of drop seizures and drop seizure-free days, two main parameters in the economic model.

Of the 21 identified publications that reported cost or resource use data for patients with LGS, six reported data from the UK.[32-35, 37, 40] However, none of these studies reported costs or resource use for health states defined by number of drop seizures and drop seizure-free days.

ERG comment: The rationales for excluding CE studies after full paper reviewing are considered appropriate given the defined inclusion 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	• drop seizure free, • ≤45 drop seizures, • >45 - ≤110 drop seizures, • >110 drop seizures, • death	Absolute instead of relative reductions were preferred to define health states as it 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 LGS who are aged 2 years or older, whose seizures are inadequately	Consistent with the therapeutic indication	B.3.2

	Approach	Source/Justification	Signpost (location in CS)
	controlled by current clinical management.	proposed to the European Medicines Agency.	
Treatment effectiveness	Treatment effectiveness was estimated based on the frequency of drop seizures, number of days without drop seizures and discontinuation rates.	The pivotal clinical trials (GWPCARE3 and GWPCARE4) 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

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
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 year.
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.
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 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			

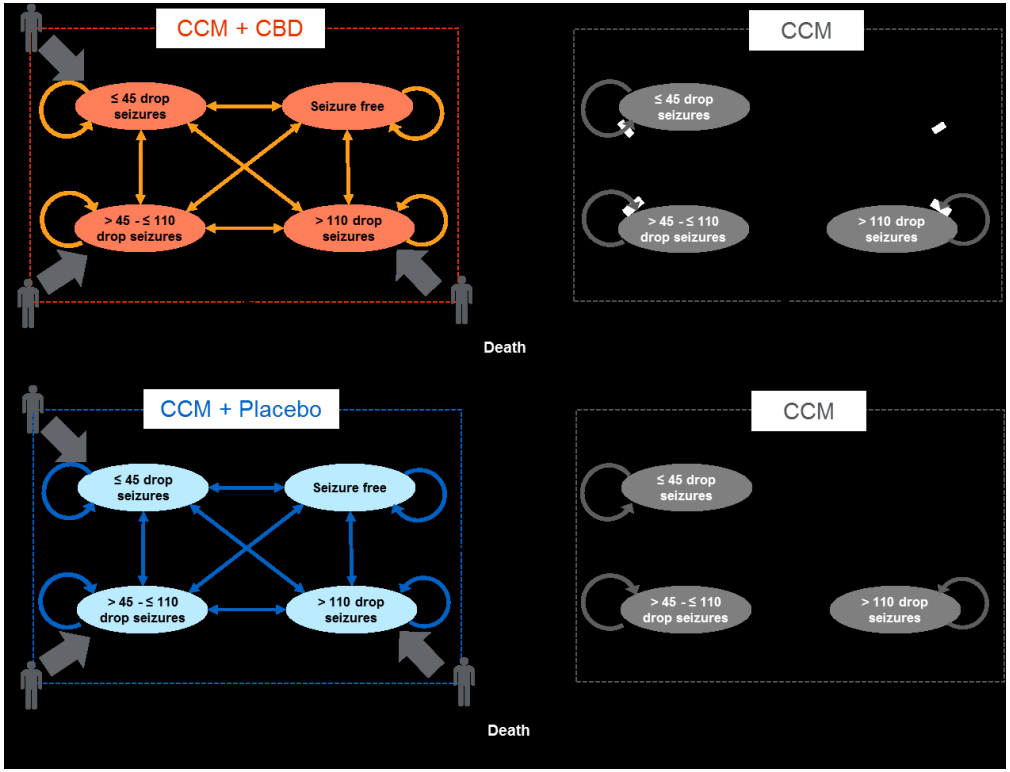
5.2.2 Model structure

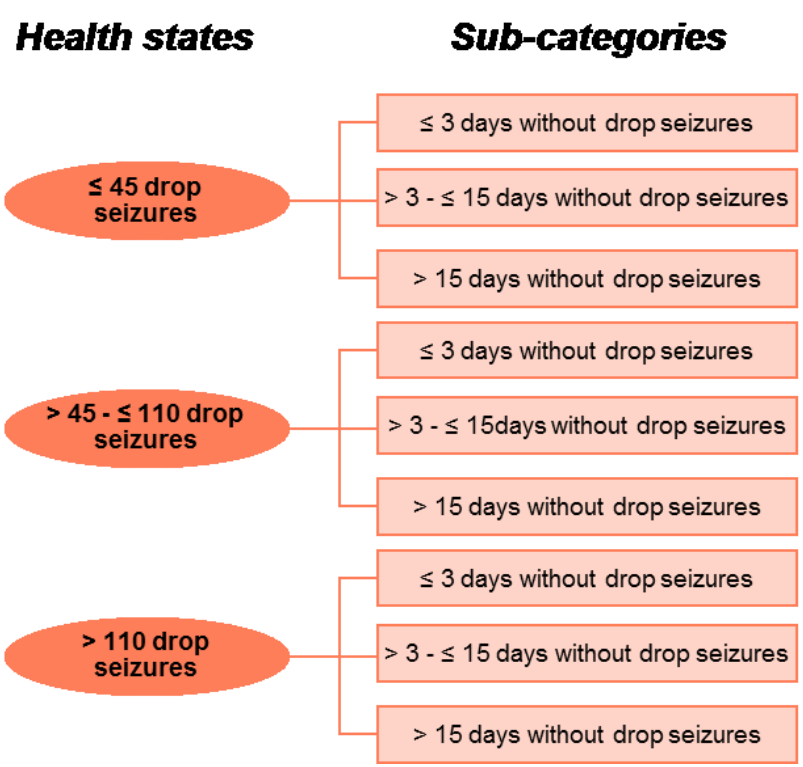
The company developed a cohort state transition model using Microsoft Excel®. The model consisted of five health states, i.e. drop seizure free, ≤45 drop seizures per 28 days, >45 - ≤110 drop seizures per 28 days, >110 drop seizures per 28 days, and death (Figure 5.1). A drop seizure was defined as "an attack or spell (atonic, tonic or tonic-clonic) involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface."[1] As improvements in patients' quality of life were assumed, by the company, to relate to the total number of drop seizures and number of drop seizure-free days, each of the drop seizure frequency health states was categorised into three sub-categories based on the number of drop seizure-free days experienced in the corresponding health state, i.e. ≤ 3 drop seizure-free days, > 3 - ≤ 15 drop seizure-free days, and > 15 drop seizure-free days (Figure 5.1). Patients receiving CCM plus CBD could transit between the four

drop 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 (CCM plus placebo) could transit between the drop seizure frequency health states during the first cycle only and returned to their baseline drop seizure frequency state afterwards (i.e. after three months). Patients entered the model via one of the three health states with drop seizures (i.e. ≤ 45, > 45 - ≤ 110, > 110 drop seizures per month). At each cycle, patients receiving CBD plus CCM either continued to receive treatment, discontinued treatment or died. When patients discontinued treatment, they returned to their baseline drop seizure frequency and remained in this state until the end of the time horizon. Patients receiving CCM without CBD could not discontinue treatment. The transition probabilities for the first cycle were derived from the GWPCARE3 and GWPCARE4 trials. For cycles two to nine, time-dependent transition probabilities for CBD were estimated using the open-label extension study, GWPCARE5.

The model cycle length was three months, no half-cycle correction was used.

Figure 5.1: Model structure: drop seizure frequency health states and corresponding heath state sub-categories





Source: Based on Figure 7 & 8 of the CS[1]
CBD: cannabidiol; CCM: current clinical management
*Revert to baseline drop seizure frequency rates

ERG comment: The main concerns of the ERG relate to: a) not incorporating non-drop seizures in the model structure; b) the assumption that patients receiving CCM only transfer back to their baseline drop seizure frequency after the first cycle; c) no half-cycle correction was used.

a) The health states defined in the model focused solely on drop-seizures and drop-seizure free days. Our concerns relate to the fact that patients with LGS who have a reduction in drop-seizures or who have become drop seizure-free, are still likely to suffer from non-drop seizures. For example, the health state drop seizure-free might include patients who are not free from non-drop seizures. When patients are still suffering from non-drop seizures, they remain at risk of SUDEP and non-SUDEP. In response to clarification question B1a[15] the company stated that in the GWPCARE studies non-drop seizures was an exploratory endpoint only. Nevertheless, it should be noted that overall seizure frequency is listed as secondary outcome in the GWPCARE studies. Additionally, the company stated that CBD-treated patients showed an improvement in non-drop seizures. Furthermore, the company provided an overview of the numbers of non-drop seizures across the drop seizure frequency-defined health states and noted that within the treatment period the median number of non-drop seizures reduced substantially across drop-seizure-based health states. In response to clarification question B1b[15] the company incorporated epilepsy-related SUDEP and non-SUDEP probabilities for the drop-seizure free health state that were >0. Overlooking the potential importance of non-drop seizures is also apparent in the utility estimates used. Particularly, the utility associated with the drop seizure-free health state is considered relatively high (compared with the age-matched general population utility) when taking into account the fact that non-drop seizures may still occur (no patient in any of the GWPCARE studies achieved complete seizure-free status). This issue is discussed further in section 5.2.8.

b) In the model, patients receiving CCM plus placebo transfer back to their baseline seizure frequency after the first cycle. In the CS and in response to clarification question B2,[15] the company stated that this was done as placebo effects were observed in both the GWPCARE3 and GWPCARE4 studies and that it was not reasonable to assume that these effects would be sustained in clinical practice. The ERG does not agree with this approach as it may be the case that this effect is also present in the CBD group (and hence is part of the demonstrated treatment 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 be likely to result in an overestimation of the 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 clarified that patients discontinuing CBD treatment are transferred back to their baseline seizure frequency. However, as the number of days without drop seizures (and corresponding utility values) seem to be treatment-dependent favouring CBD, this is not seen as a conservative approach. This issue is discussed further in sections 5.2.6 and 5.2.8 (and considered in ERG analyses).

c) In response to clarification question B3b,[15] the company stated 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 for the results of the model.

5.2.3 Population

In line with its anticipated marketing authorisation, CBD was modelled for the treatment of people with LGS who are aged 2 years or older, whose seizures are inadequately controlled by established clinical management. This is in line with the final scope issued by NICE.[41]

Baseline demographic characteristics such as mean age, weight and disease severity (i.e. frequency of drop seizures and the number of days without drop seizures) were obtained from GWPCARE3 and GWPCARE4, 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 GWPCARE3 and GWPCARE4 studies

	<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]
Mean weight	[redacted]	[redacted]	[redacted]	[redacted]
Frequency of drop seizures at baseline				
≤ 45 drop seizures per 28 days	[redacted]		[redacted]	
> 45 - ≤ 110 drop seizures per 28 days	[redacted]		[redacted]	
> 110 drop seizures per 28 days	[redacted]		[redacted]	
Number of days without drop seizures (per 28 days) at baseline				
≤ 45 drop seizures per 28 days				
≤ 3 days	[redacted]		[redacted]	
> 3 - ≤ 15 days	[redacted]		[redacted]	
> 15 days	[redacted]		[redacted]	
> 45 - ≤ 110 drop seizures per 28 days				
≤ 3 days	[redacted]		[redacted]	
> 3 - ≤ 15 days	[redacted]		[redacted]	
> 15 days	[redacted]		[redacted]	
> 110 drop seizures per 28 days				
≤ 3 days	[redacted]		[redacted]	
> 3 - ≤ 15 days	[redacted]		[redacted]	
> 15 days	[redacted]		[redacted]	
Source: Based on Table 16 in the CS[1]				

ERG comment: The main concerns of the ERG relate to the extent to which the population in the trials 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,[15] a small proportion of the patients included in GWPCARE3

and GWPCARE4 (<5%) do not match this definition (i.e. <2 prior AEDs). It is unclear to what extent these patients have influenced the parameters included in the model. However, as stated in section 3.1 the numbers of prior and concurrent AEDs taken by patients in the GWPCARE trials was representative of what might be expected in clinical practice.

5.2.4 Interventions and comparators

In the proposed licensed indication (currently awaiting marketing authorisation in the UK) for LGS, 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 utilised the maintenance dose of 10 mg/kg/day, as the company assumed that the majority of patients will receive this dose in clinical practice.

In the GWPCARE3 trial, the effectiveness of CBD was assessed at two different doses, i.e. CBD 10 mg/kg/day in addition to CCM, and CBD 20 mg/kg/day in addition to CCM. In the GWPCARE4 trial, effectiveness of CBD was assessed at a dose of CBD 20 mg/kg/day in addition to CCM. In the open-label extension study (GWPCARE5), mean modal dose during treatment was 23 mg/kg/day (min=2.5, max=30; n=364).[42]

For both trials, CCM consisted of (combinations of) clobazam, valproate, levetiracetam, lamotrigine, rufinamide, ketogenic diet, and vagus nerve stimulation. In the final scope issued by NICE, established clinical management without CBD includes combinations of sodium valproate, lamotrigine, rufinamide, topiramate, felbamate, clobazam, levetiracetam, ketogenic diet, and vagus nerve stimulation.

In the economic model, CCM was established as the following concomitant therapies: valproic acid, clobazam, lamotrigine, rufinamide, topiramate and levetiracetam. The company assumed that, although ketogenic diet and vagus nerve stimulation were included in the final scope issued by NICE[41] and are listed as second/third-line treatments for LGS (alongside AEDs) in NICE CG137,[12] 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 not explicitly incorporated as CCM in the economic model.

ERG comment: The main concerns of the ERG relate to: a) the use of GWPCARE4 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 B6a,[15] 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 GWPCARE4 and GWPCARE5 focused on substantially higher dosages of CBD (20 mg/kg/day or more). The company stated (clarification question B10a) that GWPCARE4 was only used to model scenarios in which a minority of patients are 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.'*[15] 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. It is, therefore, questionable whether the evidence from GWPCARE5 can be used for the maintenance dose of 10 mg/kg/day. 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 23 mg/kg/day.[42]

b) Contrary to (the ERG's interpretation of) the final scope issued by NICE,[41] 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 (GWPCARE3 and GWPCARE4) indicate that the company has also conducted a number of subgroup analyses that indicate a possible effect on the primary outcome of the presence or absence of specific AEDs in the CCM combination.[17, 18] In response to clarification question B8a,[15] 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 took 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 LGS are at risk of higher mortality depending on their seizure frequency. In response to clarification question B3,[15] the company stated 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, which indicates 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 (GWPCARE3 and GWPCARE4)[17, 18] and the open label extension study (GWPCARE5).[19] It should be noted that GWPCARE4 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 drop seizures, number of days without drop seizures, discontinuation rates and adverse events for both CCM plus CBD and CCM plus placebo. GWPCARE3 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 the patient subgroups <12 years and ≥12 years.

Transition probabilities between drop seizure frequency health states

During the first cycle, transition probabilities between drop seizure frequency health states (see section 5.2.2 for more details) were based on GWPCARE3 for both CCM plus CBD and CCM plus placebo. For CCM plus CBD cycles two to nine were informed by the open label extension study (GWPCARE5). After cycle nine, patients receiving CCM plus CBD were assumed to remain in their current drop seizure frequency health states. Once CBD was discontinued, patients were assumed to revert back to their baseline drop seizure frequency health state.

First cycle for CCM plus CBD and CCM plus placebo

Transition probabilities between drop seizure frequency health states (based on GWPCARE3) are reported in Table 5.5 below, for both CCM plus CBD and CCM plus placebo.

Table 5.5: Transition probabilities between drop seizure frequency health states (first cycle)[a]

		<12 years				≥12 years			
		Seizure free	≤ 45 seizures	45-110 seizures	> 110 seizures	Seizure free	≤ 45 seizures	45-110 seizures	> 110 seizures
CCM plus CBD 10 mg mg/kg/day	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45-110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCM	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45-110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 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 18.[1]

Cycles two to nine for CCM plus CBD

Transition probabilities between drop 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 drop seizure frequency health states for CCM plus CBD 10 mg/kg/day (cycles two to nine)[a]

		<12 years				≥12 years			
		Seizure free	≤ 45 seizures	45 to 110 seizures	> 110 seizures	Seizure free	≤ 45 seizures	45 to 110 seizures	> 110 seizures
Cycle 2	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45-110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45-110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45-110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45-110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45-110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		<12 years				≥12 years			
		Seizure free	≤ 45 seizures	45 to 110 seizures	> 110 seizures	Seizure free	≤ 45 seizures	45 to 110 seizures	> 110 seizures
Cycle 7	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45 to 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45 to 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45 to 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 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 identical as those presented for CBD 10 mg/kg/day plus CCM in this Table (see also CS Table 18).[1]

After cycle 9 for CCM plus CBD

After cycle 9, patients receiving CCM plus CBD were assumed to remain in their drop seizure frequency health states until CBD treatment discontinuation or death.

CBD treatment discontinuation

CBD discontinuation probabilities were dependent on the drop seizure frequency health state and were only applied for CCM plus CBD. Treatment discontinuation probabilities for cycle one were based on GWPCARE3, while GWPCARE5 was used for subsequent cycles (Table 5.7). The CBD discontinuation probabilities 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]
≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]
45-110 seizures	[redacted]	[redacted]	[redacted]	[redacted]
> 110 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 20.

Number of days without drop seizures

As described in section 5.2.2, the drop seizure frequency health states were subdivided into three groups based on the number of drop seizure-free days per 28 days (categories: ≤ 3 days, > 3 - ≤ 15 days, > 15 days, see Table 5.8). This subdivision was incorporated to reflect the impact of the number of drop seizure-free days on HRQOL and was assumed to be dependent on the treatment received, as well as the drop seizure frequency health states.

Table 5.8: Number of days without drop seizures per health state[a]

		<12 years			≥12 years		
		≤ 3 days	> 3 to ≤ 15 days	> 15 days	≤ 3 days	> 3 to ≤ 15 days	> 15 days
CCM plus CBD 10 mg mg/kg/day	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45 to 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCM	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45 to 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 110 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 19.[1]

Mortality

Patients in the drop seizure-free health state were assumed to experience all-cause age-dependent mortality probabilities derived from the national life tables for England.[43] Disease-specific mortality was incorporated for the other drop seizure frequency health states (Table 5.9). In absence of LGS-

specific mortality data, DS mortality in terms of SUDEP and non-SUDEP deaths, was retrieved from published literature.[44]

The Dravet-specific SUDEP rate of 9.32/1,000-person-years, reported by Cooper et al. (2016),[44] was converted to a 0.23% mortality probability per cycle (i.e. per three months). [redacted]. To calculate mortality probabilities for the other drop seizure frequency health states, risk ratios of [redacted] and [redacted] were assumed for the [redacted] drop seizure frequency health states respectively ([redacted] drop seizure frequency health state; no evidence provided for these risk ratios).

To obtain the non-SUDEP mortality probabilities, the Dravet-specific mortality rate (15.84/1,000-person-years) was subtracted from the Dravet-specific SUDEP rate (9.32/1000-person-years).[44] As for SUDEP mortality, this mortality rate ([redacted]) was converted to a mortality probability per cycle (i.e. [redacted]) and assumed for the [redacted] drop seizure frequency health state. Subsequently, risk ratios of [redacted] and [redacted] were assumed for the [redacted] drop seizure frequency health states respectively (relative to the [redacted] drop seizure frequency health state; no evidence was provided for these risk ratios).

Table 5.9: Disease-specific mortality probabilities

	SUDEP	Non-SUDEP
Seizure free	[redacted]	[redacted]
≤ 45 seizures	[redacted]	[redacted]
45 to 110 seizures	[redacted]	[redacted]
> 110 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 2 to 9) for drop 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 drop seizure frequencies and is 0% for some health states); d) the number of days without drop 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.

a) For drop 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[45] ([redacted])[19] 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 (response to clarification questions B7 and B10) 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 for this statement 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 B10c), 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 (clarification question B4b) that the company 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 data were not reported in the interim CSR[19] nor the clinical effectiveness section of the CS[1]) and thus could not be fully assessed by the ERG.

c) The CBD discontinuation probabilities reported in the original CS[1] as well as those reported in the revised assessment accompanying the company's clarification response[46] seemed to lack face validity. Potentially due to the relatively small sample size, CBD discontinuation does not always increase with higher drop 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 in the revised assessment provided by the company.[46] With the Exception of the CBD discontinuation probabilities for the 45 to 110 drop seizures and > 110 drop seizures health states reported in Table 2 of the revised assessment,[46] these were averaged (given the reported probabilities do not always increase with higher drop seizure frequencies as would be expected). 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
Seizure free	[redacted]	[redacted]	[redacted]	[redacted]
≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]
45 to 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]
> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]

d) The company assumed that the number of days without drop seizures is dependent on both treatment allocation and health state. The company justified this, in response to clarification question B13, by stating that CBD impacts both the frequency of drop seizures and the number of drop seizure-free

days per month and that treatment-independent number of drop 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 B13). Moreover, the number of drop seizure-free days per month is only considered as exploratory outcome in the pivotal trials and is not reported in the clinical effectiveness sections of the CS.[1] Finally, including treatment-dependent number of days without drop 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 in the CS was the statement that: '*The calculated risk ratios ensured that the annual SUDEP rate for the >110 seizure frequency category was 1.3%; i.e. consistent with the upper limit of published SUDEP death rates.*' The ERG considered this justification to be insufficient. Firstly, it is unclear why the upper limit of published SUDEP mortality probability is considered applicable to the >110 drop seizure frequency health state, particularly given this health state is only based on drop seizures and does not (directly) capture non-drop seizures. Secondly, no evidence has been provided to support the relationship (e.g. type and magnitude) between drop 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 risk ratios applied, the ERG assumed equal (non-)SUDEP mortality for the drop seizure frequency health states as derived from Cooper et al[44] while assuming a [redacted][47] for the drop seizure-free health state. This resulted in three monthly SUDEP and non-SUDEP probabilities of [redacted], respectively,[44] for the drop seizure frequency health states, and [redacted], respectively, for the drop seizure-free health state. These (non-)SUDEP probabilities for the drop seizure-free health state are potentially underestimated given that the seizure-free definition in Trinka et al[47] (used to obtain the risk ratio of [redacted]) is presumably not restricted to drop seizures only, potentially introducing bias in favour of CBD (given more patients are seizure free after CBD).

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 22).[1]

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.[46]

a) The company used different thresholds to select the most frequently occurring TEAE of special interest for CBD and CCM (either events reported in ≥3% or ≥1% of patients respectively). In response to clarification question B15 the company stated that this selection of adverse events was *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 was 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. It is also 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 B15b).

c) In their revised assessment,[46] the company assumed that adverse events could only occur until cycle 9. In the original CS base-case,[1] adverse events could occur over the entire CBD treatment duration. 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. ≤ 3 drop seizure-free days, > 3 to ≤ 15 drop seizure-free days, and > 15 drop seizure-free days; see Figure 5.1) within the four main health states: drop seizure-free, ≤45 drop seizures, >45 to ≤110 drop seizures, and >110 drop seizures. Utilities were estimated using patient vignettes that were based on the health states included in the model. In total, 39 patient vignettes were developed. Patients and/or caregivers of patients with LGS 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). [redacted] 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.[48] 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 revert to baseline drop seizure frequency after the first cycle and patients receiving CBD revert to their baseline drop seizure frequency after discontinuation of treatment. However, given that the sub-categories of drop 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 utilities per health state are displayed in Table 5.12.

Health-related quality of life data identified in the review

According to the CS,[1] the SLR identified three studies that were relevant to the NICE reference case of patients with LGS 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 drop seizures and drop seizure-free days.

Table 5.11: Health state utility values

State	Sub-category	Utility value	Reference	Justification
No drop seizures	≤ 3 drop seizure-free days	Not estimated	CS	No drop seizures
	>3 to ≤15 drop seizure-free days	Not estimated	CS	No drop seizures
	> 15 drop seizure free days	[redacted]	Vignette study by company	No utilities available in literature

≤45 drop seizures	≤ 3 drop seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	>3 to ≤15 drop seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	> 15 drop seizure free days	[redacted]	Vignette study by company	No utilities available in literature
>45 to ≤110 drop seizures	≤ 3 drop seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	>3 to ≤15 drop seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	> 15 drop seizure free days	[redacted]	Vignette study by company	No utilities available in literature
>110 drop seizures	≤ 3 drop seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	>3 to ≤15 drop seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	> 15 drop seizure free days	[redacted]	Vignette study by company	No utilities available in literature
Source: Based on Table 33 of the CS[1]				

Table 5.12: Health state utility values per treatment

Health state	Utilities for CBD10	Utilities for CBD20[a]	Utilities for CCM
No drop seizures	[redacted]	[redacted]	[redacted]
≤45 drop seizures	[redacted]	[redacted]	[redacted]
>45 to ≤110 drop seizures	[redacted]	[redacted]	[redacted]
>110 drop seizures	[redacted]	[redacted]	[redacted]

Source: Based on Table 33 of the CS[1]
[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 resulting utility estimates; c) the inclusion of caregivers QALYs; d) the lack of disutilities for adverse events and; e) the difference in utilities between CBD and CCM.

a) Utility estimates were based on patient vignettes that only presented information on drop seizure frequency and 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 conceptualisation of the respondents. In response to clarification question B17a,[15] the company stated that for methodological purposes, the vignette study could not formally measure the impact on utilities beyond condition-related factors. The company further argued that '*this is still clinically meaningful, and the use of a "live" population partially overcomes this limitation.*' However, it is unclear to what extend the population may be considered to have experience with LGS as this was not specifically part of the inclusion criteria ("[redacted]"). Both the vignette study and the use of patients to value health states are not 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, in scientific literature, to be suboptimal compared to multi-attribute utility instruments and public preferences.[49-51] As an alternative, the ERG suggested a scenario in which utilities were based on the Quality of Life in Childhood Epilepsy (QOLCE) instrument which was used in the GWPCARE4 study. In response to this clarification question (B17f),[15] the company stated that QOLCE scores were not used to estimate utilities for the base-case for the following reasons: 1) The response rate was low in the trials [redacted]); 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 considers that the QOLCE results could be used to check face validity of the vignette study.

b) The estimated utility value for the drop seizure free health state appears to be relatively high, especially given the likelihood of remaining non-drop seizures. For example, the utility for the health state "[redacted]" is [redacted], which is almost equal to published general population utilities (e.g. 0.828 for the general population in the UK and 0.84 for UK children aged two years).[52] It is possible that patients may have misinterpreted the vignettes due to the lack of information regarding, for example, frequency of non-drop seizures (e.g. interpreting drop seizure-free as completely seizure-free), and adverse events in the hypothetical health states as well as the impact on other HRQoL domains. Based on these concerns, the ERG adjusted the utility estimate for the health state "[redacted]" ([redacted]) in line with the utility value that is used in the Dravet syndrome submission ([redacted]) in the ERG base-case analysis.

c) In the revised base-case, the company included QALY decrements by caregivers and incorporated these gains in the total QALY gain of both CBD and CCM. The decrements per health state are presented in Table 5.13. The inclusion of caregivers' QALYs was not done in accordance with the NICE reference case, which states that '*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 caregivers' QALYs were discarded in the ERG base-case analysis. In addition, the method 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 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]
≤45 drop seizures	≤3 seizure-free days	[redacted]
	>3 to ≤15 seizure-free days	[redacted]
	>15 seizure free days	[redacted]
>45 to ≤110 drop seizures	≤3 seizure-free days	[redacted]
	>3 to ≤15 seizure-free days	[redacted]
	>15 seizure free days	[redacted]
>110 drop seizures	≤3 seizure-free days	[redacted]
	>3to ≤15 seizure-free days	[redacted]
	>15 seizure free days	[redacted]
Source: Based on Table 5 of the revised economic assessment [46]		

d) In the model, the occurrence of adverse events is not accompanied by loss in QALYs. In response to clarification question, B18[15] 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 technically not feasible for the ERG to implement disutilities in the model.

e) As reported in Table 5.8, the number of days without drop 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 drop 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 drop 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

According to the CS, the SLR identified six studies[32-35, 37, 40] 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 drop seizures and drop seizure-free days.

Treatment costs

[redacted]. Costs for AEDs were obtained from the NHS Electronic Drug Tariff 2018[53] 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[54] (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 17 of the CS).[1] 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.[45]) had a 33% reduction (supported by clinical opinion) in the dose of concomitant AEDs (Table 28 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 5.14). 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][16]
Clobazam*	0.65	0.45	0.0559	3.32	2.30	Auden McKenzie, 2008[55]
Valproic acid*	27.50	25.00	0.0002	0.50	0.46	Sanofi, 2006[56]
Rufinamide	26.50	36.36	0.0048	11.61	15.93	Eisai 2012[57]
Levetiracetam*	40.00	36.36	0.0002	0.73	0.66	UCB Pharma 2015[58]
Lamotrigine	8.00	2.73	0.0037	2.70	0.92	GlaxoSmithKline 2008[59]

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	
Topiramate	7.00	5.45	0.0044	2.81	2.19	Janssen-Cilag 2010[60]

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 drop seizure-free group, based on the suggestion from the literature[3, 5, 7] that there is likely to be an 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*		Costs per visit		Reference unit prices
		<12 years	≥12 years	<12 years	≥12 years	
Nurse visit	Seizure-Free	2	2	£44	£44	PSSRU 2017[61]
	≤ 45	4	4			
	>45 to ≤ 110	8	4.8			
	> 110	12	12			
Paediatric Epileptologist (<12 years) / Neurologist (≥12 years) Visit	Seizure-Free	1	0.5	£366	£0	NHS Reference Costs 2016-17[62]
	≤ 45	2	1			
	>45 to ≤ 110	4	1.2			
	> 110	6	3			
Paediatrician Visit	Seizure-Free	2	0	£196	£237	PSSRU 2017[61]
	≤ 45	4	0			
	>45 to ≤ 110	8	0			
	> 110	12	0			
Emergency department	Seizure-Free	0	0	£237	£237	NHS Reference
	≤ 45	1	1			

Resource use		Number of annual visits*		Costs per visit		Reference unit prices
		<12 years	≥12 years	<12 years	≥12 years	
	>45 to ≤ 110	2.5	2.5			Costs 2016-17[62]
	> 110	4	4			
Phone Call Follow-up	Seizure-Free	0	0	£258	£107	NHS Reference Costs 2016-17[62]
	≤ 45	2	1			
	>45 to ≤ 110	5	2.5			
	> 110	12	6			
Dentist	Seizure-Free	2	2	£127	£127	PSSRU 2017[61]
	≤ 45	2	2			
	>45 to ≤ 110	2	2			
	> 110	2	2			
Hospitalisation	Seizure-Free	0	0	£598 in general ward £1,583 in ICU	£460 in general ward £1,299 in ICU	NHS Reference Costs 2016-17[62]
	≤ 45	0.5	0.5			
	>45 to ≤ 110	1.25	1.25			
	> 110	2	2			
Institutionalisation[$]	Seizure-Free	0%	0%	£0	£1,337	PSSRU 2017[61]
	≤ 45	0%	10%			
	>45 to ≤ 110	0%	10%			
	> 110	0%	10%			
Cost of Rescue Medication by intake	Seizure-Free	0	0	£34	£34	BNF 2018[63]
	≤ 45	2	2			
	>45 to ≤ 110	5	5			
	> 110	8	8			

Source: Based on Table 30 and Table 31 of the CS
*Based on clinical opinion.
[$]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 LGS, 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.[62]

Adverse event related costs

Commonly identified TEAEs were included in the analysis as one visit to a specialised nurse (£44 per visit, PSSRU 2017),[61] based on the opinion of clinical experts who indicated that these events were unlikely to be resource intensive.

ERG comment: The main 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.

a) In the pivotal trials, an escalation period (or treatment period) of two weeks was used (i.e. 5 mg/kg/day to start, titrated up to the target dose over two weeks). In response to clarification question B6c,[15] the company clarified that for simplicity, no escalation period was assumed in the model and hence, patients were considered to enter the model on their maintenance dose. The ERG expects no large implications from the simplification and agrees with the company that this may slightly over-estimate the treatment costs (e.g., for the first week in the cycle).

b) In the initial CS,[1] a zero percentage of the patients in the drop 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 LGS, including non-drop seizures. Hence, in response to clarification question B19a,[15] the company included a 2% risk of institutionalisation for patients in the seizure-free health state. It remains unclear, however, to what extend the patients' risk of institutionalisation is associated with drop 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,[46] the ERG used a 2% institutionalisation risk for patients aged above 18 years in the drop seizure-free category.

c) In response to clarification question B9,[15] the company stated that the effects of 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, costs of both the ketogenic diet and the vagus nerve stimulation are not included in the model. This most likely results in an underestimation of the CCM costs, which is likely to favour CBD (as patients treated with CBD are estimated to live longer and hence the CCM treatment duration is likely to be longer for CBD).

d) It was stated that patients in both the intervention and comparator groups receive the same clinical management, but for some AED, a dose reduction of 33% was applied for CBD plus CCM. In response to clarification question B22a,[15] 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,[45, 64] and it is unclear from the evidence what percentage of dose reduction/increase occurred 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 drop seizure-free health state. The ERG has explored the impact of this assumption in a scenario

in which resource use for the drop 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 likely be higher for CBD (these patients are estimated to live longer) despite monitoring requirements being similar for CBD and CCM. However, the ERG does not expect this issue to have a substantial impact on the results.

g) In response to clarification question B5a,[15] the company stated that it was not possible to definitively conclude whether the mean weights at baseline in the clinical trials were representative of those for the LGS population in the UK. No data were identified in the literature and there were too few UK patients in the GWPCARE3 and GWPCARE4 trials ([redacted] 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,[15] the company clarified that this was done to account for the asymmetric weight distribution due to outliers. The ERG considers that this assumption was not reasonable as the weights were 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 in their base-case analyses.

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 + placebo	[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 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 B27,[15] 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[46] and economic model[65] accompanying the clarification response. 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 that these revised results submitted should also be interpreted with extreme caution. 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 + placebo	£91,799	1.26	-	-	-
CCM + CBD	£140,706	2.84	£48,907	1.58	£30,970

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]	--	--	--

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
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

Figure 5.2: Tornado diagram presenting the results of the initial deterministic sensitivity analysis

[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 including patients aged between 12 and 55 years only [redacted]), varying the CBD dosage [redacted]) and varying the long-term CBD discontinuation [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 adopting a time horizon of 20 years ([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 GWPCARE3 trial only (clarification question B10c); 2) a scenario analysis using the average treatment discontinuation probability across the health states (clarification question B12c); 3) a scenario analysis using equal number of days without seizures across treatment allocation (clarification question B13b); 4) a scenario analysis in which utilities are based on the QOLCE instrument from the phase III trials (clarification question B17f); and 5) a scenario assuming a 0% dose reduction of concomitant AEDs (clarification question B22b). 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 not to the requested discontinuation rates). This hampered the review of the ERG.

b) Based on CS Table 37 some parameters (e.g. non-SUDEP costs) were not included in the PSA. In response to clarification question B25d,[15] the company stated 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. [66]). In response to clarification question B25,[15] the company stated 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, 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,[14] the company provided a revision of the original submission[46] and economic model.[65] 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 should also be interpreted with extreme caution. 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 PSA and 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 incremental costs, which resulted in a slightly increased ICER (£31,107) (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 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 to the care givers utility decrements and discount rates of outcomes and costs. 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	£140,136	2.83	--	--	--
CCM	£91,822	1.27	£48,314	1.56	£31,107

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

Figure 5.3: Tornado diagram presenting the results of the revised deterministic sensitivity analysis

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 using a time horizon of 10 years ([redacted]). The three most influential scenarios that decreased the ICER were all patients aged 2 to 5 years at model entry ([redacted]), including patients aged between 2 and 11 years only [redacted]), and varying the approach to modelling mortality risk [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 drop seizure-free patients (at year 1) and 10-year CCM mortality, were compared against evidence (see CS Appendix J).[1]

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 extended clarification phase, the company submitted their clarification responses, a revised assessment[46] and a revised economic model.[65] 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 B27. In the clarification phase, the company submitted a revised model that produced QALYs that did not exceed the time horizon, however the company did not highlight the exact changes in the model (code), making it difficult for the ERG to examine the changes made in response to clarification question B27. Particularly given that the updated economic model submitted during the clarification phase included multiple adjustments (which were mostly not requested by the ERG).

c) In addition, the ERG regarded the VBA coded model as lacking transparency. Although the company helpfully provided detailed information regarding model implementation in response to clarification question B23, 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 recalculated QALYs and costs. 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, 4.652 versus 4.748). For the costs this was true to a lesser extent (estimated CBD discounted total costs £140,706 versus £159,201). 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 £70,774 versus £86,399).

- 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 0.43 (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 0.13 is produced (excluding carer QALYs). This suggests that there are fundamental problems with the economic model (i.e. VBA code) 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 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.

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).[67] The ERG has major concerns with both the original CS base-case and the revised CS base-case (see 5.2). Therefore, as described 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). It should be noted 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 mortality probabilities (section 5.2.6).
   The ERG adjusted the health state dependent SUDEP and non-SUDEP mortality probabilities.
4) Adjusted discontinuation probabilities (section 5.2.6).
   The ERG adjusted the CBD discontinuation probabilities (Table 5.10) to improve face validity of this input parameter.
5) 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.

6) Adjusted utility for seizure-free health state (section 5.2.8).
   The ERG adjusted the seizure-free health state utility (assuming the DS seizure-free health state utility).
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 (nine 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.

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-drop 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	+/-	-	-
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	+/-	-	-
Relatively high seizure-free utility values	+	ERG base-case	Scenario
Lack of disutilities for adverse events	+	-	-
Resources and costs (section 5.2.9)			
The dose escalation period in the model is not in line with the escalation period used in the pivotal trials	-	-	-

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
The percentage of patients who are institutionalized 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	+	-	-

[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

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 £80,205 per QALY gained (assuming a constant treatment effect after 27 months) and £176,638 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 WTP threshold of £20,000 per QALY gained while these probabilities were [redacted] respectively, at a WTP 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 5.4: Cost effectiveness acceptability curve: ERG base-case assuming a constant treatment effect after 27 months

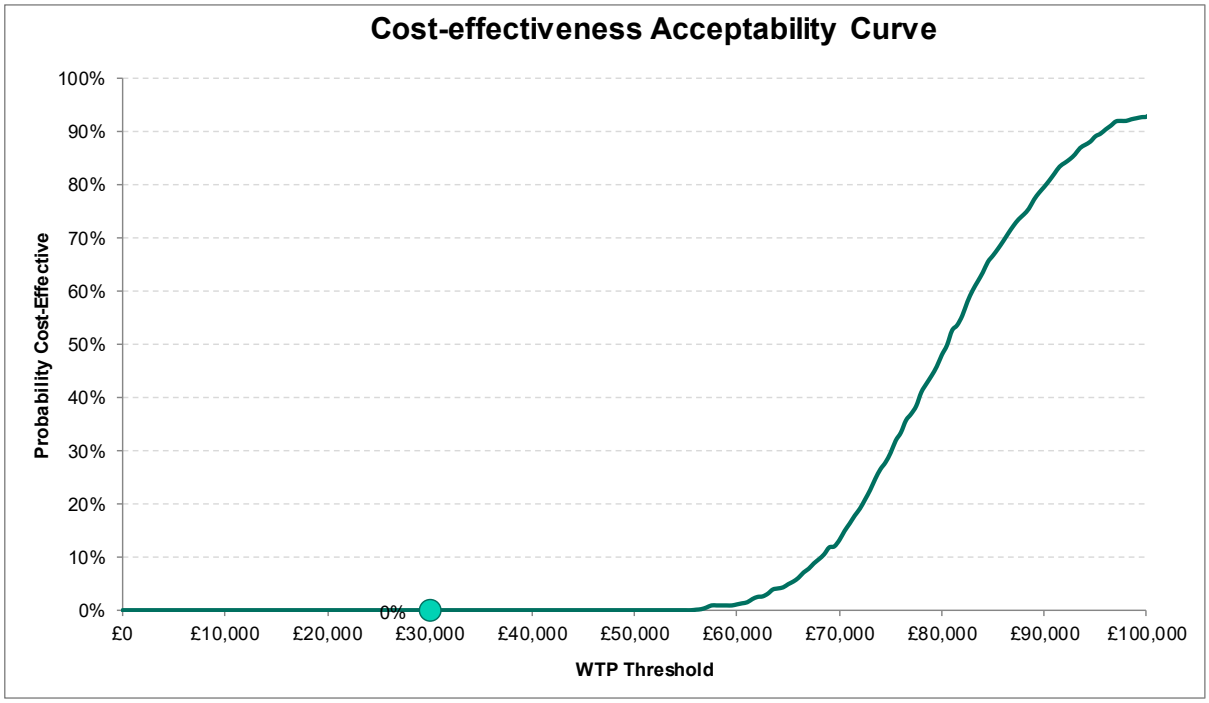
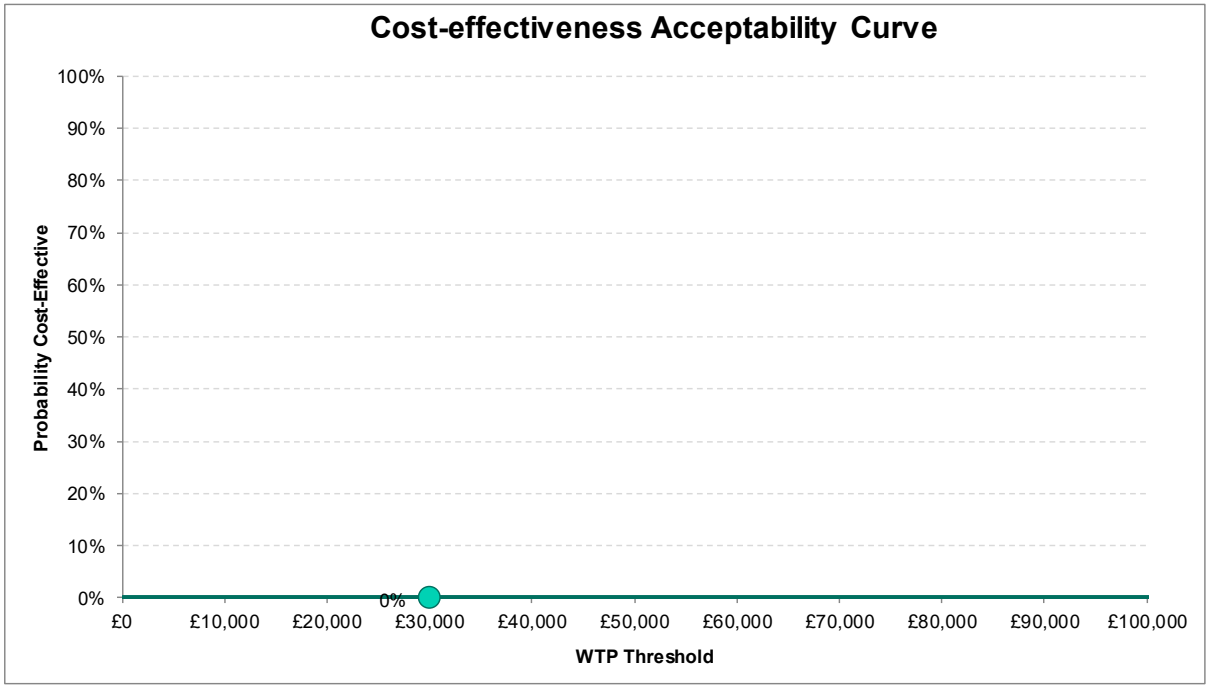


Figure 5.5: Cost effectiveness acceptability curve: ERG base-case assuming no constant treatment effect after 27 months



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) LGS. The model structure was focussed on drop seizures and did not explicitly capture non-drop 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. 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.

The ERG considers that key uncertainties in this cost effectiveness assessment are 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 23 mg/kg/day). 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. This uncertainty is, in part, reflected in the ERG base-case ICER range. Another source of uncertainty was the estimated health state utility values. The ERG considered the methodology to be not in line the NICE reference case, and the resulting utility values questionable (particularly given the high seizure-free utility values relative to the general population utility values). Finally, the model validity (as well as transparency) can be regarded as a major limitation of the current assessment. Although 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. The ERG considers that 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 (£31,107) should be interpreted with extreme caution given the highlighted validity issues and adjustments (model structure and input) made by the company. The ERG has incorporated various adjustments to the original 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 £80,205 per QALY gained and £176,638 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 + placebo	£90,183	15.451			
CCM + CBD	£221,141	20.298	£130,958	4.847	£27,019
Fixing errors (company's revised model, setting the input parameters as in the original CS)					
CCM + placebo	£90,461	3.764			
CCM + CBD	£241,155	5.150	£150,695	1.386	£108,717
Fixing errors + time horizon of 20 year					
CCM + placebo	£111,533	4.510			
CCM + CBD	£299,126	6.238	£187,593	1.728	£108,552
Fixing errors + adjusted mortality probabilities					
CCM + placebo	£90,993	3.743			
CCM + CBD	£237,747	5.035	£146,754	1.292	£113,560
Fixing errors + adjusted discontinuation probabilities					
CCM + placebo	£90,461	3.764			
CCM + CBD	£165,733	4.815	£75,273	1.051	£71,612
Fixing errors + treatment independent number of days without seizures					
CCM + placebo	£90,461	3.764			
CCM + CBD	£241,155	5.102	£150,695	1.338	£112,641
Fixing errors + adjusted utility for seizure-free health state					
CCM + placebo	£90,461	3.764			
CCM + CBD	£241,155	5.052	£150,695	1.288	£116,964

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) vs BSC
Fixing errors + institutionalization risk in the seizure-free category					
CCM + placebo	£90,461	3.764			
CCM + CBD	£242,142	5.150	£151,682	1.386	£109,429
Fixing errors + AED dose reduction for CBD					
CCM + placebo	£90,461	3.764			
CCM + CBD	£241,523	5.150	£151,062	1.386	£108,982
ERG base-case (assuming constant treatment effect after 27 months)					
CCM + placebo	£112,381	4.476			
CCM + CBD	£190,991	5.516	£78,610	1.041	£75,541
ERG base-case (assuming no treatment effect after 27 months)					
CCM + placebo	£112,381	4.476			
CCM + CBD	£180,889	4.898	£68,508	0.422	£162,206

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 + placebo	[redacted]	[redacted]			
CCM + CBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (assuming constant treatment effect after 27 months)					
CCM + placebo	£112,771	4.484			
CCM + CBD	£204,563	5.629	£91,791	1.144	£80,205
ERG base-case (assuming no treatment effect after 27 months)					
CCM + placebo	£112,904	4.474			
CCM + CBD	£189,777	4.909	£76,873	0.435	£176,638

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 + placebo	£112,771	4.484			
CCM + CBD	£204,563	5.629	£91,791	1.144	£80,205
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 + placebo	£112,032	4.471			

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) vs BSC
CCM + CBD	£306,618	5.620	£194,585	1.149	£169,415
ERG base-case (assuming constant treatment effect after 27 months) + include caregivers QALY					
CCM + placebo	£112,509	1.403			
CCM + CBD	£204,499	3.642	£91,990	2.240	£41,075
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 + placebo	£113,357	4.479			
CCM + CBD	£205,883	5.627	£92,526	1.148	£80,602
ERG base-case (assuming constant treatment effect after 27 months) + only use evidence based on the 10 mg/kg/day CBD dose					
CCM + placebo	£112,940	4.481			
CCM + CBD	£205,035	5.619	£92,095	1.139	£80,872

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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.

Figure A.1: 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 nine.

DARE, HTA & NHS EED (CRD): up to 2018/03/31
Searched 26.3.19

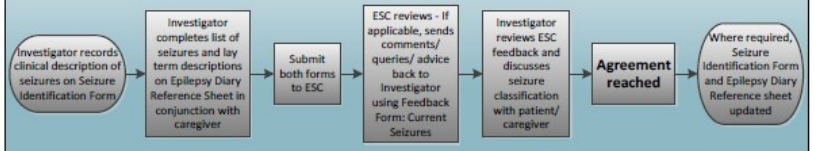
Line	Search	Hits	
1	MeSH DESCRIPTOR Lennox Gastaut Syndrome EXPLODE ALL TREES	1	
2	MeSH DESCRIPTOR Epilepsies, Myoclonic EXPLODE ALL TREES	4	
3	#1 OR #2	5	
4	(child* or infan*)	10960	
5	#3 AND #4	5	
6	(Dravet* syndrome) OR (Lennox Gastaut) OR (childhood epilep* encephalopath*)	13	
7	((severe myoclonic epilepsy) OR (SMEI) OR LGS)	8	
8	#5 OR #6 OR #7	17	

The original company submission search of the CRD databases retrieved nine results.

Appendix 2: Additional information on collection of seizure data

Role of the Epilepsy Study Consortium (ESC)

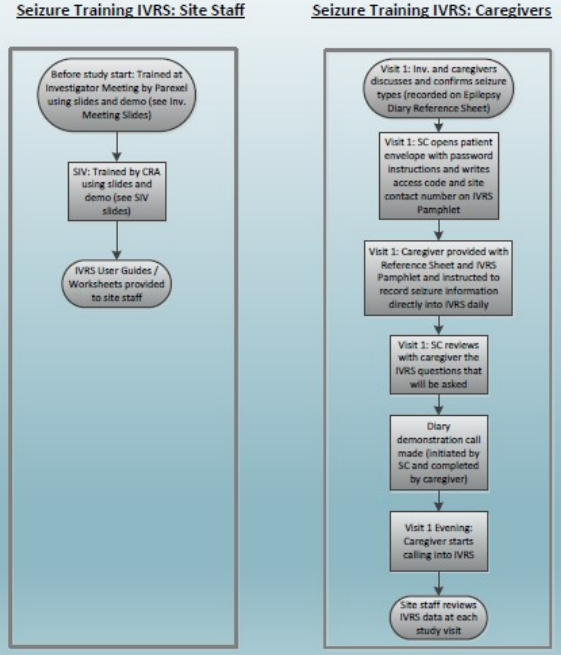
To ensure accuracy of seizure identification and reporting across the 3 pivotal trials, seizure types were verified by member(s) of a committee of independent experts from the ESC. For study GWEP1332B, the ESC had the additional responsibility of confirming the diagnosis of DS.



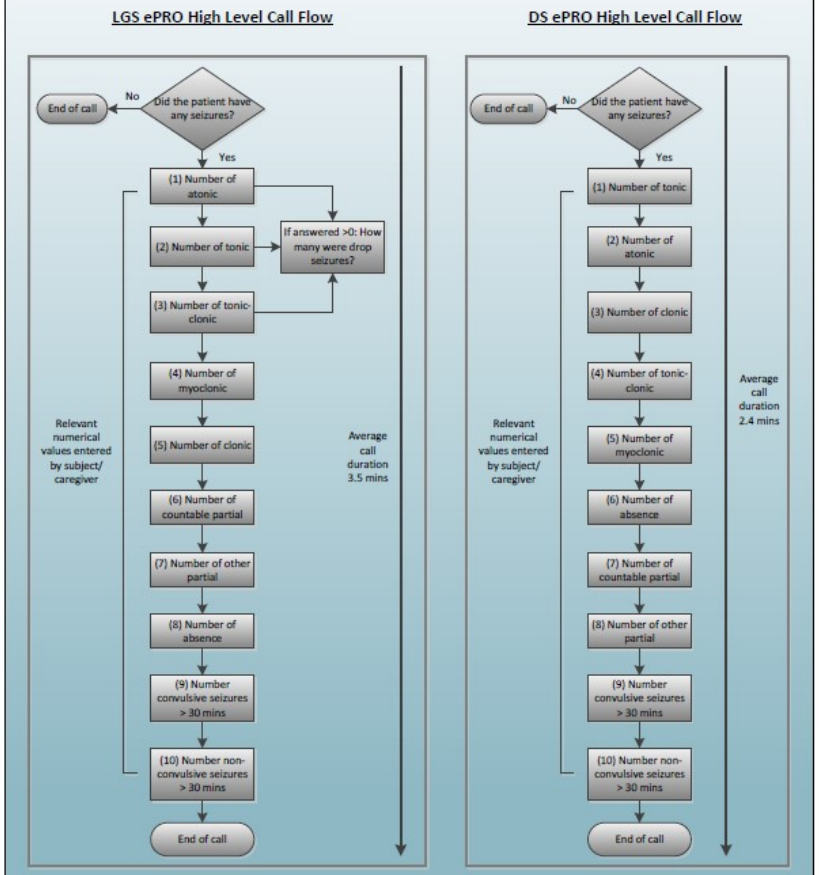
Use of IVRS

Throughout each pivotal trial, seizures were recorded daily on a validated electronic patient reported outcomes (ePRO) system using IVRS (Perceptive myTrials®). For the majority of patients all assessments, including daily seizure recording, were completed on their behalf by caregivers. This included all ages, children and adults, due to the prevalence of cognitive and development impairment in the LGS and DS patients being studied.

Training on IVRS



IVRS Questions Posed to the Caregiver



ePRO calls could be made in the local language and had to be made daily between 6 PM and midnight local time. The calls were to be reflective of the number of seizures since the last call on the previous day or the last 24 hours if no call was made. If a call was missed, there was an opportunity to enter data for the previous day only.

Total seizure counts for seizure clusters were estimated based on frequency of seizures during the cluster and duration of the cluster.

Question from NICE technical team	Company response	ERG comments
Issue 1: Positioning of CBD in the Lennox-Gastaut syndrome (LGS) 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 AED). The patients included in the two RCTs were broadly representative of this population; the proportion of participants who had fewer than two prior AEDs was low (<5%)."*
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 LGS 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 LGS in the trials were based on international guidelines, which are similar to the NICE guidelines for patients with LGS. UK specialist clinicians agree that the participants in the GWPCARE trials reflect the characteristics of people with LGS seen in practice in the NHS (based on e.g. age, gender, seizure types, concomitant anti-epileptic drugs).	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: *"Difficult to establish, as published data on LGS in adulthood are scarce. Many will be undiagnosed, and may be on inappropriate treatments already. Adult LGS management is likely to be suboptimal in many cases."*

<table>
<tr><th colspan="3">Issue 3: Composition of current clinical management</th></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 LGS 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>Valproate</td><td>[redacted]</td><td></td><td>[redacted]</td><td>50</td></tr>
<tr><td>Clobazam</td><td>[redacted]</td><td></td><td>[redacted]</td><td>30</td></tr>
<tr><td>Lamotrigine</td><td>[redacted]</td><td></td><td>[redacted]</td><td>50</td></tr>
<tr><td>Rufinamide</td><td>[redacted]</td><td></td><td>[redacted]</td><td>5</td></tr>
<tr><td>Topiramate</td><td>[redacted]</td><td></td><td>[redacted]</td><td>30</td></tr>
<tr><td>Levetiracetam</td><td>[redacted]</td><td></td><td>[redacted]</td><td>60</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>
</table>

<table>
<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></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>Valproate</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>Clobazam</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>Lamotrigine</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>Rufinamide</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>
<tr><td>Levetiracetam</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
</table>
</td>
<td></td>
</tr>
<tr><td colspan="4">Issue 4: Impact of concurrent anti-epileptic drug use on CBD efficacy</td></tr>
<tr>
<td>Would the efficacy of CBD differ depending on which antiepileptic drugs it is used alongside?</td>
<td colspan="2">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.</td>
<td>The ERG considers that this question remains open. As is stated in the ERG report: “[The company] assumed that the effectiveness of CBD does not vary with the combinations of AEDs to which it is added. This assumption is crucial to the validity of the ‘mixed’ CCM comparator. The ERG considers that there is currently a lack of evidence to support this assumption.”</td>
</tr>
<tr><td colspan="4">Issue 5: Criteria for stopping treatment</td></tr>
<tr>
<td>Would treatment stop if there was no improvement in seizure frequency? How would this be</td>
<td colspan="2">In most cases, CBD treatment would be expected to stop if there were 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,</td>
<td>It is unclear to the ERG:
1. whether the proposed 6 months stopping rule is clinically plausible;</td>
</tr>
</table>

defined, and would this be related to drop seizure frequency, total seizure frequency or both? At what time-point(s) would response to treatment be assessed?	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 drop-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 drop seizures from baseline in GWPCARE3/4. 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	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 5% 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).

	‘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 drop-seizure free health state, long-term discontinuation rates remain at 0.5%.	
Issue 6: Ignoring non-drop seizures in the model		
Is excluding non-drop seizures from the model appropriate?	Drop seizures (which include atonic, tonic and tonic-clonic seizures) are those involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair, or hitting the patient’s head on a surface. These are the seizure types about which parents/caregivers of patients with LGS are most concerned, as they can lead to serious injury/hospitalisation. Reduction in drop seizures was the primary endpoint in the CBD LGS Phase 3 trials. Non-drop 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 non-drop seizures is lower in health states with fewer drop seizures. Therefore, it is the change in QoL in moving from higher to lower drop-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 impact of excluding non-drop seizures is unclear to the ERG. The main ERG concerns relate to input parameters used for the drop-seizure free health state that may reflect the health state where patients are also non drop-seizure free (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-drop seizures in the >110 drop seizures health state only that would be required to reduce the QALYs. However, that does not show the additional effect on utility of non-drop seizures given that there is no estimate of the number of drop seizures for each health state (including drop-seizure free) nor is there any disutility associated with a drop seizure.

	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-drop seizures have on individuals' quality of life?	Patients with LGS typically experience many seizures a month. In GWPCARE3, some patients were having >400 seizures per month at baseline. Drop seizures are assessed as the primary endpoint in trials for LGS because they are clinically identifiable, easy to count, and drive the morbidity. Drop seizures were chosen as the basis for the model structure for exactly 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-drop 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-drop seizures strongly tracks drop-seizure health states. As such, there is unrealised patient benefit associated with non-drop seizures that is not captured in the model. Providing a deterministic quantification of this benefit is challenging. Non-drop 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.	See response to previous issue.

	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 drop-seizure health state (i.e. >110 drop 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 0.094, or about a 10% 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 7: Number of days without drop seizures		
Is CBD likely to increase the number of drop seizure-free days, in addition to reducing drop 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	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

	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 8 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 drop-seizure free days, and this assumption has been retained in the Company's Updated Base Case.	maintain a benefit after stopping CBD and hence would prefer the "number of seizure-free days" to be treatment independent.
Issue 8: 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	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 LGS and DS is very variable. In the CBD studies, it was up to 27%. In other LGS trials, it has varied from a 5% worsening to 12% improvement (Ostendorf AP, *et al*. *Neuropsychiatr*	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

should the relative efficacy of CBD compared with current clinical management remain constant over time?	*Dis Treat*. 2017;13:1131-40). A recent study in DS showed a placebo effect of <2%. The absolute impact of CBD in LGS on drop seizures from baseline is very consistent across studies at 40-50%, which is also seen on convulsive seizures in DS. This magnitude of effect was observed in the open-label GWPCARE5 study for patients entering from the placebo arms of GWPCARE3 and 4 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 GWPCARE3 and GWPCARE4 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	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 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 costs would substantially decrease in this scenario.

	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 9: Use of data from open label extension study		
Are the results from the open label extension study (GWPCARE 5), where patients had an average maintenance dose of CBD of ********** generalisable to the expected maintenance dose of **********?	No dose response was seen in the GWPCARE3 trial in LGS or in the GWPCARE2 trial in DS. 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 (≥6 to <16 mg/kg/day) and those who were on a high dose (≥16 to <21 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 GWPCARE3/4 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	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 LGS. The CS did not include any comparison between the 10 mg/kg/day and 20 mg/kg/day arms of GWPCARE3, 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 ≥16 to <21 mg/kg/day subgroups included only [redacted] and [redacted] patients respectively, i.e. the majority of patients in GWPCARE5 ([redacted]) were on doses >20 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

	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.	ERG comments in ERG report sections 4.2.5, 4.2.9 and 5.2.6.
Issue 10: 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 drop 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 (5%), which is the best long-term real-world data set currently available (Laux LC, et al. *Epilepsy Research* 2019;154:13-20.).	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 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).

	In the Company's Updated Base Case, 52% of patients are on treatment by 3 years, and 37% 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 17) 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 17 below).	No AED dose reduction is consistent with the ERG preferred assumptions (see ERG report).
Issue 11: 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?	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:	The ERG notes that the company's response does not address the question of whether an increase in CBD dose may be considered in 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).

• 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	• 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.	

<table>
<tr><td>would this be?</td><td></td><td></td></tr>
<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="3">Issue 12: Time horizon</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 5.4% 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="3">Issue 13: Relationship between mortality rates and number of seizures</td></tr>
<tr><td>Is an association between number of drop seizures and increased epilepsy-related mortality rates plausible? If</td><td><table><tr><td></td><td>Risk ratio</td></tr></table></td><td>The reported risk ratios reflect the risk ratio for being seizure-free: presumably this is not restricted to drop-seizures only. Hence, it is unclear to what degree this evidence supports the association between number of drop seizures and increased epilepsy-related mortality.</td></tr>
</table>

possible please estimate the increased (value greater than 1) or reduced risk (value less than 1) compared with the >45 and ≤ 110 seizures category in the following table:	<table><tr><td></td><td>Seizure free</td><td>≤ 45 seizures</td><td>>45 to ≤ 110 seizures (**reference**)</td><td>> 110 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> 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.	
What proportion of patients with LGS 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 14: Health-related quality of life of people with LGS		
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 LGS and DS 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. All other identified cost-utility studies in LGS and DS used these analogues. As outlined in the company's response to B17c of the ERG's Clarification Questions, the health states investigated in Verdian *et al* were not close surrogates for	No comments

	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. Verdian *et al* did assess the utility score in one health state defined by seizure frequency (82-112 drop seizures per month). This score closely aligns with those in the company's model with comparable seizure frequency. Utility scores for patients with a high response in Verdian (≥75% reduction) also align to the seizure-free health state in the CBD model. Average utility scores for DS populations reported in the large DISCUSS survey showed similar scores to the company's own health states in LGS, 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 15: Health-related quality of life of carers of people with LGS		
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 LGS 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".	As described in the ERG report, the inclusion of carer QALYs was not done in accordance with the NICE reference case and the 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 >3 times as large than the decrements for patients? If the carer disutilities are multiplied by 1.8 (assuming that each patient with LGS has 1.8 carers) as done by the company, this would result in decrements for caregivers that are 5.5 to 11.7 times 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?	No studies providing caregiver utilities in LGS have been identified from the literature. However, in Dravet syndrome, a survey (Campbell JD, et al. *Epilepsy & Behavior* 2018;80:152-156) assessed caregiver utilities on the EQ-5D VAS. The disutility (0.33 +/- 0.21) is at the mid-point of those measured in the company's vignette study (0.27 and 0.40 for the two health states with the highest numbers of seizures), validating the plausibility of the company's disutility values.	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 VAS-rated 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. Moreover, Campbell et al. 2018 have also estimated caregivers' utility by using the EQ-5D Index score and demonstrated a utility score of 0.78 (±0.17), which would

	A scenario using the disutility score from Campbell *et al* shows a similar ICER to the Company's Updated Base Case. (See scenario in Table 4 of the separate 'Response Addendum' document).	result in a smaller utility decrement (also smaller than found in the company's vignette study).
How many carers would a child with LGS be expected to have? Would this be expected to remain the same after the person reaches adulthood?	The literature indicates that ≥1 carer for patients with severe epilepsy syndromes 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 many children with LGS, the need for ≥1 carer remains the same after they reach adulthood. Cognitive impairment is noted in up to 95% of patients with LGS within 5 years of disease onset, and functional impairment renders 87% of patients with LGS unable to live independently, with 58% being completely dependent on others for all activities of daily living (Camfield C, Camfield P. *Developmental Medicine & Child Neurology* 2008). 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 LGS has 1.8 carers.	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)?
Issue 16: 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 LGS. 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: *"Potentially yes, in the context of multiple therapies and comorbidities."*
Issue 17: 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 has assumed that there are no reductions in concomitant AEDs. The dose reduction of concomitant AEDs is included as a scenario analysis. Please see the scenario analyses in Table 4 of the separate 'Response Addendum' document.	No AED dose reduction is consistent with the ERG preferred assumptions (see ERG report).

<table>
<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>Company Valproate</td><td></td><td></td></tr>
<tr><td>Clobazam</td><td></td><td></td></tr>
<tr><td>Lamotrigine</td><td></td><td></td></tr>
<tr><td>Rufinamide</td><td></td><td></td></tr>
<tr><td>Topiramate</td><td></td><td></td></tr>
<tr><td>Levetiracetam</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>

NICE National Institute for Health and Care Excellence

Technical engagement response form

Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome [ID1308]

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. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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 CBD in the Lennox-Gastaut syndrome (LGS) 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 LGS 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 LGS in the trials were based on international guidelines, which are similar to the NICE guidelines for patients with LGS. UK specialist clinicians agree that the participants in the GWPCARE trials reflect the characteristics of people with LGS seen in practice in the NHS (based on e.g. age, gender, seizure types, concomitant anti-epileptic drugs).
Issue 3: 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 LGS 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".

<table>
<tr><td></td><td>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></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>Valproate</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>Clobazam</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>Lamotrigine</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>Rufinamide</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>
<tr><td>Levetiracetam</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
</table>
</td></tr>
<tr><td colspan="2">Issue 4: Impact of concurrent anti-epileptic drug use on CBD efficacy</td></tr>
<tr><td>Would the efficacy of CBD differ depending on which antiepileptic drugs it is used alongside?</td><td>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.</td></tr>
<tr><td colspan="2">Issue 5: Criteria for stopping treatment</td></tr>
<tr><td>Would treatment stop if there was no improvement in seizure frequency? How would this be defined, and would this be related to drop seizure frequency, total seizure frequency or both? At what time-point(s) would response to treatment be assessed?</td><td>In most cases, CBD treatment would be expected to stop if there were 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.</td></tr>
</table>

	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 drop-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 drop seizures from baseline in GWPCARE3/4. 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 [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 drop-seizure free health state, long-term discontinuation rates remain at [redacted]%.
Issue 6: Ignoring non-drop seizures in the model	
Is excluding non-drop seizures from the model appropriate?	Drop seizures (which include atonic, tonic and tonic-clonic seizures) are those involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair, or hitting the patient's head on a surface. These are the seizure types about which parents/caregivers of patients with LGS are most concerned, as they can lead to serious injury/hospitalisation. Reduction in drop seizures was the primary endpoint in the CBD LGS Phase 3 trials. Non-drop 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 non-drop seizures is lower in health states with fewer drop seizures. Therefore, it is the change in QoL in moving from higher to lower drop-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-drop seizures have on individuals' quality of life?	Patients with LGS typically experience many seizures a month. In GWPCARE3, some patients were having >400 seizures per month at baseline. Drop seizures are assessed as the primary endpoint in trials for LGS because they are clinically identifiable, easy to count, and drive the morbidity. Drop seizures were chosen as the basis for the model structure for exactly 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-drop 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-drop seizures strongly tracks drop-seizure health states. As such, there is unrealised patient benefit associated with non-drop seizures that is not captured in the model. Providing a deterministic quantification of this benefit is challenging. Non-drop 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 drop-seizure health state (i.e. >110 drop 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 10% 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 7: Number of days without drop seizures	
Is CBD likely to increase the number of drop seizure-free days, in addition to reducing drop 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 8 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 drop-seizure free days, and this assumption has been retained in the Company's Updated Base Case.
Issue 8: 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	The ERG acknowledged in its report that the placebo effect in the GWPCARE trials for CBD was high.

CBD compared with current clinical management remain constant over time?	The placebo effect seen in clinical trials for both LGS and DS is very variable. In the CBD studies, it was up to 27%. In other LGS trials, it has varied from a 5% worsening to 12% improvement (Ostendorf AP, *et al*. *Neuropsychiatr Dis Treat*. 2017;13:1131-40). A recent study in DS showed a placebo effect of <2%. The absolute impact of CBD in LGS on drop seizures from baseline is very consistent across studies at 40-50%, which is also seen on convulsive seizures in DS. This magnitude of effect was observed in the open-label GWPCARE5 study for patients entering from the placebo arms of GWPCARE3 and 4 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 GWPCARE3 and GWPCARE4 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 9: Use of data from open label extension study	
Are the results from the open label extension study (GWPCARE 5), where patients had an average maintenance dose of CBD of [redacted]	No dose response was seen in the GWPCARE3 trial in LGS or in the GWPCARE2 trial in DS. 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

generalisable to the expected maintenance dose of [redacted]?	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 GWPCARE3/4 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 10: 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 drop 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 17) 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 17 below).
Issue 11: 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

<table>
<tr><td></td><td>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.</td></tr>
<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></tr>
<tr><td colspan="2">Issue 12: Time horizon</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></tr>
<tr><td colspan="2">Issue 13: Relationship between mortality rates and number of seizures</td></tr>
<tr><td>Is an association between number of drop 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 >45 and ≤ 110 seizures category in the following table:</td><td>
<table>
<tr><td></td><td colspan="4">Risk ratio</td></tr>
<tr><td></td><td>Seizure free</td><td>≤ 45 seizures</td><td>>45 to ≤ 110 seizures (reference)</td><td>> 110 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>
</table>

	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.
What proportion of patients with LGS 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 14: Health-related quality of life of people with LGS	
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 LGS and DS 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. All other identified cost-utility studies in LGS and DS used these analogues. As outlined in the company's response to B17c of the ERG's Clarification Questions, 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.

	Verdian *et al* did assess the utility score in one health state defined by seizure frequency (82-112 drop seizures per month). This score closely aligns with those in the company's model with comparable seizure frequency. Utility scores for patients with a high response in Verdian (≥75% reduction) also align to the seizure-free health state in the CBD model. Average utility scores for DS populations reported in the large DISCUSS survey showed similar scores to the company's own health states in LGS, 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 15: Health-related quality of life of carers of people with LGS	
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 LGS 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?	No studies providing caregiver utilities in LGS have been identified from the literature. However, in Dravet syndrome, a survey (Campbell JD, et al. *Epilepsy & Behavior* 2018;80:152-156) assessed caregiver utilities on the EQ-5D VAS. The disutility (0.33 +/- 0.21) is at the mid-point of 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. (See scenario in Table 4 of the separate 'Response Addendum' document).

How many carers would a child with LGS be expected to have? Would this be expected to remain the same after the person reaches adulthood?	The literature indicates that ≥1 carer for patients with severe epilepsy syndromes 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 many children with LGS, the need for ≥1 carer remains the same after they reach adulthood. Cognitive impairment is noted in up to 95% of patients with LGS within 5 years of disease onset, and functional impairment renders 87% of patients with LGS unable to live independently, with 58% being completely dependent on others for all activities of daily living (Camfield C, Camfield P. *Developmental Medicine & Child Neurology* 2008). 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 LGS has 1.8 carers.
Issue 16: 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 LGS. 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 17: 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.

<table>
<tr><td></td><td>Nonetheless, based on the comments from the ERG and the NICE technical team, in the Company's Updated Base Case, the company has assumed that there are no reductions in concomitant AEDs.
The dose reduction of concomitant AEDs is included as a scenario analysis. Please see the scenario analyses in Table 4 of the separate 'Response Addendum' document.</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>Company Valproate</td><td></td><td></td></tr>
<tr><td>Clobazam</td><td></td><td></td></tr>
<tr><td>Lamotrigine</td><td></td><td></td></tr>
<tr><td>Rufinamide</td><td></td><td></td></tr>
<tr><td>Topiramate</td><td></td><td></td></tr>
<tr><td>Levetiracetam</td><td></td><td></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></td></tr>
</table>

Appendix 1

Issue 7
Table 1: Mean number of drop seizure-free days per 28 days over the treatment period

	GWPCARE3 Study 1414			GWPCARE4 Study 1423	
	CBD 20 mg/kg/day (n= 76)	CBD 10 mg/kg/day (n= 73)	Placebo (n= 76)	CBD 20 mg/kg/day (n= 86)	Placebo (n= 85)
Treatment period P-value (vs placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Issue 8

Table 2: Outcomes on the primary endpoint for patients in GWPCARE3 and 4 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 drop-seizure frequency for patients on CBD in GWPCARE3 and 4, and for patients on a maintenance dose of <21 mg/kg/day of CBD in GWPCARE5 who were previously on placebo in GWPCARE3 and 4. 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 GWPCARE3 and 4 studies).

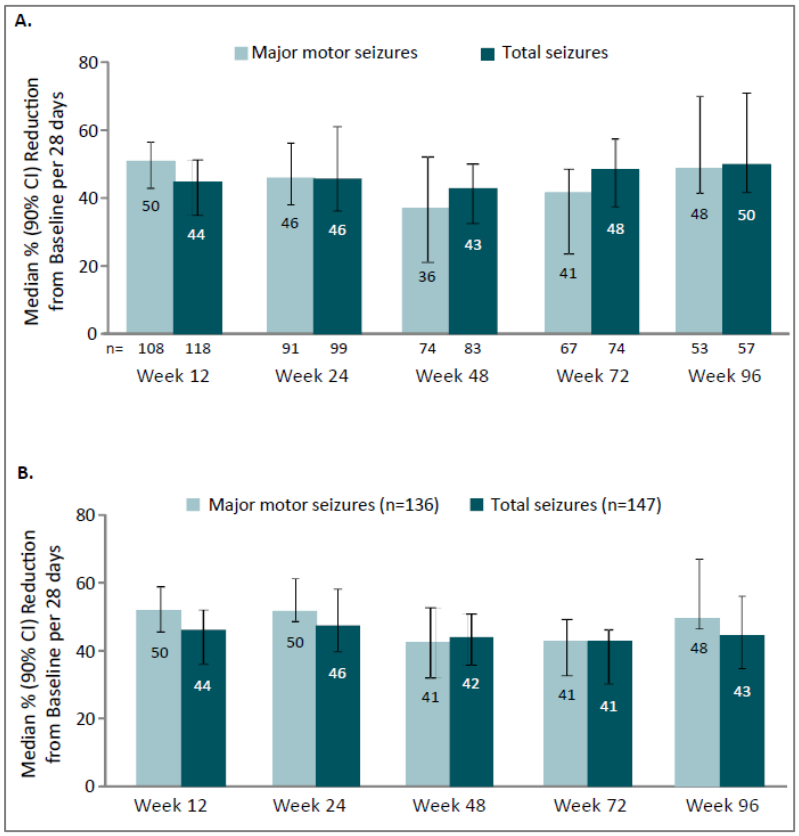
Issue 8

Table 3: Outcomes on the key secondary endpoint for patients in GWPCARE3 and 4 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]	

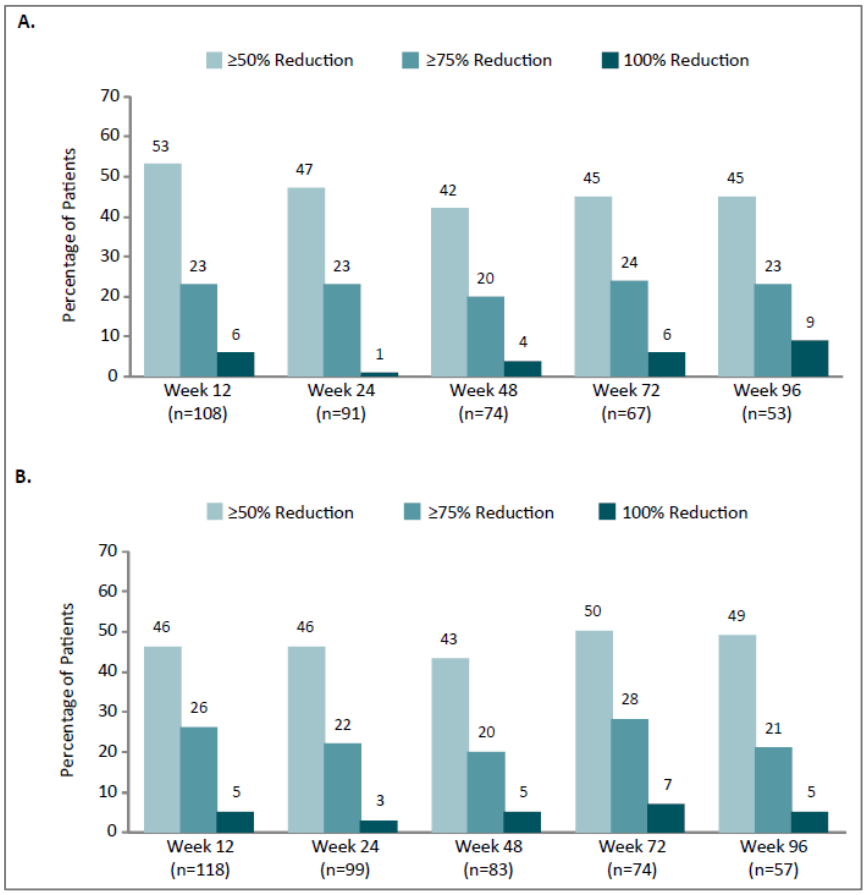
Proportion of patients achieving ≥50% reduction in drop-seizure frequency on CBD in GWPCARE3 and 4, and in patients on a maintenance dose of <21 mg/kg/day of CBD in GWPCARE5 who were previously on placebo in GWPCARE3 and 4. Outcomes for transitioning placebo patients are re-baselined to the start of the GWPCARE5 study and measured at 12 weeks (vs 14 weeks for patients on CBD in the GWPCARE3 & 4 studies).

Issue 8
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 8
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 Lennox-Gastaut syndrome [ID1308]

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 32 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 drop seizure health states for patients not on CBD (i.e. either on CCM, or having discontinued CBD). The company feels that this was a reasonable design choice to account for likely changes in drop seizure frequency over time in LGS 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 8 of the technical report, the company provided an explanation as to why applying the relative treatment effect observed in the GWPCARE3 and GWPCARE4 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 9), 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 GWPCARE3 and GWPCARE4 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]

*Note: the QALY change in CCM patients is spread across the patient and an average of 1.8 caregivers, and a time horizon of 50 years. It does not represent a worse-than-death outcome for any one individual in the CCM arm.

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 17 p66 of Document B)	Issue 3	[redacted]	[redacted]	[redacted]
Outcomes from GWPCARE3/4 (used in cycle 1 of Company's Updated Base Case) applied for cycles 1-8 in both the CBD+CCM and CCM arms (ERG's scenario).	Issues 8 and 9	[redacted]	[redacted]	[redacted]
Relative treatment effect applied for cycles 1-2 only (as per base case in the company's response to the technical report 27th June 2019).	Issue 8	[redacted]	[redacted]	[redacted]
Long-term discontinuation rates (cycles 10 onwards) increased from 5% to 10% per cycle for all health states other than drop-seizure free patients.	Issue 10	[redacted]	[redacted]	[redacted]
Time horizon (% patients still on CBD, % patients alive on CBD+CCM/CCM): • 15 years (9.82%, 79.3%/78.6%) • 20 years (7.35%, 73.1%/72.3%) • 30 years (5.66%, 61.8%/60.7%) 40 years (4.95%, 48.9%/50.0%)	Issue 12	[redacted]	[redacted]	[redacted]
Utilities for health states taken from analogues in Verdian *et al* 2018[2]. Utilities across seizure-free day health sub-states made uniform.	Issue 14	[redacted]	[redacted]	[redacted]

Scenario	Rationale	Inc. Costs	Inc. QALYs	ICER
Caregiver disutilities for the two health states with the most drop seizures taken from those reported for DS patients in Campbell *et al* 2018[1] (-0.33 per caregiver on EQ-5D VAS)	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 28 p89 of Document B)	Issue 17	[redacted]	[redacted]	[redacted]
Incident population only (age 2-5 years at model entry)	Existing scenario	[redacted]	[redacted]	[redacted]
Average dose of 11.51 mg/kg/day (as per the Company's Revised Base Case March 2019; see Table 41 p118 of Document B)	Existing scenario	[redacted]	[redacted]	[redacted]
Mean instead of median body weight across age ranges in the weight table	Table 3, NICE technical report	[redacted]	[redacted]	[redacted]
Sensitivity analysis - QoL impact of non-drop seizure reductions. Additive disutility per person* required to increase incremental QALY gain in base case by: • 5% - 0.031 • 10% - 0.062 • 20% - 0.123	Issue 6	[redacted]	[redacted]	[redacted]

1. Campbell J, *et al*. Epilepsy & Behavior 2018;80:152-156.

2. 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 drop-seizure health state (>110 drop-seizures per month).

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. 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 each age group (tab "# DAYS")	CBD + CCM -1.16 CCM -1.53 Inc. QALY gain 0.37	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 drop seizure health state distributions are 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". (Note probabilities for drop seizure free health state set to 0%) • Discontinuation rates set to 5% for health states in all cohorts and cycles across both age groups in tab "DISCONTINUATION" • Stopping rules switched off in tab "GLOBAL SETTINGS"	Zero inc. 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 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 inc. 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 "≤45 seizures", and 0% for all others, for both age groups in tab "COHORT DEFINITION" • Probabilities are set to 100% for the SFD substates "≤3 days", and 0% in all others, for 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%, 20% (variably) for all health states in all cohorts and cycles	Zero inc. QALY gain	Yes. A zero QALY gain is maintained under all changes, as expected. Note – as long as discontinuation rates are uniform across all health states and cohorts, 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% (or any other value) • Set to 100% for one set of cycle time points, and all others are set to 0% • Varied only in one age group, highlighting that age groups are now "separated", and discontinuing CBD patients are not "aging"
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 all patients ≥12 years old.	Zero inc. 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 "≤45 seizures" in "Long-Term" cycles (10%)	Zero inc. QALY gain at 2 years At 50 years: CBD + CCM -1.71 CCM -1.55 Inc. QALY gain -0.16	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 to 8 cycles (2 years), alongside the uniform discontinuation rates in cycles 1-8, would be expected to give a null result. Form 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 "≤45 seizures" health state to 5% returns a null result.

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 inc. 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 inc. 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 GWPCARE3 & 4 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 £2344	-20%	+20%	Assumption

Parameter	Base Case	Lower Bound	Upper Bound	References
Hospitalisation Costs	Between £0 and £969	-20%	+20%	Assumption
Rescue Med Costs	Between £0 and £54	-20%	+20%	Assumption
Institutionalisation Costs	Between £0 and £1604	-20%	+20%	Assumption
Daily Cost ICU				
Adults	£1,299	£643	£4,482	Tables 33 & 39 of Document B
Paediatric	£1,583	£784	£5,867	
Daily Cost General Ward				
Adults	£460	£402	£807	Tables 33 & 39 of Document B
Paediatric	£597	£560	£760	
Phone Call Follow-up				
Neurologist	£107	£57	£153	Tables 33 & 39 of Document B
Paediatric neurologist	£258	£55	£234	
Emergency Department Visit				
Per episode	£237	£56	£838	Tables 33 & 39 of Document B
Non-SUDEP costs, days in ICU				
2 - 11 years	7.00	-20%	+20%	Tables 33 & 39 of Document B
12 - 55 years	7.00	-20%	+20%	
% of institutionalisation				
Seizure-Free	2.00%	1.6%	2.4%	Tables 33 & 39 of Document B
≤45 seizures	10.00%	8.00%	12.00%	
>45 - ≤110 seizures	10.00%	8.00%	12.00%	
>110 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	11.51	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%	
≤45 seizures				
2 - 11 years	1	-10%	+10%	Assumption
12 - 55 years	1	-10%	+10%	
>110 seizures				
2 - 11 years	1	-10%	+10%	Assumption
12 - 55 years	1	-10%	+10%	
SUDEP – Probabilities				
>45 - ≤110 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%	
≤45 seizures				
2 - 11 years	1	-10%	+10%	Assumption
12 - 55 years	1	-10%	+10%	
>110 seizures				
2 - 11 years	1	-10%	+10%	Assumption
12 - 55 years	1	-10%	+10%	
Non-SUDEP – Probabilities				
>45 - ≤110 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; >15 days	[redacted]	[redacted]	[redacted]	Based on standard errors from Vignette study Table 26 of Document B
≤45 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
≤45 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	
≤45 seizures; >15 days	[redacted]	[redacted]	[redacted]	
>45 - ≤110 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
>45 - ≤ 110 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	
>45 - ≤110 seizures; >15 days	[redacted]	[redacted]	[redacted]	
>110 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
>110 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	
>110 seizures; >15 days	[redacted]	[redacted]	[redacted]	
Caregiver utility decrements				
Seizure-Free; >15 days	[redacted]	[redacted]	[redacted]	Based on standard errors from Vignette study
≤45 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
≤45 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	
≤45 seizures; >15 days	[redacted]	[redacted]	[redacted]	
>45 - ≤110 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
>45 - ≤110 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	

Parameter	Base Case	Lower Bound	Upper Bound	References
>45 - ≤110 seizures; >15 days	[redacted]	[redacted]	[redacted]	
>110 seizures; ≤3 days	[redacted]	[redacted]	[redacted]	
>110 seizures; >3 - ≤15 days	[redacted]	[redacted]	[redacted]	
>110 seizures; >15 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]	758.80	0.02	Gamma
6 - 11 years		[redacted]	N/A	N/A	[redacted]	831.68	0.03	Gamma
12 - 17 years		[redacted]	N/A	N/A	[redacted]	690.87	0.06	Gamma
18 - 55 years		[redacted]	N/A	N/A	[redacted]	1211.40	0.05	Gamma
Subsequent cycle discontinuation								
2 - 11 years	Seizure-Free	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	≤45 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>45 - ≤110 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>110 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
	≤45 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>45 - ≤110 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	>110 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
≤45 seizures		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
>45 - ≤110 seizures		[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
>110 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
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	> 45 - ≤ 110 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	> 110 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
	≤ 45 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	> 45 - ≤ 110 seizures	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Uniform
	> 110 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
	≤45 seizures	£675	£337	£1,012	172.13	15.37	43.91	Gamma

Parameters		Base case	Min	Max	SE	Alpha	Beta	Distribution
	>45 - ≤110 seizures	£1,380	£690	£2,070	352.08	15.37	89.82	Gamma
	>110 seizures	£2,344	£1,172	£3,515	597.84	15.37	152.51	Gamma
12 - 55 years	Seizure-Free	£106	£53	£160	27.14	15.37	6.92	Gamma
	≤45 seizures	£235	£118	£353	60.01	15.37	15.31	Gamma
	>45 - ≤110 seizures	£381	£191	£572	97.30	15.37	24.82	Gamma
	>110 seizures	£718	£359	£1,077	183.23	15.37	46.74	Gamma
Hospitalisation Costs								
2 - 11 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤45 seizures	£242	£121	£364	61.83	15.37	15.77	Gamma
	>45 - ≤110 seizures	£606	£303	£909	154.58	15.37	39.43	Gamma
	>110 seizures	£969	£485	£1,454	247.32	15.37	63.09	Gamma
12 - 55 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤45 seizures	£63	£31	£94	16.01	15.37	4.08	Gamma
	>45 - ≤110 seizures	£157	£78	£235	40.02	15.37	10.21	Gamma
	>110 seizures	£251	£125	£376	64.03	15.37	16.33	Gamma
Rescue Med Costs								
2 - 11 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤45 seizures	£14	£7	£20	3.47	15.37	0.89	Gamma
	>45 - ≤110 seizures	£34	£17	£51	8.67	15.37	2.21	Gamma
	>110 seizures	£54	£27	£82	13.88	15.37	3.54	Gamma
12 - 55 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤45 seizures	£14	£7	£20	3.47	15.37	0.89	Gamma
	>45 - ≤110 seizures	£34	£17	£51	8.67	15.37	2.21	Gamma
	>110 seizures	£54	£27	£82	13.88	15.37	3.54	Gamma
Institutionalisation Costs								
18 - 55 years	Seizure-Free	£321	£160	£481	81.86	15.37	20.88	Gamma
	≤45 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
	>45 - ≤110 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
	>110 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
12 – 55 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
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
≤45 seizures		10.00%	8.00%	12.00%	N/A	N/A	N/A	Uniform
>45 - ≤110 seizures		10.00%	8.00%	12.00%	N/A	N/A	N/A	Uniform
>110 seizures		10.00%	8.00%	12.00%	N/A	N/A	N/A	Uniform
Utilities								
Patient utilities - Values estimated based on SE								
No seizures	>15 days	[redacted]	N/A	N/A	[redacted]	57.46	18.82	Beta
≤45 seizures	≤3 days	[redacted]	N/A	N/A	[redacted]	33.98	68.77	Beta
	>3 - ≤15 days	[redacted]	N/A	N/A	[redacted]	79.21	95.52	Beta
	>15 days	[redacted]	N/A	N/A	[redacted]	89.02	70.30	Beta
>45 - ≤110 seizures	≤3 days	[redacted]	N/A	N/A	[redacted]	31.04	76.19	Beta
	>3 - ≤15 days	[redacted]	N/A	N/A	[redacted]	64.78	96.37	Beta
	>15 days	[redacted]	N/A	N/A	[redacted]	74.23	83.26	Beta
>110 seizures	≤3 days	[redacted]	N/A	N/A	[redacted]	21.72	70.61	Beta
	>3 - ≤15 days	[redacted]	N/A	N/A	[redacted]	54.90	87.83	Beta
	>15 days	[redacted]	N/A	N/A	[redacted]	38.37	45.35	Beta
Caregiver utility decrements – values based on SE								
>45 - ≤110 seizures	≤3 days	[redacted]	N/A	N/A	[redacted]	16.768	0.016	Gamma
	>3 - ≤15 days	[redacted]	N/A	N/A	[redacted]	16.768	0.016	Gamma
	>15 days	[redacted]	N/A	N/A	[redacted]	16.768	0.016	Gamma
>110 seizures	≤3 days	[redacted]	N/A	N/A	[redacted]	20.943	0.019	Gamma
	>3 - ≤15 days	[redacted]	N/A	N/A	[redacted]	20.943	0.019	Gamma
	>15 days	[redacted]	N/A	N/A	[redacted]	20.943	0.019	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 Lennox-Gastaut syndrome [ID1308]

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 GWPCARE3 and GWPCARE4 trials.

Efficacy

The efficacy of cannabidiol for the adjunctive therapy of seizures associated with LGS was evaluated in two Phase 3 studies, GWPCARE3 and GWPCARE4.

Approximately 50% 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 LGS studies

		Overall	N	Subgroup With Clobazam	N
DROP SEIZURES PER 28 DAYS Percentage Reduction from Baseline[a]					
GWPCARE3	Placebo	17.2%	76	[redacted]	[redacted]
	10 mg/kg/day	37.2%	73	[redacted]	[redacted]
	20 mg/kg/day	41.9%	76	[redacted]	[redacted]
GWPCARE4	Placebo	21.8%	85	[redacted]	[redacted]
	20 mg/kg/day	43.9%	86	[redacted]	[redacted]
Difference or Percent Reduction Compared with Placebo (95% CI), p-value[b]					
GWPCARE3	10 mg/kg/day	19.2%		[redacted]	
		(7.7%, 31.2%)		[redacted]	
		p=0.0016		[redacted]	
	20 mg/kg/day	21.6%		[redacted]	
		(6.7%, 34.8%)		[redacted]	
		p=0.0047		[redacted]	
GWPCARE4	20 mg/kg/day	17.2%		[redacted]	
		(4.1%, 30.3%)		[redacted]	
		p=0.0135		[redacted]	
≥50% REDUCTION IN DROP SEIZURES (RESPONDER ANALYSIS) Percentage of ≥50% Responders, p-value[d]					
GWPCARE3	Placebo	14.5%	76	[redacted]	[redacted]
	10 mg/kg/day	35.6%	73	[redacted]	[redacted]
		p=0.0030		[redacted]	

	20 mg/kg/day	39.5%	76	[redacted]	[redacted]
		p=0.0006		[redacted]	
GWPCARE4	Placebo	23.5%	85	[redacted]	[redacted]
	20 mg/kg/day	44.2%	86	[redacted]	[redacted]
		p=0.0043		[redacted]	
TOTAL SEIZURES PER 28 DAYS					
Percentage Reduction from Baseline[a]					
GWPCARE3	Placebo	19%	76	[redacted]	[redacted]
	10 mg/kg/day	36%	73	[redacted]	[redacted]
	20 mg/kg/day	38%	76	[redacted]	[redacted]
GWPCARE4	Placebo	14%	85	[redacted]	[redacted]
	20 mg/kg/day	41%	86	[redacted]	[redacted]
Difference or Percent Reduction Compared with Placebo, p-value[b]					
GWPCARE3	10 mg/kg/day	19.5%		[redacted]	
		P=0.002		[redacted]	
	20 mg/kg/day	18.8%		[redacted]	
		P=0.009		[redacted]	
GWPCARE4	20 mg/kg/day	21.1%		[redacted]	
		0.001		[redacted]	
MEAN CGIC SCORE AT LAST VISIT					
Percentage patients with any improvement, p-value					
GWPCARE3	Placebo	44%	76	[redacted]	[redacted]
	10 mg/kg/day	66%	73	[redacted]	[redacted]
		P=0.002		[redacted]	
	20 mg/kg/day	57%	76	[redacted]	[redacted]
		P=0.04		[redacted]	
GWPCARE4	Placebo	34%	85	[redacted]	[redacted]
	20 mg/kg/day	58%	86	[redacted]	[redacted]
		P=0.0012		[redacted]	
EXPLORATORY ENDPOINT - DROP SEIZURE-FREE DAYS GAINED					
Mean number of drop seizure-free days gained versus baseline					
GWPCARE3	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	10 mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]
	20 mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]
GWPCARE4	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	20 mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference, p-value					
GWPCARE3	10 mg/kg/day	[redacted]		[redacted]	
		[redacted]		[redacted]	
	20 mg/kg/day	[redacted]		[redacted]	
		[redacted]		[redacted]	
GWPCARE4	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 LGS trial data

Pooled LGS trial data	**Overall**		**Subgroup with clobazam**	
	All CBD (N=235) n (%)	**Placebo (N=161) n (%)**	**All CBD (N=[redacted]) n (%)**	**Placebo (N=[redacted]) n (%)**
AEs	**207 (88.1)**	**114 (70.8)**	[redacted]	[redacted]
Mild	86 (36.6)	66 (41.0)	Data N/A	Data N/A
Moderate	90 (38.3)	40 (24.8)	Data N/A	Data N/A
Severe	31 (13.2)	8 (5.0)	Data N/A	Data N/A
AEs leading to discontinuation	19 (8.1)	2 (1.2)	[redacted]	[redacted]
SAEs	46 (19.6)	12 (7.5)	[redacted]	[redacted]
Deaths	1 (0.4)*	0	[redacted]	[redacted]

**Death attributed to acute respiratory distress syndrome and not considered to be treatment-related*

Selected adverse events in pooled LGS patients

Adverse reaction	**Overall**		**Subgroup with clobazam**	
	All CBD (N=235) n (%)	**Placebo (N=161) n (%)**	**All CBD (N=[redacted]) n (%)**	**Placebo (N=[redacted]) n (%)**
Somnolence/sedation	64 (27.2)	14 (8.7)	[redacted]	[redacted]
Decreased appetite	43 (18.3)	8 (5.0)	[redacted]	[redacted]
Diarrhoea	72 (30.6)	44 (27.3)	[redacted]	[redacted]
Pyrexia	27 (11.5)	19 (11.8)	[redacted]	[redacted]
Fatigue	18 (7.7)	4 (2.5)	[redacted]	[redacted]
Vomiting	23 (9.8)	23 (14.3)	[redacted]	[redacted]

Updated Economic Outcomes – On-Clobazam Population
Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome [ID1308]

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.

This document provides cost-utility outcomes for the population of patients who were on clobazam (CLB) at baseline in the GWPCARE3 and GWPCARE4 trials. These outcomes also serve as the company's response to Issue 4 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	£188,438	-1.35	-	-	-	-	-
CCM + CBD	£240,956	0.45	**£52,519**	**1.79**	**£29,280**	53.92%	4.51%

*Note: the QALY change in CCM patients is spread across the patient and an average of 1.8 caregivers, and a time horizon of 50 years. It does not represent a worse-than-death outcome for any one individual in the CCM arm.

Table 2. Costs in the Company's Updated Base Case

Cost categories	CCM + CBD	CCM	Difference
Total costs per patient	£240,956	£188,438	£52,519
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	**-**	**£52,519**	**1.79**	**£29,280**
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 17 p66 of Document B)	Issue 3	[redacted]	[redacted]	[redacted]
Outcomes from GWPCARE3/4 (used in cycle 1 of Company's Updated Base Case) applied for cycles 1-9 in both the CBD+CCM and CCM arms (ERG's scenario).	Issues 8 & 9	[redacted]	[redacted]	[redacted]
Long-term discontinuation rates (cycles 10 onwards) increased from 5% to 10% per cycle for all health states other than drop-seizure free patients.	Issue 10	[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 12	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted] [redacted] [redacted]
Utilities for health states taken from analogues in Verdian *et al* 2018[2]. Utilities across seizure-free day health sub-states made uniform.	Issue 14	[redacted]	[redacted]	[redacted]
Caregiver disutilities for the two health states with the most drop seizures taken from those reported for DS patients in Campbell *et al* 2018[1] (-0.33 per caregiver on EQ-5D VAS)	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 28 p89 of Document B)	Issue 17	[redacted]	[redacted]	[redacted]
Incident population only (age 2-5 years at model entry)	Existing scenario	[redacted]	[redacted]	[redacted]

Average dose of 11.51 mg/kg/day (as per the Company's Revised Base Case March 2019; see Table 41 p118 of Document B)	Existing scenario	[redacted]	[redacted]	[redacted]
Sensitivity analysis - QoL impact of non-drop seizure reductions. Additive disutility per person* required to increase incremental QALY gain in base case by: • 5% - [redacted] • 10% - [redacted] • 20% - [redacted]	Issue 6	[redacted]	[redacted]	[redacted]

1. Campbell J, *et al*. Epilepsy & Behavior 2018;80:152-156.

2. Verdian L, *et al*. Abstract 1.352 presented at the 62nd meeting of the American Epilepsy Society 2008.

*Scenarios assume 1 patient and an average of 1.8 caregivers. Disutilities assigned only to patients in the highest drop-seizure health state (>110 drop-seizures per month).

The sensitivity analyses to address Issue 6 (last row) would require an additive QoL decrease of about 18% 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 GWPCARE3, GWPCARE4 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 drop 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 drop 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 drop 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

NICE National Institute for Health and Care Excellence

Technical engagement response form

Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome [ID1308]

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. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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 CBD in the Lennox-Gastaut syndrome (LGS) 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 should be made clear that CBD is not a first line treatment, and that other standard treatments should have been considered 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 LGS seen in practice in the NHS?	Difficult to establish, as published data on LGS in adulthood are scarce. Many will be undiagnosed, and may be on inappropriate treatments already. Adult LGS management is likely to be suboptimal in many cases.
Issue 3: Composition of current clinical management	
Does current clinical management as described in the trial reflect clinical practice in the NHS?	Answering as an adult neurologist, it is likely that the existing clinical practice is variable in reality, and not well documented, and may not be well reflected in the trial for various reasons, including inter-nation variations in drug availability

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
Valproate	[redacted]		[redacted]	50
Clobazam	[redacted]		[redacted]	30
Lamotrigine	[redacted]		[redacted]	50
Rufinamide	[redacted]		[redacted]	5
Topiramate	[redacted]		[redacted]	30
Levetiracetam	[redacted]		[redacted]	60

Issue 4: Impact of concurrent anti-epileptic drug use on CBD efficacy	
Would the efficacy of CBD differ depending on which antiepileptic drugs it is used alongside?	This seems likely, but data in adults are sparse, so difficult to judge.
Issue 5: Criteria for stopping treatment	
Would treatment stop if there was no improvement in seizure frequency? How would this be defined, and would this be related to drop 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, drop and convulsive seizures are most 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 drop and 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 6: Ignoring non-drop seizures in the model	
Is excluding non-drop seizures from the model appropriate?	No, see above
How big an impact do non-drop seizures have on individuals' quality of life?	When convulsive seizures are present, they will have an important effect on quality of life
Issue 7: Number of days without drop seizures	
Is CBD likely to increase the number of drop seizure-free days, in addition to reducing drop seizure frequency?	If the question refers to real life, rather than trial or model data, this is very difficult to answer. It will depend on the patient and their existing pattern of drops – many per day or single episodes per day.
Issue 8: 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 9: Use of data from open label extension study	
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]?	Not sure how this question can be answered. Why are figures redacted? It would seem unlikely that results could be generalizable to an expected maintenance dose that differs from an average maintenance dose.
Issue 10: 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 drop 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 on the same drug (combination), in my general experience, should be apparent within a year.
If the dose of other anti-epileptic drugs had been reduced (see issue 17) would the dose be increased back to standard levels if the efficacy of CBD was reduced?	Yes, seems likely
Issue 11: 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. Lennox-Gastaut syndrome is due to a large variety of underlying genetic causes, with 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?	Routinely, 3, 6, 12 months after initiation and at each follow-up thereafter
Issue 12: 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 13: Relationship between mortality rates and number of seizures	
Is an association between number of drop 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 >45 and ≤ 110 seizures category in the following table:	

	Risk ratio			
	Seizure free	≤ 45 seizures	>45 to ≤ 110 seizures (**reference**)	> 110 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 LGS 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.	in my view it is not possible to answer this question currently. Data on this aspect of LGS in adults are very limited.
Issue 14: Health-related quality of life of people with LGS	
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 15: Health-related quality of life of carers of people with LGS	
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?	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?	For adult patients, I am not aware of good quality data on this issue
How many carers would a child with LGS be expected to have? Would this be expected to remain the same after the person reaches adulthood?	Cannot comment for children. For adults, typically 2 carers attend with the patient in clinic.
Issue 16: 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?	Potentially yes, in the context of multiple therapies and comorbidities.
Issue 17: 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?	Potentially yes. But meaningful estimates in my opinion are not possible given the lack of available data.
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
Valproate		
Clobazam		
Lamotrigine		

	Rufinamide			
	Topiramate			
	Levetiracetam			
Are there situations where increasing the dose of a concomitant anti-epileptic drug after starting CBD is appropriate?	Unlikely in my opinion			

Question from NICE technical team	Company response	ERG comments
Issue 1: Positioning of CBD in the Lennox-Gastaut syndrome (LGS) 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 AED). The patients included in the two RCTs were broadly representative of this population; the proportion of participants who had fewer than two prior AEDs was low (<5%)."*
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 LGS 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 LGS in the trials were based on international guidelines, which are similar to the NICE guidelines for patients with LGS. UK specialist clinicians agree that the participants in the GWPCARE trials reflect the characteristics of people with LGS seen in practice in the NHS (based on e.g. age, gender, seizure types, concomitant anti-epileptic drugs).	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: *"Difficult to establish, as published data on LGS in adulthood are scarce. Many will be undiagnosed, and may be on inappropriate treatments already. Adult LGS management is likely to be suboptimal in many cases."*

<table>
<tr><th colspan="3">Issue 3: Composition of current clinical management</th></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 LGS 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>Valproate</td><td>***</td><td></td><td>***</td><td>50</td></tr>
<tr><td>Clobazam</td><td>***</td><td></td><td>***</td><td>30</td></tr>
<tr><td>Lamotrigine</td><td>***</td><td></td><td>***</td><td>50</td></tr>
<tr><td>Rufinamide</td><td>***</td><td></td><td>***</td><td>5</td></tr>
<tr><td>Topiramate</td><td>***</td><td></td><td>***</td><td>30</td></tr>
<tr><td>Levetiracetam</td><td>**</td><td></td><td>**</td><td>60</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>
</table>

<table>
<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></td>
<td>
<table>
<tr><th rowspan="3">Anti-epileptic drug</th><th colspan="4">Proportion of patients</th></tr>
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<tr><td>Levetiracetam</td><td>**</td><td></td><td>**</td><td></td></tr>
</table>
</td>
<td></td>
</tr>
<tr><td colspan="4">Issue 4: Impact of concurrent anti-epileptic drug use on CBD efficacy</td></tr>
<tr>
<td>Would the efficacy of CBD differ depending on which antiepileptic drugs it is used alongside?</td>
<td colspan="2">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.</td>
<td>The ERG considers that this question remains open. As is stated in the ERG report: “[The company] assumed that the effectiveness of CBD does not vary with the combinations of AEDs to which it is added. This assumption is crucial to the validity of the ‘mixed’ CCM comparator. The ERG considers that there is currently a lack of evidence to support this assumption.”</td>
</tr>
<tr><td colspan="4">Issue 5: Criteria for stopping treatment</td></tr>
<tr>
<td>Would treatment stop if there was no improvement in seizure frequency? How would this be</td>
<td colspan="2">In most cases, CBD treatment would be expected to stop if there were 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,</td>
<td>It is unclear to the ERG:
1. whether the proposed 6 months stopping rule is clinically plausible;</td>
</tr>
</table>

defined, and would this be related to drop seizure frequency, total seizure frequency or both? At what time-point(s) would response to treatment be assessed?	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 drop-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 drop seizures from baseline in GWPCARE3/4. 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 [redacted]% per cycle in all	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).

	'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 drop-seizure free health state, long-term discontinuation rates remain at [redacted]%.	
Issue 6: Ignoring non-drop seizures in the model		
Is excluding non-drop seizures from the model appropriate?	Drop seizures (which include atonic, tonic and tonic-clonic seizures) are those involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair, or hitting the patient's head on a surface. These are the seizure types about which parents/caregivers of patients with LGS are most concerned, as they can lead to serious injury/hospitalisation. Reduction in drop seizures was the primary endpoint in the CBD LGS Phase 3 trials. Non-drop 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 non-drop seizures is lower in health states with fewer drop seizures. Therefore, it is the change in QoL in moving from higher to lower drop-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 impact of excluding non-drop seizures is unclear to the ERG. The main ERG concerns relate to input parameters used for the drop-seizure free health state that may reflect the health state where patients are also non drop-seizure free (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-drop seizures in the >110 drop seizures health state only that would be required to reduce the QALYs. However, that does not show the additional effect on utility of non-drop seizures given that there is no estimate of the number of drop seizures for each health state (including drop-seizure free) nor is there any disutility associated with a drop seizure.

	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-drop seizures have on individuals' quality of life?	Patients with LGS typically experience many seizures a month. In GWPCARE3, some patients were having >400 seizures per month at baseline. Drop seizures are assessed as the primary endpoint in trials for LGS because they are clinically identifiable, easy to count, and drive the morbidity. Drop seizures were chosen as the basis for the model structure for exactly 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-drop 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-drop seizures strongly tracks drop-seizure health states. As such, there is unrealised patient benefit associated with non-drop seizures that is not captured in the model. Providing a deterministic quantification of this benefit is challenging. Non-drop 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.	See response to previous issue.

	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 drop-seizure health state (i.e. >110 drop 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 10% 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 7: Number of days without drop seizures		
Is CBD likely to increase the number of drop seizure-free days, in addition to reducing drop 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	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

	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 8 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 drop-seizure free days, and this assumption has been retained in the Company's Updated Base Case.	maintain a benefit after stopping CBD and hence would prefer the "number of seizure-free days" to be treatment independent.
Issue 8: 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	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 LGS and DS is very variable. In the CBD studies, it was up to 27%. In other LGS trials, it has varied from a 5% worsening to 12% improvement (Ostendorf AP, *et al*. *Neuropsychiatr*	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

should the relative efficacy of CBD compared with current clinical management remain constant over time?	*Dis Treat*. 2017;13:1131-40). A recent study in DS showed a placebo effect of <2%. The absolute impact of CBD in LGS on drop seizures from baseline is very consistent across studies at 40-50%, which is also seen on convulsive seizures in DS. This magnitude of effect was observed in the open-label GWPCARE5 study for patients entering from the placebo arms of GWPCARE3 and 4 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 GWPCARE3 and GWPCARE4 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	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 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 costs would substantially decrease in this scenario.

	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 9: Use of data from open label extension study		
Are the results from the open label extension study (GWPCARE 5), where patients had an average maintenance dose of CBD of ********** generalisable to the expected maintenance dose of **********?	No dose response was seen in the GWPCARE3 trial in LGS or in the GWPCARE2 trial in DS. 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 GWPCARE3/4 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	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 LGS. The CS did not include any comparison between the 10 mg/kg/day and 20 mg/kg/day arms of GWPCARE3, 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 <[redacted] 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

	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.	ERG comments in ERG report sections 4.2.5, 4.2.9 and 5.2.6.
Issue 10: 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 drop 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 (■%), which is the best long-term real-world data set currently available (Laux LC, et al. *Epilepsy Research* 2019;154:13-20.).	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 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).

	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 17) 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 17 below).	No AED dose reduction is consistent with the ERG preferred assumptions (see ERG report).
Issue 11: 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	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:	The ERG notes that the company's response does not address the question of whether an increase in CBD dose may be considered in 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).

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/n	• 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.	

<table>
<tr><td>on-responders would this be?</td><td></td><td></td></tr>
<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="3">Issue 12: Time horizon</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="3">Issue 13: Relationship between mortality rates and number of seizures</td></tr>
<tr><td>Is an association between number of drop seizures and increased epilepsy-related mortality rates plausible? If</td><td><table><tr><td></td><td>Risk ratio</td></tr></table></td><td>The reported risk ratios reflect the risk ratio for being seizure-free: presumably this is not restricted to drop-seizures only. Hence, it is unclear to what degree this evidence supports the association between number of drop seizures and increased epilepsy-related mortality.</td></tr>
</table>

<table>
<tr>
<td>possible please estimate the increased (value greater than 1) or reduced risk (value less than 1) compared with the >45 and ≤ 110 seizures category in the following table:</td>
<td>
<table>
<tr><th></th><th>Seizure free</th><th>≤ 45 seizures</th><th>>45 to ≤ 110 seizures (reference)</th><th>> 110 seizures</th></tr>
<tr><td>Company</td><td>0.42</td><td>****</td><td>1.0</td><td>****</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>

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.
</td>
<td></td>
</tr>
<tr>
<td>What proportion of patients with LGS treated with current clinical management would be expected to be alive:
• 15 years after starting</td>
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treatment, • 20 years after starting treatment, • 50 years after starting treatment.		
Issue 14: Health-related quality of life of people with LGS		
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 LGS and DS 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. All other identified cost-utility studies in LGS and DS used these analogues. As outlined in the company's response to B17c of the ERG's Clarification Questions, the health states investigated in Verdian *et al* were not close surrogates for	No comments

	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. Verdian *et al* did assess the utility score in one health state defined by seizure frequency (82-112 drop seizures per month). This score closely aligns with those in the company's model with comparable seizure frequency. Utility scores for patients with a high response in Verdian (≥75% reduction) also align to the seizure-free health state in the CBD model. Average utility scores for DS populations reported in the large DISCUSS survey showed similar scores to the company's own health states in LGS, 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 15: Health-related quality of life of carers of people with LGS		
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 LGS 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".	As described in the ERG report, the inclusion of carer QALYs was not done in accordance with the NICE reference case and the 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 >3 times as large than the decrements for patients? If the carer disutilities are multiplied by 1.8 (assuming that each patient with LGS has 1.8 carers) as done by the company, this would result in decrements for caregivers that are 5.5 to 11.7 times 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?	No studies providing caregiver utilities in LGS have been identified from the literature. However, in Dravet syndrome, a survey (Campbell JD, et al. *Epilepsy & Behavior* 2018;80:152-156) assessed caregiver utilities on the EQ-5D VAS. The disutility (0.33 +/- 0.21) is at the mid-point of 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.	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 VAS-rated 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. Moreover, Campbell et al. 2018 have also estimated caregivers' utility by using the EQ-5D Index score and demonstrated a utility score of 0.78 (±0.17), which would

	A scenario using the disutility score from Campbell *et al* shows a similar ICER to the Company's Updated Base Case. (See scenario in Table 4 of the separate 'Response Addendum' document).	result in a smaller utility decrement (also smaller than found in the company's vignette study).
How many carers would a child with LGS be expected to have? Would this be expected to remain the same after the person reaches adulthood?	The literature indicates that ≥1 carer for patients with severe epilepsy syndromes 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 many children with LGS, the need for ≥1 carer remains the same after they reach adulthood. Cognitive impairment is noted in up to 95% of patients with LGS within 5 years of disease onset, and functional impairment renders 87% of patients with LGS unable to live independently, with 58% being completely dependent on others for all activities of daily living (Camfield C, Camfield P. *Developmental Medicine & Child Neurology* 2008). 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 LGS has 1.8 carers.	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)?
Issue 16: 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 LGS. 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: *"Potentially yes, in the context of multiple therapies and comorbidities."*
Issue 17: 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 has assumed that there are no reductions in concomitant AEDs. The dose reduction of concomitant AEDs is included as a scenario analysis. Please see the scenario analyses in Table 4 of the separate 'Response Addendum' document.	No AED dose reduction is consistent with the ERG preferred assumptions (see ERG report).

<table>
<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>Company Valproate</td><td></td><td></td></tr>
<tr><td>Clobazam</td><td></td><td></td></tr>
<tr><td>Lamotrigine</td><td></td><td></td></tr>
<tr><td>Rufinamide</td><td></td><td></td></tr>
<tr><td>Topiramate</td><td></td><td></td></tr>
<tr><td>Levetiracetam</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 adjuvant treatment of seizures associated with Lennox-Gastaut syndrome

The technical report addresses the company's initial submission to NICE, where the population in the decision problem was *people with Lennox-Gastaut 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.

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 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 Lennox-Gastaut syndrome (LGS) treatment pathway is appropriate (see issue 1).
- **The patients in the GWPCARE trials largely reflect people with LGS seen in the NHS** (see issue 2).
- **The company's updated analyses using the mix of anti-epileptic drugs from the GWPCARE trials is appropriate** (see issue 3).
- There is no evidence to support considering CBD to have equal efficacy regardless of the different combinations of anti-epileptic drugs (see issue 4).
- **The stopping criteria suggested by NHS England are appropriate** (see issue 5).
- **It is appropriate to use drop 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 6).
- It is not appropriate to assume in the model that the number of days without drop seizures will depend on treatment allocation (see issue 7).
- The relative treatment effect observed in the CBD trials should be maintained for the entire duration of the model (see issue 8).

- **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 9).
- The treatment effect of CBD may decrease over time (see issue 10).
- The company should take into account both the costs and benefits of dose escalation in its scenario analyses (see issue 11).
- **A 50-year time horizon is suitable for decision-making, but a lifetime time horizon would be more appropriate** (see issue 12).
- **The company's assumptions about epilepsy-related mortality are appropriate** (see issue 13).
- 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 14).
- It is important to capture the impact of caring for someone with LGS, 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 15).
- The effect of adverse events associated with CBD on quality of life should be included in the model (see issue 16).
- **The company's assumption that there is no reduction in use of anti-epileptic drugs for people who have CBD is appropriate** (see issue 17).

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 (n=73) and did not include people with LGS who are over 55 years of age.
- 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 £23,108 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-drop 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 CBD in the Lennox-Gastaut 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 LGS 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. It also does not appear to be consistent with the eligibility criteria for GWPCARE3 where the range of prior anti-epileptic drugs across the treatment groups was 0 to 22. In addition, the prior use of anti-epileptic drugs in GWPCARE4 ranges from 0 to 28. So, the ERG was concerned that the numbers of prior and concurrent anti-epileptic drugs taken by trial participants may not be in line with the proposed positioning of CBD in the LGS treatment pathway. **The company** provided further information in its clarification and reported that the number of participants who had discontinued fewer than two prior anti-epileptic drugs was low (<5%).
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 LGS treatment pathway.

Technical report template 2 – AFTER technical engagement

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 should be made clear that CBD is not a first line treatment, and that other standard treatments should be considered first. **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 LGS 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 LGS 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 (GWPCARE3 and GWPCARE4). Both trials were conducted in people with LGS, between the ages of 2 and 55 years, whose seizures were inadequately controlled (at least two drop seizures per week during the four-week baseline period of the studies) on existing anti-epileptic drugs (CS,p28-29). **The company** reported that one of the two key trials (GWPCARE3) 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. The ERG commented that the number recruited from the UK to GWPCARE3 was small (n=[redacted]). Additionally, both of the trials excluded patients over the age of 55 years in both trials (ERG report, p41-42). Baseline demographic characteristics provided in the clinical study reports (CSRs) show that [redacted] of participants in GWPCARE3 and [redacted] of participants in GWPCARE4 were adults (age 18 to 55 years). 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 3).
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 LGS who are older than 55 years.
Summary of comments	**Comments received from clinicans** Difficult to establish, as published data on LGS in adulthood are scarce. Many will be undiagnosed, and may be on inappropriate treatments already. Adult LGS management is likely to be suboptimal in many cases.

	Comments received from company The diagnostic criteria for LGS in the trials were based on international guidelines, which are similar to the NICE guidelines for patients with LGS. UK specialist clinicians agree that the participants in the GWPCARE trials reflect the characteristics of people with LGS 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 the 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 LGS seen in the NHS.

Issue 3 –Composition of current clinical management

<table>
<tr><td>Questions for engagement</td><td>a) Does current clinical management as described in the trial reflect current 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 antiepileptic drugs specified in the table below:

<table>
<tr><th rowspan="2">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>Valproate</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>Clobazam</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>Lamotrigine</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>Rufinamide</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>
<tr><td>Levetiracetam</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
</table>
</td></tr>
<tr><td>Background/description of issue</td><td>Clinical management of people with LGS consists primarily of antiepileptic drugs. Polypharmacy is common in this population and people with LGS can be on a number of anti-epileptic drugs at any given time. In addition to anti-epileptic drugs, vagus nerve stimulation (VNS) and ketogenic diet are also used. The composition of current clinical management in the GWPCARE3 and GWPCARE4 trials, is described in company submission tables 7-8. However, 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 LGS using each anti-epileptic drug. The data from the trials and the those used in the model are presented in the table below.

<table>
<tr><th>Anti-epileptic drug use</th><th>GWPCARE3</th><th>GWPCARE4</th><th>Model input <12 years*</th></tr>
</table>
</td></tr>
</table>

	CBD 10 mg	CBD 20 mg	Placebo	CBD 20 mg	Placebo	
N	73	76	76	86	85	
Median	3	3	3	3	3	
Range	1 to 5	0 to 5	1 to 5	1 to 5	1 to 4	
Prior anti-epileptic drug use (n)						
Clobazam	37	36	37	41	43	[redacted]
Valporate	27	28	30	36	33	[redacted]
Levetiracetam	22	24	23	24	34	[redacted]
Lamotrigine	22	20	25	33	34	[redacted]
Rufinamide	19	26	20	24	22	[redacted]
VNS	15	17	21	26	25	
Ketogenic diet	6	6	6	4	10	
*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.

[redacted].

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

<table>
<tr><td></td><td>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.</td></tr>
<tr><td>Summary of comments</td><td>
Comments received from clinicans
It is likely that existing clinical practice is variable, not well documented, and may not be well reflected in the trial for various reasons, including regional variations in prescribing.
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; lacosamide, clonazepam, zonisamide and felbamate.
<table>
<tr><th rowspan="3">Anti-epileptic drug</th><th colspan="6">Proportion of patients</th></tr>
<tr><th colspan="3"><12 years</th><th colspan="3">≥12 years</th></tr>
<tr><th>Company original values</th><th>Company revised values</th><th>Clinical experts</th><th>Company original values</th><th>Company revised values</th><th>Clinical experts</th></tr>
<tr><td>Valproate</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>[redacted]</td><td>[redacted]</td><td>50%</td></tr>
<tr><td>Clobazam</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>[redacted]</td><td>[redacted]</td><td>30%</td></tr>
<tr><td>Lamotrigine</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>[redacted]</td><td>[redacted]</td><td>50%</td></tr>
<tr><td>Rufinamide</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>[redacted]</td><td>[redacted]</td><td>5%</td></tr>
<tr><td>Topiramate</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>[redacted]</td><td>[redacted]</td><td>30%</td></tr>
<tr><td>Levetiracetam</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>[redacted]</td><td>[redacted]8</td><td>60%</td></tr>
</table>
</td></tr>
<tr><td>Technical team judgement after engagement</td><td>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 levetiracetam 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</td></tr>
</table>

Issue 4 – Impact of concurrent anti-epileptic drug use on CBD efficacy

<table>
<tr><td>Questions for engagement</td><td>a) Would the efficacy of CBD differ depending on which antiepileptic drugs it is used alongside?</td></tr>
<tr><td>Background/description of issue</td><td>In the economic model, current clinical management is considered to be a ‘basket’ of choices of anti-epileptic drugs.
The company assumed that the effectiveness of CBD does not vary with the combinations of anti-epileptic drugs to which it is added, however, it conducted a number of subgroup analyses based on the presence or absence of various anti-epileptic drugs. The company did not consider the results of these subgroup analyses to be relevant to clinical prescribing and noted that the subgroups have small numbers with low statistical power. It noted that “[redacted]”.
The results of these subgroup analyses are presented in the table below.
<table>
<tr><td></td><td colspan="3">GWPCARE3</td><td colspan="2">GWPCARE4</td></tr>
<tr><td></td><td>CBD 10 mg</td><td>CBD 20 mg</td><td>Placebo</td><td>CBD 20 mg</td><td>Placebo</td></tr>
<tr><td></td><td colspan="3">≥50% reduction in drop seizures</td><td colspan="2">≥50% reduction in drop seizures</td></tr>
<tr><td colspan="6">Clobazam Use</td></tr>
<tr><td>Yes</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>No</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="6">Valproic Acid Use</td></tr>
<tr><td>Yes</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>No</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="6">Lamotrigine Use</td></tr>
<tr><td>Yes</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>No</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="6">Levetiracetam Use</td></tr>
<tr><td>Yes</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td></tr>
</table>

	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Rufinamide Use					
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Source: GWPCARE3 CSR, Tables 8.4.1.5.2-1/2, and GWPCARE4 CSR, Table 8.4.1.2.2.16-1 *: p-value for CBD versus placebo <0.05, calculated using a Fisher's exact test					
	The ERG questions the validity of the company's assumption, which is crucial to the validity of the 'mixed' current clinical management comparator. The ERG considers that there is currently a lack of evidence to support this assumption. **The technical team** notes that although the subgroup analysis results for [redacted].					
Why this issue is important	It is important to ensure that the efficacy of CBD seen in the trial is not affected by the composition of current clinical management (for example by treatment interactions) and therefore generalisible to NHS practice. This assumption is crucial to the validity of the company's current clinical management comparator. There is currently a lack of evidence to support this assumption. Some of the subgroup analyses, though based on small numbers, show significant differences.					
Technical team preliminary judgement and rationale	Considering CBD to have equal efficacy regardless of the different combinations of anti-epileptic drugs is not supported by evidence. Assuming that the exact composition of current clinical management has no impact on the efficacy of CBD is not appropriate, as interaction might exist. Scenario analyses showing the impact of different comparators, using the subgroup data, could be informative.					
Summary of comments	**Comments received from clinicans** It is difficult to judge whether the efficacy of CBD would differ depending on which antiepileptic drugs it is used alongside, because data in adults are sparse. However, some difference seems likely. **Comments from company** Pre-specified subgroup analyses showed no statistically significant interaction between use of any concomitant anti-epileptic drug on the primary and key secondary endpoints in the 10 mg/kg/day arm of GWPCARE3.					
Technical team judgement after engagement	It is likely that the efficacy of CBD will differ depending on which anti-epileptic drug(s) is concurrently used. Scenario analyses exploring the clinical and cost effectiveness of CBD in subgroups based on concurrent use of specific anti-epileptic drugs are appropriate and informative in assessing the impact of this potential interaction on the model results.					

Issue 5 – Criteria for stopping treatment

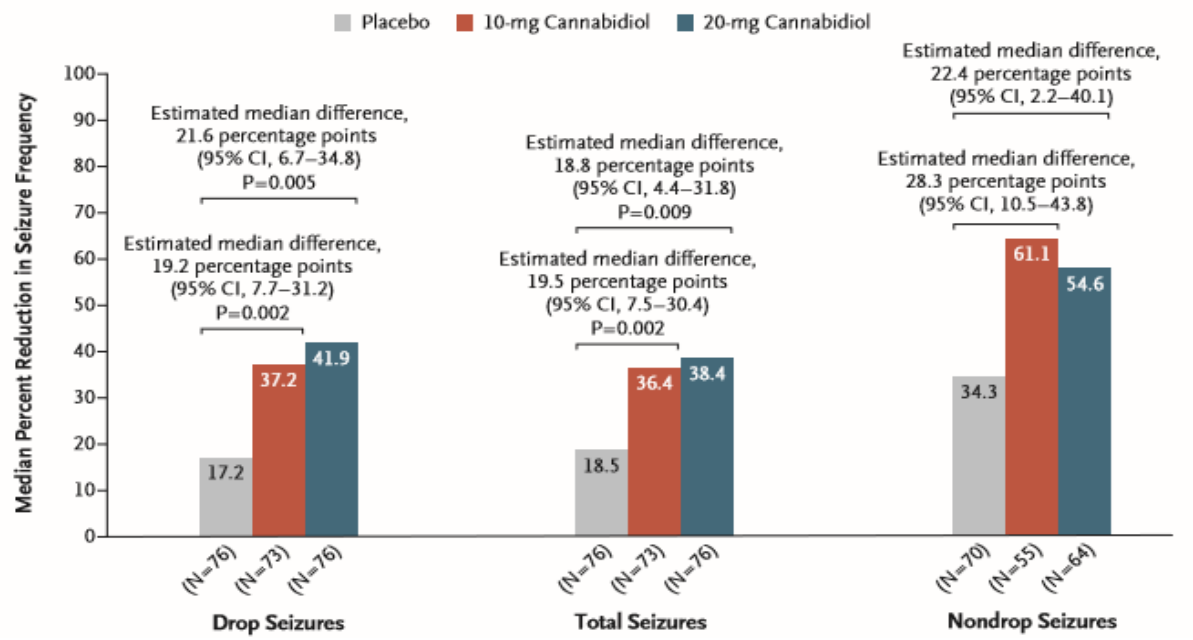
Questions for engagement	a) Would treatment stop if there was no improvement in seizure frequency? How would this be defined, and would this be related to drop seizure frequency, total seizure frequency or both? At what time-point(s) would response to treatment be assessed?
Background/description of 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 drop seizures over time (see company's revised economic assessment [REA] p4–7). No stopping rule was included in the clinical trial. In an attempt to incorporate the effects of a stopping rule, the company proposes that after 2 years of treatment with CBD: • if seizure burden remains high (>110 drop seizures per month), [redacted]% of people stop treatment • if people continue to experience between 45 and 110 drop 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 (i.e. drop seizures in Lennox Gastaut syndrome, convulsive seizures in Dravet syndrome) 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 seen a reduction in seizure frequency (of either drop 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** Drop 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 drop 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. **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 incorporates a one-off discontinuation at 6 months in each 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 drop seizures from baseline in GWPCARE3/4. The reduction in drop 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). **Comments from the ERG** It is 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 base case analysis is appropriate. However, clinicians' stated that review would first occur at 3 months rather than 6 months.

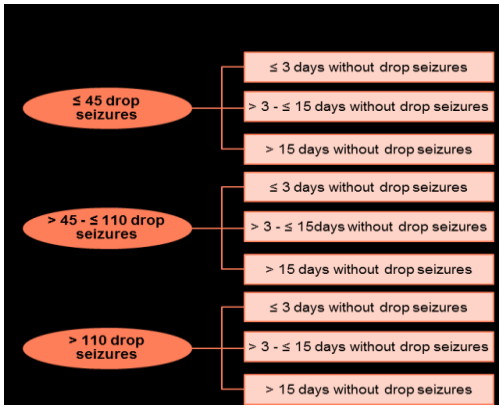
Issue 6 – Ignoring non-drop seizures in the model

Questions for engagement	a) Is excluding non-drop seizures from the model appropriate? b) How big an impact do non-drop seizures have on individuals' quality of life?
Background/description of issue	It is likely for people with LGS that have fewer or no drop-seizures to still have non-drop seizures. Non-drop seizures carry a risk of sudden and non- sudden unexpected death in epilepsy, adversely affect quality of life. **The company** focused on drop-seizures and drop-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-drop seizures from the model and considered that seizure-free days to be more relevant to the estimation of quality of life values than drop seizure-free days. **The Technical team** notes that non-drop seizures and total seizures were both included as secondary outcomes in the GWCARE3 trial. The results showed significant reduction in both outcomes in favour of CBD as indicated in Figure 4 of the company's submission presented below. The technical team notes that this may represent an uncaptured benefit of CBD on quality of life.

	
Why this issue is important	The exclusion of non-drop seizures from the model may result in unrealistically high quality of life values for the drop-seizure free health states, since patients in this state can still experience non-drop seizures which have an adverse effect on quality of life. However, since non-drop 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-drop 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** When drop seizures are present, they will have an important effect on quality of life. **Comments received from company** Drop 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. Drop seizures were chosen as the basis for the model structure for these reasons, and because it was the primary endpoint of the trials. Non-drop 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-drop 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-drop seizures is lower in health states with fewer drop 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. **Comments received from the ERG** The company's scenario analysis does not show the additional effect on utility of non-drop seizures given that there is no estimate of the number of non-drop seizures for each health state (including drop-seizure free) nor is there any disutility associated with a drop seizure.
Technical team judgement after engagement	It is appropriate to use drop seizures as the main outcome in the model. The benefits of a reduction in non-drop 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 7 – Number of days without drop seizures

Questions for engagement	a) Is CBD likely to increase the number of drop seizure-free days, in addition to reducing drop seizure frequency?
Background/description of issue	Improvements in quality of life of people with LGS is assumed to relate to both the total number of drop seizures and number of drop seizure-free days **The company** subdivided the drop seizure frequency health states into three sub-categories based on the number of drop seizure-free days per 28 days. It assumed that the number of days without drop seizures depends on treatment, based on evidence from the trials (CS, p58-60).  . **The ERG** does not agree with this assumption as it noted 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. It preferred to assume that the number of drop-seizure free days was the same for both treatment arms.
Why this issue is important	Including treatment-dependent number of days without drop 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 drop seizures will depend on treatment allocation.
Summary of comments	**Comments received from clinicans** It is difficult to determine whether CBD will increase the number of drop-seizure free days because this will depend on the patient and their existing pattern of drop-seizures. **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 drop-seizure free days, and this assumption has been retained in the company's updated base case. **Comments received from the ERG** 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 8 – 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 LGS 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 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 clinicians** Both placebo and drug effects may vary over time, typically with regression to the mean. **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. In other LGS trials, it has varied from a 5% worsening to a 12% improvement. The absolute impact of CBD in LGS on drop 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 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). **Comments received from the ERG** The ERG disagrees that maintaining the relative treatment effect for the duration of the model would unduly penalising CBD. 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 of the model. 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 9 – 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, p66–69). Treatment benefit was maintained for CBD from 27 months (see issue 10). **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 10) and does not account for dose escalation (see issue 11) or stopping rules (see issue 5).
Summary of comments	**Comments received from clinicians** It would seem unlikely that results could be generalisable to an expected maintenance dose that differs from an average maintenance dose.

	Comments received from company No dose response was seen 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. 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 company's updated base case extends the Phase 3 GWPCARE3/4 data to 2 cycles (6 months) in both the CBD with current clinical management and current clinical management arms, and then applies the GWPCARE5 data up to 2 years for CBD patients. A scenario analysis extending the Phase 3 data in both arms to 2 years does not substantially change the ICER. **Comments received from the ERG** The post hoc analysis was reported only in terms of tests for statistically significant difference, no outcome results provided for the subgroups. In addition, the <[redacted] 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 >20 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.
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 10 – 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 drop 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 17) would the dose be increased back to standard levels if the efficacy of CBD was reduced?
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, p66). **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, p105-107).
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 is likely to overestimate the ICER as they assume people continue to take CBD, which would be unlikely as 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. 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. **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 drop-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. **Comments received from the ERG** Waning of treatment effect and treatment discontinuation are 2 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.
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 11 – 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? • 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 with a reduction in drop seizures of 75% or more [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 10mg/kg/day dose had no effect. It is likely the dose would be increased if the effect appeared to lessen over time or if there is a partial response, if this dose increase is tolerated. 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 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 12 – 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	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.
Why this issue is important	People with LGS 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** 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. **Comments received from the ERG** The ERG prefers a lifetime time horizon.

Technical team judgement after engagement	The technical team notes that [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 can be used for decision making, although a lifetime time horizon would be more appropriate.

Issue 13 – Relationship between mortality rates and number of seizures

<table>
<tr><td>Questions for engagement</td><td>a) Is an association between number of drop 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 >45 and ≤ 110 seizures category in the following table:
<table>
<tr><td></td><td colspan="4">Risk ratio</td></tr>
<tr><td></td><td>Seizure free</td><td>≤ 45 seizures</td><td>>45 to ≤ 110 seizures (reference)</td><td>> 110 seizures</td></tr>
<tr><td>Company</td><td>0.42</td><td>[redacted]</td><td>[redacted]</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>
b) What proportion of patients with LGS 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></tr>
<tr><td>Background/description of issue</td><td>The company estimates the mortality of people with LGS by using data from the literature for people with Dravet Syndrome which was adjusted 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 the unadjusted literature 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 drop seizures (ERG report,p83).</td></tr>
</table>

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 14 – Health-related quality of life of people with LGS

<table>
<tr><td>Questions for engagement</td><td>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?</td></tr>
<tr><td>Background/description of issue</td><td>The company derived EQ-5D quality of life values for each health state from a survey of people with LGS and their carers (CS, p76-85). The company did this because there are limited literature data available for quality of life values for LGS and those available are not defined based on the number of drop seizures or number of drop seizure-free days. The quality of life values derived from the survey are summarised below.

<table>
<tr><th>Health state (number of drop seizures)</th><th>Sub-state (number of seizure free days)</th><th>Mean quality of life scores</th></tr>
<tr><td>No seizures</td><td>No seizures</td><td>[redacted]</td></tr>
<tr><td rowspan="3">≤ 45 seizures</td><td>≤ 3 drop seizure-free days</td><td>[redacted]</td></tr>
<tr><td>>3 to ≤15 drop seizure-free days</td><td>[redacted]</td></tr>
<tr><td>> 15 drop seizure free days</td><td>[redacted]</td></tr>
<tr><td rowspan="3">>45 - ≤ 110 seizures</td><td>≤ 3 drop seizure-free days</td><td>[redacted]</td></tr>
<tr><td>>3 to ≤15 drop seizure-free days</td><td>[redacted]</td></tr>
<tr><td>> 15 drop seizure free days</td><td>[redacted]</td></tr>
<tr><td rowspan="3">> 110 seizures</td><td>≤ 3 drop seizure-free days</td><td>[redacted]</td></tr>
<tr><td>>3 to ≤15 drop seizure-free days</td><td>[redacted]</td></tr>
<tr><td>> 15 drop seizure free days</td><td>[redacted]</td></tr>
</table>

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 quality of life instruments and public preferences (ERG report, p84-85). The ERG</td></tr>
</table>

	suggested exploring a scenario where quality of life values 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. In response to ERG's comment relating to the quality of life value of the drop seizure-free health state, the company used the utility value for the DS convulsive seizure-free health state ([redacted]) instead of the value derived from the vignette study ([redacted])
Why this issue is important	There is uncertainty around the values used to represent the quality of life of patients with LGS. 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 LGS presents challenges for assessing the quality of life of people with LGS. 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 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 drop seizures or number of drop 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.
Summary of comments	**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 in LGS, both at a European level (Lagae et al, 2018) 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. **Comments received from the ERG** The ERG's main reservations relate to the methodology used to elicit utility values as well as the resulting utility estimates.
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 15 – Health-related quality of life of carers of people with LGS

<table>
<tr><td>Questions for engagement</td><td>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 LGS be expected to have? Would this be expected to remain the same after the person reaches adulthood?</td></tr>
<tr><td>Background/description of issue</td><td>The company included the quality of life of carers of people with LGS 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 LGS has one carer and that care continues into adulthood. The increasing impact of caring for someone with LGS 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>≤45 seizures</td><td>-</td></tr>
<tr><td>>45 - ≤110 seizures</td><td>[redacted]</td></tr>
<tr><td>>110 seizures</td><td>[redacted]</td></tr>
</table>

The ERG has similar concerns as with quality of life data for individuals with LGS (see issue 14) and further noted that the methods of deriving quality of life methods may be unsuitable because caregivers were only asked to evaluate three vignette tasks in total, therefore the results lack</td></tr>
</table>

	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 for Dravet Syndrome but had not discussed these further in its revised economic assessment or considered using values from these studies as scenario analyses. These values could potentially be used for LGS as well.
Why this issue is important	There is uncertainty around the values used to represent the quality of life of carers of people with LGS. 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.
Technical team preliminary judgement and rationale	The technical team agrees that it is important to capture the impact of caring for someone with LGS in the model in line with the NICE methods guide. However, there is substantial uncertainty associated 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 LGS (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** For adults, typically 2 carers attend with the patient in clinic. **Comments from company** No studies providing caregiver utilities in LGS have been identified from the literature. Carer quality of life values are in line with those found in the literature for DS. A survey assessing caregiver utilities using EQ-5D-VAS (Campbell et al., 2018) provided disutility values (0.33 +/- 0.21) that is at the midpoint of those measured by the company's vignette study. (0.27 and 0.40 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 LGS has 1.8 carers. **Comments received from the ERG** The plausibility of the estimated disutilities for caregivers is questionable. For instance, the decrements for caregivers are more than 3 times as large as the decrements for patients. If the carer disutilities are multiplied by 1.8 (assuming that each patient with LGS has 1.8 carers) as done by the company, this would result in decrements for caregivers that are 5.5 to 11.7 times as large than the decrements for patients. The decrements provided by the company are based on the difference between the VAS-rated utility and perfect health (i.e., utility of 1). The average utility in the population is lower than 1, so the disutility for providing care based on Campbell et al. 2018 is likely to be overestimated. Also, if multiple carers are involved, it is uncertain whether utility decrements should be on an additive scale (e.g. not everyone in a family 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 LGS require 1.8 carers is plausible and in line with evidence.

Issue 16 – 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, GWPCARE3 and GWPCARE4, 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.
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** Adverse event 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 LGS. 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.

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.

Issue17– Reduction in the concomitant use of anti-epileptic drugs

<table>
<tr><td>Questions for engagement</td><td>
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:
<table>
<tr><th>Drug</th><th>% of patients</th><th>% dose reduction</th></tr>
<tr><td>Valproate</td><td></td><td></td></tr>
<tr><td>Clobazam</td><td></td><td></td></tr>
<tr><td>Lamotrigine</td><td></td><td></td></tr>
<tr><td>Rufinamide</td><td></td><td></td></tr>
<tr><td>Topiramate</td><td></td><td></td></tr>
<tr><td>Levetiracetam</td><td></td><td></td></tr>
</table>
c) Are there situations where increasing the dose of a concomitant anti-epileptic drug after starting CBD is appropriate?
</td></tr>
<tr><td>Background/description of issue</td><td>
The company positions CBD as an add-on therapy to other anti-epileptic drugs.
The company assumed that adding CBD will reduce the dose of some of the concomitantly used anti-epileptic drugs by 33%.
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 for whom a dose adjustment was observed.
</td></tr>
</table>

Why this issue is important	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.
Technical team preliminary judgement and rationale	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.
Summary of comments	**Comments received from clinicians** Meaningful estimates of dose reductions 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. **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. 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 as it is programmed with a design feature that leads to QALY gain for CBD under equivalence assumptions.	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 GWPCARE3 trial only included 73 patients in the 10mg/kg/day dose arm. The effectiveness estimates for this dose are highly uncertain.	Unknown	The company considers that 73 patients is a clinically meaningful sample size, especially given the orphan nature of LGS. All arms in the GWPCARE3 trial were balanced, and the study was adequately powered. As shown in Section B.2.6 p36 of the Company's Evidence Submission, 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	**–**	**£53,929**	**2.33**	**£23,108**
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	£56,231	2.33	£24,095
Equal number of days without drop seizures (see issue 7) ***Source: calculated by technical team***	Including differential number of days without drop seizures depending on treatment allocation may introduce bias in the model	£53,929	2.30	£23,409
Relative treatment effect maintained for the whole model time horizon (see issue 8)	Assuming constant relative treatment benefit for CBD compared with current clinical management			unknown [a]
Decrease in treatment effect over time (see issue 10)	The efficacy of CBD is likely to decrease over time			unknown [a]
Use the average dose of 11.51 mg/kg/day (see issue 11) ***Source: company scenario analysis***	To reflect the fact that a proportion of people will increase to 20mg/kg/day dose	£62,758	2.32	£27,030
Lifetime horizon (see issue 12)	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 stimulations was not included in the model. Underestimation of this cost 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.
Body weight	The ERG considered the use of median rather than mean body weight to be inappropriate. Hence, the mean weight was used in the ERG base-case analysis.
Dose titration period	The titration period in the clinical trials is not included in the model, which uses the maintenance dose of CBD from 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.
Quality of life value for the seizure-free state	The ERG commented on the quality of life value used by the company for the drop seizure free health state ([redacted]) as it appears to be relatively high, given the likelihood of having non-drop seizures. The ERG suggested that it is possible that patients may have misinterpreted the vignettes. Based on these concerns, the ERG adjusted the quality of life estimate for the health state "[redacted]" ([redacted]) in line with the quality of life value that is used in the Dravet syndrome submission ([redacted]) in the ERG 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 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 unlikely to represent a step change in treatment since no patient in any of the included trials achieved complete freedom from seizures.
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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