in collaboration with:

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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

Authors
Marie Westwood, Reviews Manager, Kleijnen Systematic Reviews Ltd, UK
Bram Ramaekers, Health Economist, Maastricht UMC
Willem Witlox, Health Economist, Maastricht UMC
Ben Wijnen, Health Economist, Maastricht UMC
Debra Fayter, Systematic Reviewer, KSR Ltd
Steve Ryder, Health Economist, KSR Ltd
Nigel Armstrong, Health Economist, KSR Ltd
Titas Buksnys, Health Economist, KSR Ltd
Gill Worthy, Statistician, KSR Ltd
Kate Misso, Information Specialist, KSR Ltd
Manuela Joore, Health Economist, Maastricht UMC
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to
Marie Westwood, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, UK
YO19 6FD

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Marie Westwood acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Willem Witlox, Ben Wijnen, Steve Ryder, Titas Buksnys and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Kate Misso acted as information specialist, critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ABN	Association of British Neurologists
AE	Adverse 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:

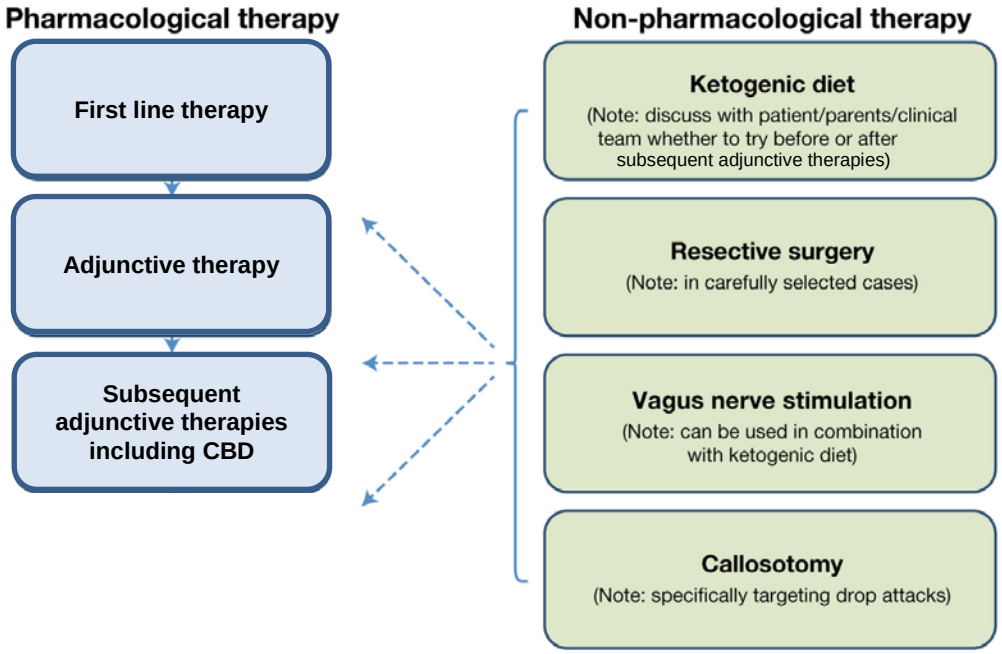
The references relating to the prevalence and aetiology of cognitive impairment were for review articles, rather than primary research. The professional organisation submission, from the Association of British Neurologists (ABN),[11] included the following statement: '*There are many other comorbidities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



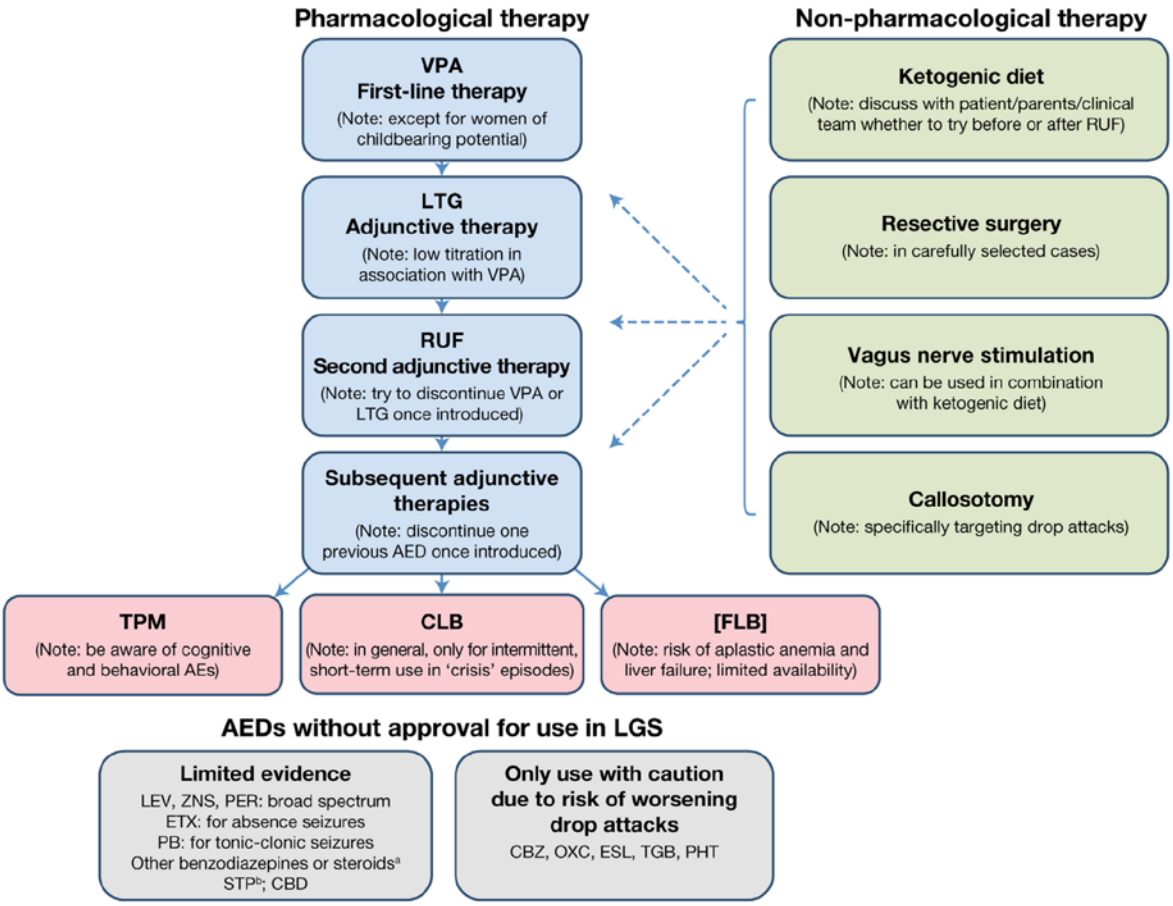
Source: Figure 2 in the CS[1]

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			

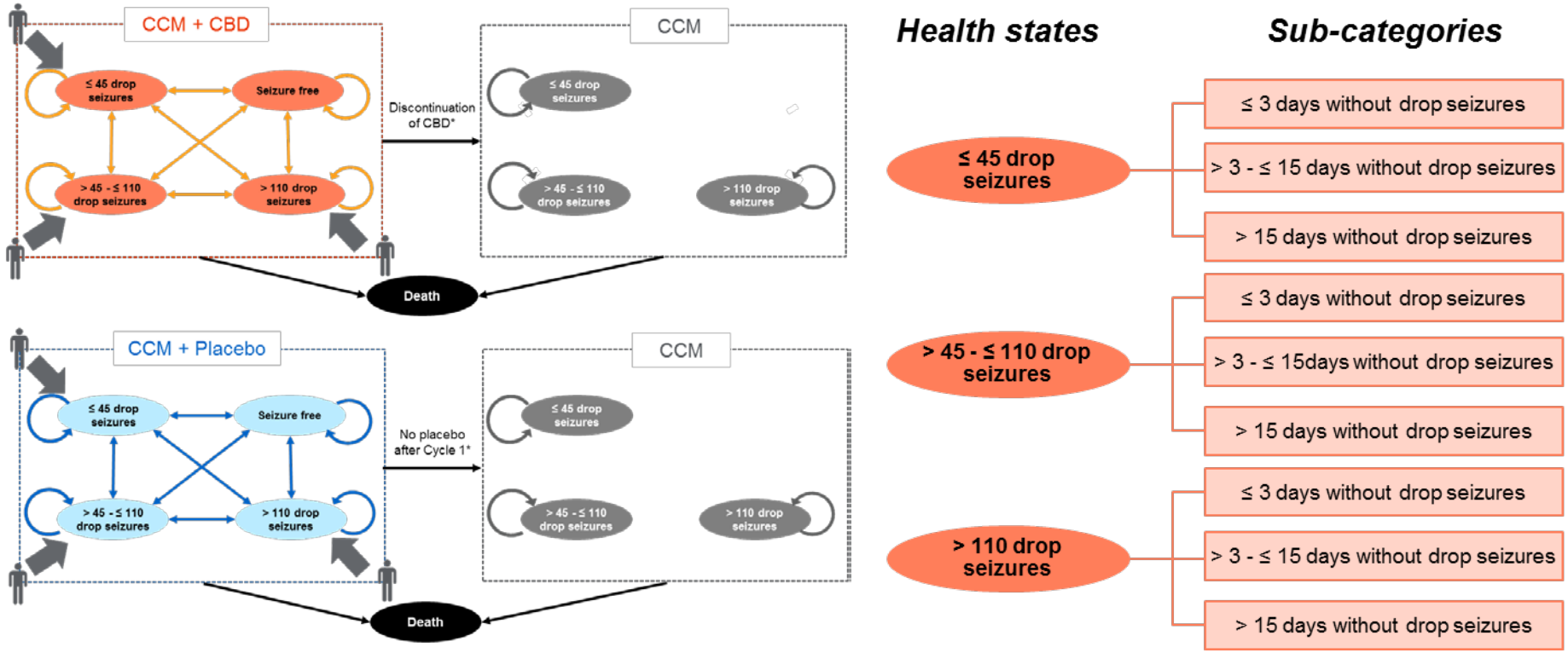
5.2.2 Model structure

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, $> 45 - \leq 110$, > 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]							
	≤ 45 seizures								
	45 to 110 seizures								
	> 110 seizures								
Cycle 8	Seizure free								
	≤ 45 seizures								
	45 to 110 seizures								
	> 110 seizures								
Cycle 9	Seizure free								
	≤ 45 seizures								
	45 to 110 seizures								
	> 110 seizures								

[a] The transition probabilities for CBD 20 mg/kg/day plus CCM (not used in the company base-case), are identical as those presented for CBD 10 mg/kg/day plus CCM in this Table (see also CS Table 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

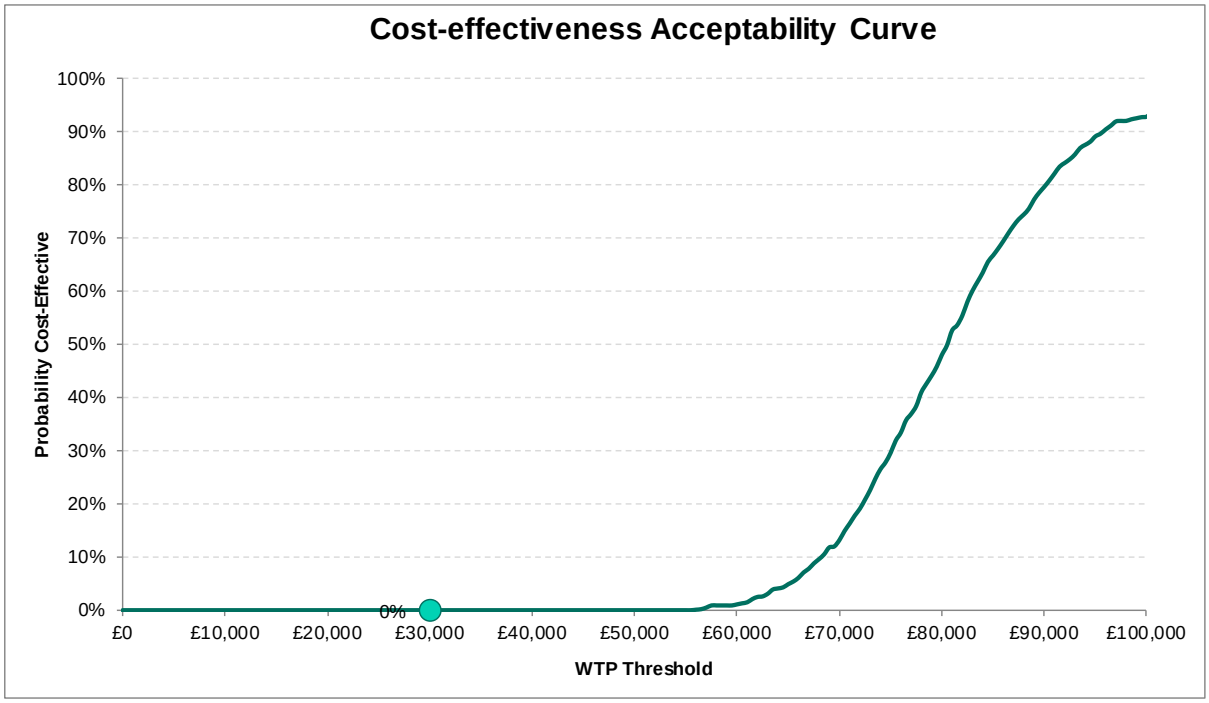
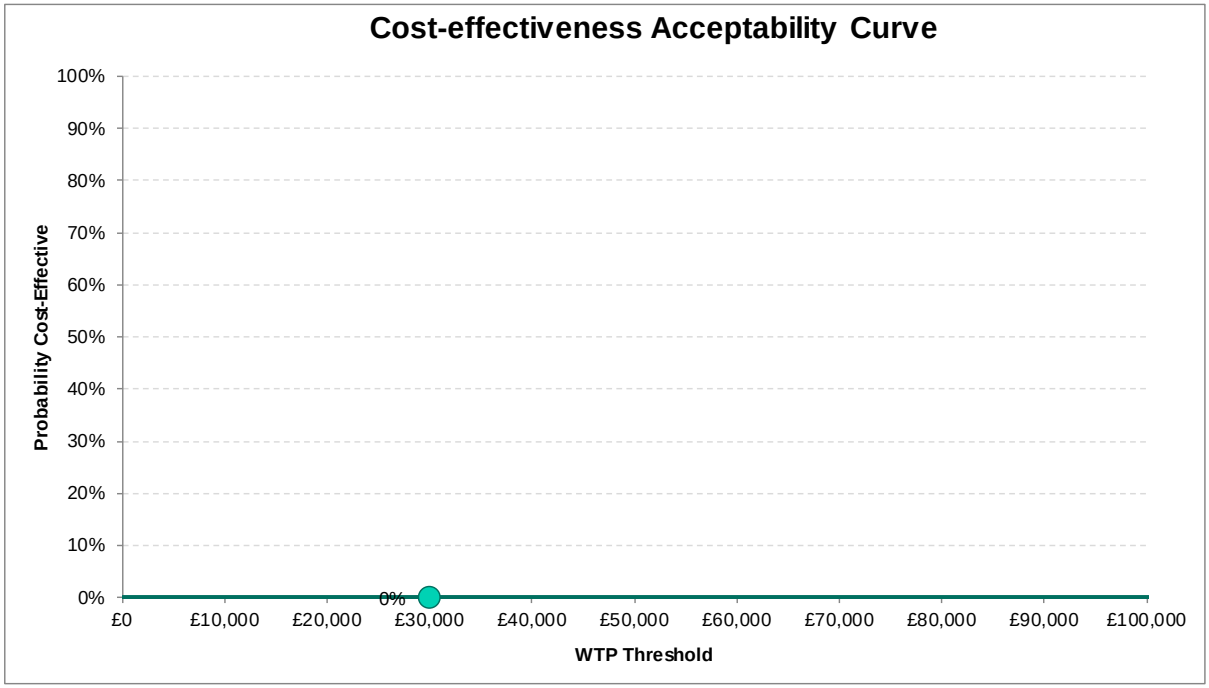


Figure 5.5: Cost effectiveness acceptability curve: ERG base-case assuming no constant treatment effect after 27 months



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

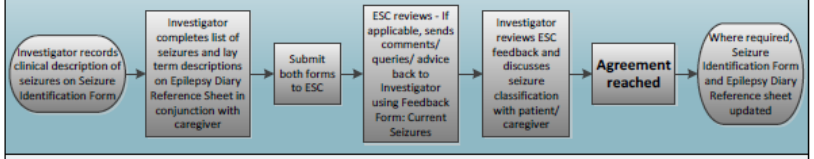
Line	Search	Hits	
1	MeSH DESCRIPTOR Lennox Gastaut Syndrome EXPLODE ALL TREES	1	
2	MeSH DESCRIPTOR Epilepsies, Myoclonic EXPLODE ALL TREES	4	
3	#1 OR #2	5	
4	(child* or infan*)	10960	
5	#3 AND #4	5	
6	(Dravet* syndrome) OR (Lennox Gastaut) OR (childhood epilep* encephalopath*)	13	
7	((severe myoclonic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

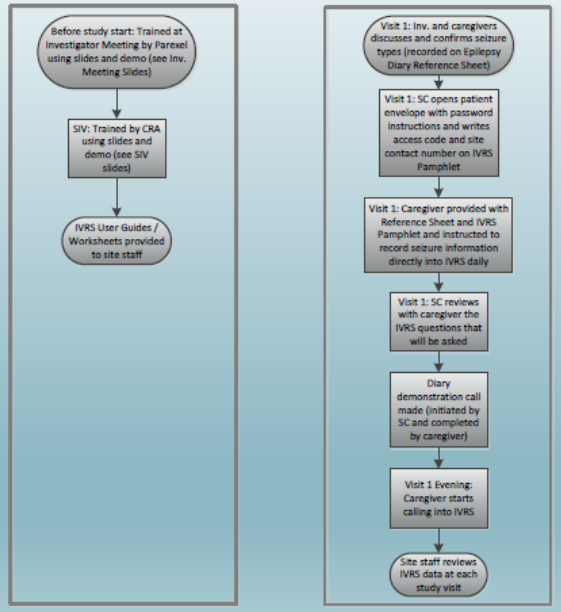
To ensure accuracy of seizure identification and reporting across the 3 pivotal trials, seizure types were verified by member(s) of a committee of independent experts from the ESC. For study GWEP1332B, the ESC had the additional responsibility of confirming the diagnosis of DS.



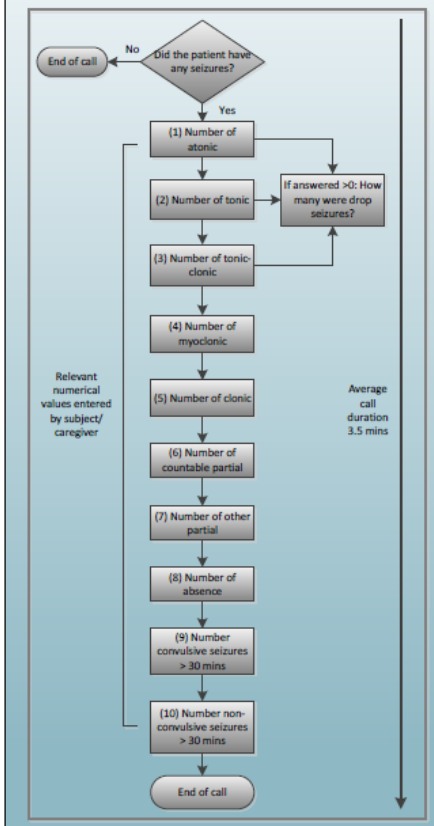
Use of IVRS

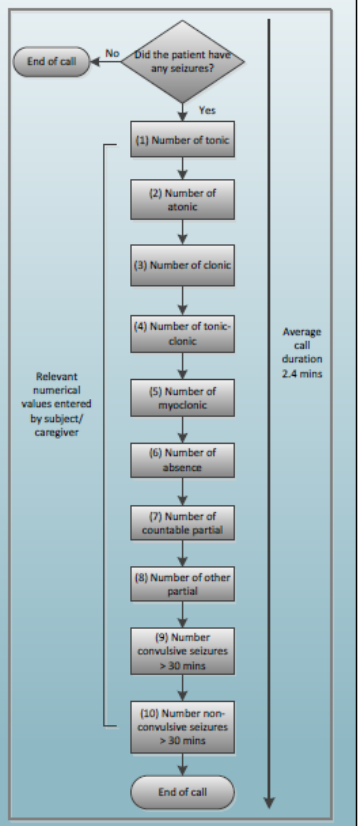
Throughout each pivotal trial, seizures were recorded daily on a validated electronic patient reported outcomes (ePRO) system using IVRS (Perceptive myTrials®). For the majority of patients all assessments, including daily seizure recording, were completed on their behalf by caregivers. This included 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.