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Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Contributions of authors

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

Abbreviations

ABN	Association of British Neurologists
AE	Adverse events
AED	Anti-epileptic drug
BI	Budget impact
BIC	Bayesian information criterion
CBD	Cannabidiol
CCM	Current clinical management
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CG	Clinical guideline
CGIC	Caregiver global impression of change
CGICSD	Caregiver global impression of change in seizure duration
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
DS	Dravet syndrome
EEG	Electroencephalogram
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
ERG	Evidence Review Group
FDA	Food and Drug Administration
HR	Hazard ratio
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LGS	Lennox-Gastaut syndrome.
LYS	Life year saved
MAH	Marketing authorisation holder
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
mg	Milligram
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
OR	Odds ratio
PAS	Patient access scheme
PCT	Primary Care Trust
PRESS	Peer review of electronic search strategies
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
RCT	Randomised controlled trial

RR	Relative risk; risk ratio
SAE	Serious adverse events
SD	Standard deviation
SF-36	Short form 36
SGEs	Symptomatic generalised epilepsies
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SSW	Slow spike-wave
STA	Single technology appraisal
SUDEP	Sudden unexplained death in epilepsy
TEAEs	Treatment-emergent adverse events
TESAEs	Treatment-emergent serious adverse events
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
WTP	Willingness to pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population defined in the NICE scope is 'people with Dravet syndrome (DS) whose seizures are inadequately controlled by established clinical management'. The company extended the scope to 'people with DS where current clinical management is unsuitable or not tolerated'. This addition is consistent with the pathway outlined in the relevant NICE guidance (CG137).

The submission relied, primarily, on two randomised controlled trials (RCTs) (GWPCARE1 and GWPCARE2) of cannabidiol (CBD) (Epidyolex®) as an add-on treatment to current clinical management (CCM). Although the decision problem did not specify any age restriction and the expected licenced indication for Epidyolex® is for patients two years of age and older, neither of the key trials in the submission included adult patients (over the age of 18 years). Although DS has its onset in childhood, it is expected that patients will continue taking cannabidiol into adulthood.

The treatment pathway proposed by the company placed CBD as a third-line treatment (i.e. for patients who have inadequate seizure control with first-line and at least one adjunctive anti-epileptic drug (AED)). However, the baseline characteristics for GWPCARE1 and GWPCARE2 indicated that approximately 16% of participants included in these studies had previously tried and discontinued fewer than two prior AED. It should be noted that these patients may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled.

The description of the comparators in the company submission (CS) is in line with the NICE scope (established clinical management without cannabidiol), which may include combinations of: sodium valproate, topiramate, clobazam, stiripentol, levetiracetam, ketogenic diet and vagus nerve stimulation. The comparator used in the key trials (GWPCARE1 and GWPCARE2) was current clinical management (CCM), which includes various combinations of different AEDs. Different combinations of AEDs were not considered as separate comparators. It should be noted that the use of a 'mixed' CCM comparator assumes that the effectiveness of CBD does not vary with the combinations of AEDs to which it is added. The Evidence Review Group (ERG) questions the validity of this assumption.

The CS focused primarily on convulsive seizures as these were the primary outcome in the two main trials. Although mortality was investigated, the two main randomised trials were of 14 weeks' duration so could not provide long-term data on sudden unexpected death in epilepsy (SUDEP) and other deaths.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS identified two international RCTs of cannabidiol (GWPCARE 1, GWPCARE2) and an ongoing open-label extension study (GWPCARE5) as relevant to the submission. Both RCTs were conducted in patients aged 2 to 18 years with DS, whose seizures were incompletely controlled with previous AEDs and who had had at least four convulsive seizures per week in the past 28 days. The intervention was cannabidiol in addition to current clinical management (CCM) and the comparator was CCM without cannabidiol (i.e. CCM plus placebo). GWPCARE1 compared cannabidiol (20 mg/kg/day) in addition to CCM and CCM plus placebo. GWPCARE2 was a three-arm study, comparing two doses of cannabidiol (10 mg/kg/day and 20 mg/kg/day) in addition to CCM and CCM plus placebo. Both randomised trials had a dose escalation phase (14 days in GWPCARE1 and seven or 11 days in GWPCARE2) followed by a 12-week treatment period. GWPCARE1 included patients from the UK (three centres recruited 16 patients overall) but GWPCARE2 did not include patients from the UK.

GWPCARE1 had a total of 120 patients and GWPCARE2 198. Patients had used on average four or five prior anti-epileptic drugs (AEDs).

Patients in GWPCARE2, who received 10 mg/kg/day CBD in addition to CCM, achieved better convulsive seizure frequency outcomes than those who received CCM + Placebo ([redacted] A higher proportion of patients in the 10 mg/kg/day CBD group achieved at least a 50% reduction in convulsive seizures, during the treatment period, than in the placebo group ([redacted]). [redacted] patients in the CBD group of GWPCARE2 and [redacted] in the placebo group achieved freedom from convulsive seizures for the whole 14-week treatment period. Patients in the 10 mg/kg/day CBD group of GWPCARE2 experienced fewer seizures overall, during the 14-week treatment period, than those in the placebo group ([redacted]). Safety data appeared to indicate a pattern of gastrointestinal and 'tiredness'-related adverse events (AEs) in patients taking CBD, as well as a detrimental effect on markers of liver function. With respect to markers of liver function, the company noted that '*cases of raised liver transaminases resolved either spontaneously or with dose adjustments of CBD or concomitant AEDs'*. The rates of individual, treatment-related AEs were generally higher in the 20 mg/kg/day CBD groups than in the 10 mg/kg/day CBD group.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS included a systematic review of the evidence of CBD for DS. The submission and response to clarification provided sufficient details for the evidence review group (ERG) to appraise most of the literature searches. A range of databases were searched, and additional searches of conference proceedings and trials registers were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. Errors and omissions in the search strategies were queried during clarification, and as corrected strategies were not provided in the clarification response, the ERG remains concerned about potentially relevant missed evidence.

Although the CS included two international RCTs and an open-label extension study, there are some limitations in applying this evidence to UK practice. Firstly, as has been mentioned in section 1.1, the randomised trials did not include any adult patients. Secondly, the ERG notes that three UK sites recruited a total of 16 patients to GWPCARE1, and that GWPCARE2 did not have any UK patients. This is most relevant when considering the nature of background current clinical management, which is the comparator in the trials. Current clinical management is considered to be a 'basket' of choices of AED and although the company conducted a number of subgroup analyses based on the presence or absence of various AEDs, they assumed that there were no treatment interaction effects. The ERG questions this assumption.

In addition, a major limitation of the evidence is the small size of the data set relating to the 10 mg cannabidiol dose to be used in practice. Just [redacted] patients in GWPCARE 2 and none in GWPCARE1 received the 10 mg/kg/day dose (this trial compared 20 mg/kg/day CBD to placebo). In the open-label extension study, GWPCARE5, the average dose was [redacted] with patients receiving [redacted] making this study less relevant to the decision problem.

A further limitation was the short-term nature of the RCTs (14 weeks including a 1one to two-week titration followed by a treatment maintenance phase of 12 weeks). There is a lack of long-term efficacy and safety data particularly based on the 10 mg/kg/day CBD dose. Any observations of reduction in seizures in the short-term trials, particularly convulsive seizures, may not be sustained in the long-term and the effects on outcomes relating to mortality (especially SUDEP) are unknown. Any long-term or rarer adverse events for the 10 mg/kg/day dose are unclear.

1.4 Summary of cost effectiveness submitted evidence by the company

The company developed a cohort state transition model using Microsoft Excel®. The model consisted of five health states, that were mainly based on the convulsive seizure frequency and the number of convulsive seizure-free days.

In line with its anticipated marketing authorisation and the final scope issued by NICE, CBD was considered in the cost effectiveness model for the treatment of patients with DS who are aged two years or older and in whom the condition is inadequately controlled by the established current clinical management (CCM) in the UK.

In the CS, the base-case analysis utilises the maintenance dose of 10 mg/kg/day as the company assumes that the majority of patients will receive this dose in clinical practice.

The analysis takes an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was three months with a 15-year time horizon.

The main sources of evidence on treatment effectiveness are the pivotal clinical trials (GWPCARE1 and GWPCARE2) and the open label extension study (GWPCARE5). It should be noted that GWPCARE1 is not used in the base-case analyses, only in the scenario analyses that used CBD 20 mg/kg/day. These studies are used to obtain evidence for the frequency of convulsive seizures, number of days without convulsive seizures, discontinuation rates and adverse events for both CCM plus CBD and CCM. GWPCARE2 was mainly used to inform treatment effectiveness during cycle one, while GWPCARE5 (in combination with assumptions) was used for subsequent cycles. Moreover, treatment effectiveness was estimated separately for patient subgroups <12 years and ≥12 years. Long-term treatment effectiveness was extrapolated assuming a constant treatment effect by assuming that CBD patients remain in the same health state until CBD discontinuation or death.

Adverse events were based on a pooled analysis considering both the DS and Lennox-Gastaut syndrome (LGS) phase III trials (GWPCARE1, GWPCARE2, GWPCARE3 and GWPCARE4).

Health state utilities were estimated using patient vignettes using a visual analogue scale. Health state utilities were assumed to be treatment dependent due to differences in number of days without convulsive seizures between CBD and CCM. The impact of adverse events on health-related quality of life was not incorporated in the model.

The cost categories included in the model were costs associated with treatment (drug acquisition costs included concomitant therapies and costs associated with treatment-related AEs), health state costs and mortality costs. Unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and clinical opinion.

CBD resulted in higher costs and quality-adjusted life year(s) (QALYs) than CCM resulting in an incremental cost effectiveness ratio (ICER) of [redacted], the company's revised analysis, resulted in an ICER of £36,046.

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

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The submission and response to clarification provided sufficient details for the ERG to appraise most of the literature searches. A range of databases were searched, and additional searches of conference proceedings and trials registers were conducted. Searches were carried out in accordance with the NICE

guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. Errors and omissions in the search strategies were queried during clarification, and as corrected strategies were not provided in the clarification response, the ERG remains concerned about potentially relevant missed evidence.

The ERG considered that the economic model and base-case analyses described in the CS only partly met the NICE reference case. Deviations from the NICE reference case included the restricted time horizon of 15 years and the method used to estimate utilities.

The main concern of the ERG related to the model structure was the assumption that patients receiving CCM transfer back to their baseline convulsive seizure frequency after the first cycle. The company clarified that this was done as a placebo effect was observed in both the GWPCARE1 and GWPCARE2 studies and argued it was not reasonable to assume that these effects would be sustained in clinical practice. The ERG disagrees with the approach as it may be the case that the placebo effect is also present in the CBD group (and hence is part of the demonstrated effects) and these patients do not transfer back to their baseline seizure frequency after the first cycle. Removing the placebo effect for CCM while not removing this for CBD would most likely induced bias (similar to that which might be expected with pre-post comparisons) and thus might result in an overestimated treatment effect for CBD.

The ERG had multiple concerns related to the estimation of treatment effectiveness in the CS. These issues mainly concerned the extrapolation of treatment effectiveness. Firstly, extrapolation of evidence from GWPCARE5, using CBD 20 mg/kg/day as maintenance dose (mean modal dose during treatment was [redacted]) to model the effectiveness of CBD 10 mg/kg/day beyond three months. It is debatable whether this evidence is representative for a CBD maintenance dose of 10 mg/kg/day. Secondly, the extrapolation after 27 months is uncertain due to the lack of evidence beyond this time period. After 27 months the company assumed a constant treatment effectiveness, i.e. assuming that CBD patients remain in the same health state until CBD discontinuation or death while assuming a constant CBD discontinuation probability. Thirdly, it is questionable whether the evidence can be extrapolated to patients aged 18 year above given the large majority of patients in the trials ([redacted] based on GWPCARE1 and GWPCARE2) is aged below 18 year. The uncertainty related to extrapolation is, in part, reflected in the ERG base-case ICER range.

Another source of uncertainty was the estimated health state utility values. In addition to the use of methodology that is not in line the NICE reference case, the (implicit) use of treatment dependent health state utility values is not considered appropriate by the ERG. Particularly for patients that, after CBD discontinuation, reverted back to their baseline frequency of convulsive seizures, the treatment benefit (compared with CCM) potentially induced by the difference in number of days without convulsive seizures between the treatments, is questionable.

The model validity and transparency can be regarded as a major limitation of the current assessment. Despite the company attempting to resolve validity issues (e.g. estimated QALYs that are larger than the time horizon) during the clarification phase, the ERG still considered the model validity of the revised model to be problematic. Particularly because the model failed to provide the expected results to internal validity tests performed by the ERG. For instance, changing the clinical effectiveness input parameters for CBD 10 mg/kg/day to the clinical effectiveness input parameters for CCM still resulted in a QALY benefit of 0.36 for CBD (while 0.00 would be expected). Accordingly, the ERG believes, there are fundamental problems with the economic model that potentially induce a QALY gain for CBD 10 mg/kg/day. Consequently, the cost effectiveness results, calculated using the economic model submitted by the company, lack credibility. Due to the complexity and limited transparency of the

model, the ERG was unable to satisfactory resolve these validation issues within the available timeframe.

Due to the abovementioned validity issues, the ERG considers the original CS ICER ([redacted] per QALY gained) as well as the revised base-case ICER submitted by the company (£36,046 per QALY gained, including QALYs gained by caregivers) as not credible given the validity issues and adjustments (to the model structure and inputs that were not requested by the ERG) made by the company.

The ERG base-case consisted of an ICER range reflecting the uncertainty surrounding the extrapolation of treatment effectiveness. The probabilistic ERG base-case indicated that the ICER, for CBD compared with CCM, would range between £76,013 per QALY gained (assuming a constant treatment effect after 27 months) and £477,476 per QALY gained (assuming no treatment effect after 27 months).

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

In the company base-case (probabilistic), the ICER of CBD compared with CCM was estimated to be [redacted] per QALY gained. However, this ICER was based on technically implausible QALY estimates and is, according to the ERG, not informative/seriously flawed. Similarly, the revised base-case ICER submitted by the company ([redacted]) should be interpreted with extreme caution given the validity issues and adjustments (model structure and input) made by the company. The ERG has incorporated various adjustments to the CS base-case (using the revised economic model with input parameters from the original CS as starting point). The ERG base-case consisted of an ICER range, reflecting the uncertainty surrounding the long-term extrapolation of treatment effectiveness. The ERG base-case (probabilistic) indicated that the probabilistic ICER, for CBD compared with CCM, would range between [redacted] per QALY gained and [redacted] per QALY gained. However, it should be reiterated that some of the abovementioned potential biases (model structure, validity) could not be explored by the ERG. Consequently, the ICERs reported are likely to be underestimations of the true ICERs.

2. BACKGROUND

In this report the ERG provides a review of the evidence submitted by GW Research Ltd. in support of cannabidiol, trade name Epidyolex®, for the treatment of patients with Dravet syndrome. In this section we outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken from section B.1.3 of the company submission (CS) with subsections referenced as appropriate.

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

The underlying health problem of this appraisal is Dravet syndrome, a severe form of epilepsy affecting children and adults.

Dravet syndrome, previously known as severe myoclonic epilepsy of infancy (SMEI), is a rare disease. The CS cited a prevalence of 0.4 in 10,000 people.[1] We note that at the time of designation of cannabidiol as an orphan drug the EMA accepted that Dravet syndrome affected fewer than 0.5 in 10,000 people in the European Union (EU).[2] Extrapolating this to a UK population gives approximately 3,300 people potentially affected by Dravet syndrome. Even among epilepsy patients the syndrome is rare.

The role of genetic mutation in Dravet syndrome is highlighted in the CS and the company cited sources indicating that *'70-85% of individuals with clinical features of DS test positive for mutations of the SCN1A gene*'.[1] We further add that in Dravet syndrome, the gene mutation nearly always arises spontaneously. However, some people with Dravet syndrome may have some history of febrile seizures or epilepsy in their extended family.[3]

The company explained that DS typically starts '*in the first year of life with prolonged, repeated clonic or unilateral seizures in developmentally normal children, associated in many instances (estimates range from 39-72%) with a fever*.' The company considered the development of multiple types of seizure over time. '*Patients with DS present with different seizure patterns, but most include combinations of severe convulsive seizures, including generalised tonic-clonic and clonic seizures, as well as myoclonic, atypical absence and focal seizures*.'[1]

The burden of disease was highlighted by the company '*Children with DS experience severe symptoms including prolonged convulsive seizures, resulting in emergency hospital visits.*'[1] The company detailed the cognitive, functional and neuromotor impairments that can arise with Dravet syndrome. The role of seizures on the development of the young brain was mentioned.

The company cited a DS mortality rate of 20% with most deaths occurring before the age of 10. They further stated that '*Patients with DS are at high risk of SUDEP and status epilepticus, which cause around a half and a third of deaths in DS respectively*'.[1] These data are from a review that found that 73% of deaths were before the age of 10. This review also provided a breakdown of cause of death based on 177 deaths: 87 (49%) SUDEP, 56 (32%) status epilepticus, 14 (8%) drowning/accidents, nine (5%) fatal infections and six (3%) other causes with the remainder unknown.[4]

The company stated that '*High seizure frequency is a significant predictor of early death (18), with persistent seizures strongly related to excess mortality (19). Standardised mortality ratios are especially high among those with convulsive seizures (20).*' The references cited are from general epilepsy populations. The company stated that '*Clinical opinion recommends that the most effective prevention strategy for death related to epilepsy, and especially SUDEP, is to reduce the frequency of seizures*'.[1]

The impact on family and caregivers is made explicit. '*DS is also associated with many consequences and comorbidities that can result in lifelong impairment, so that patients are completely dependent upon caregivers for daily activities.*'[1] The company referenced surveys including a European survey of caregivers of patients with DS which captured about 15% of the DS patient population under the age of 18 in France, Germany, Italy, Spain, and the UK.[5] This survey found that '*more than a third (34%) were unemployed, of whom 81% had given up their job due to their role as a caregiver.*'[1]

ERG comment: The company provided a good overview of the underlying health problem of Dravet syndrome illustrating the seriousness of the condition and its impact on patients and their families. The ERG checked the references provided to support the statements in the company submission. In general, these were appropriately referenced. Where citations did not match an alternative source was checked.

However the CS did not explicitly mention the stages of Dravet syndrome described by Dravet '(1) the febrile or diagnostic stage in the first year; (2) the worsening (preferred to ''catastrophic'') stage between one and five years: period with frequent seizures and statuses, behavioural deterioration, and neurologic signs; and (3) the stabilisation stage after five years: convulsive seizures decrease and occur mainly in sleep, myoclonic and absence seizures can disappear, focal seizures persist or decrease; mental development and behaviour tend to improve but cognitive impairment persists, although of variable degree.'[6] The stabilisation and decrease in convulsive seizures after five years is relevant to this submission.

There was brief mention in the CS of adolescence and adulthood in relation to nocturnal seizures and risk of SUDEP. However, it is important to emphasise that DS is not just a childhood condition. In October 2018 a US Dravet Syndrome Foundation survey found that 80% of children with DS survive to adulthood.[7] Therefore a high proportion of those eligible for cannabidiol are not fully represented in the main trials which included patients only up to age 18 years.

2.2 Critique of company's overview of current service provision

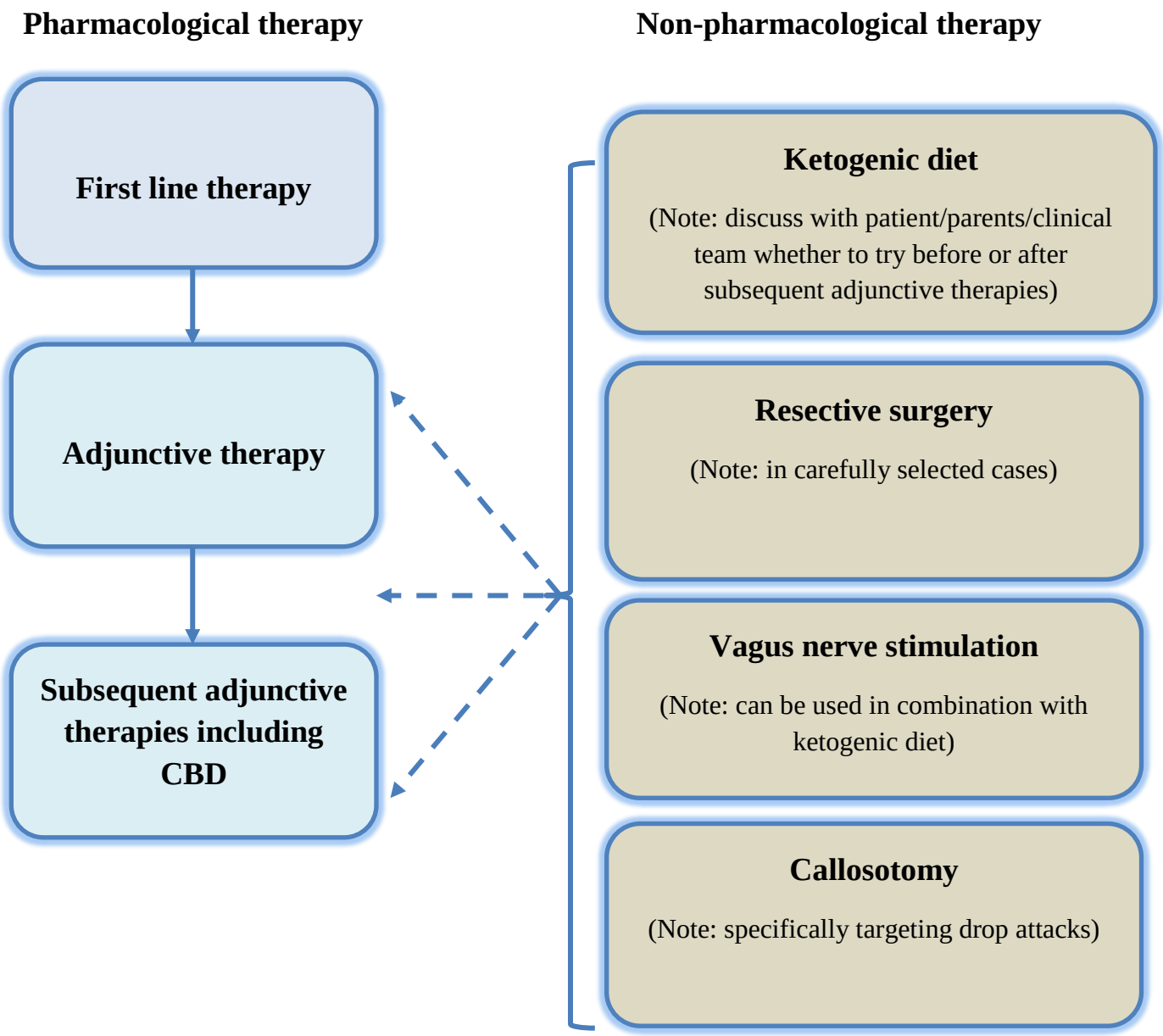
The main clinical guideline relevant to this submission is CG137. This NICE guideline (referred to in the CS) recommends consideration of sodium valproate or topiramate as a first-line treatment for DS and if seizures are inadequately controlled, clobazam or stiripentol as an adjunctive treatment.[8] The company also referred to a North American consensus panel set of recommendations[9] which are not discussed as they are less relevant to a UK population.

The company highlighted the current unmet need for treatment to reduce seizure frequency and severity and to improve the overall condition of patients with DS. This is due to existing medications being only partially effective. As part of the submission we received a statement from Professor Sisodiya from the Association of British Neurologists (Epilepsy Advisory Group) who stated that '*most patients with Dravet syndrome do not become seizure-free with currently available treatments*'.[10] In practice patients with DS need to take a combination of anti-epileptic drugs in an attempt to control their seizures. The company cited a study illustrating how physicians have '*to balance seizure control effectiveness, adverse event burden, and the side-effect profile of combinations*'.[11]

The place of CBD in the current pathway, according to the company, is as '*an add-on treatment for refractory seizures in people aged 2 years of age and older once two other appropriate AEDs, trialled to a maximum tolerated dose, have failed to achieve seizure-freedom*'.[1] Figure 2.1 shows the proposed treatment pathway for patients with Dravet syndrome.

The company stated that '*The introduction of cannabidiol in the DS treatment pathway aligns with current clinical management. No service design will be required.*'[1]

Figure 2.1: Proposed treatment pathway for DS including CBD (Source Figure 2 of CS)



ERG comment: The company's overview of the current pathway is appropriate. However the ERG asked a number of questions relating to the place of CBD in the pathway.[12] The questions are given below with the company's responses and our interpretation.

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

Company response: *'No. This was added as it is in line with the recommendations in NICE Clinical guideline 137 (CG137). Patients may discontinue AEDs because of tolerability issues, not just lack of seizure control. In addition, certain AEDs are not suitable for DS patients. For example, NICE CG137 states that carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin should not be given to patients with DS as they may worsen seizures.*'[12]

ERG interpretation: The ERG agrees with the response provided and notes that the additional wording '*People with Dravet syndrome where current clinical management is unsuitable or not tolerated*' is consistent with the wording around recommendations for third-line AEDs in CG137.[8]

ERG question A3: Under 'Placement of CBD within the care pathway' (page 25 of the company submission) and at other points in the document, it is stated that: '*For patients with Dravet syndrome (DS) considered for treatment with CBD, it will be an add-on treatment for refractory seizures in people aged 2 years of age and older once two other appropriate anti-epileptic drugs (AEDs), trialled to a maximally tolerated dose, have failed to achieve seizure freedom.*'[13]

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

Company response: '*No'*

ERG interpretation: The company did not elaborate on this response. However it appears to be inconsistent with the therapeutic indications stated in the submitted summary of product characteristics (SmPC), which does not include any limitation based on prior trials of other AEDs:'Epidyolex is indicated for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.' [10]

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

Company response: '*The number of patients at baseline in each arm of GWPCARE1 and GWPCARE 2 on 0, 1, and ≥2 prior AEDs is shown in the table below.*'

Table 2.1: Prior AEDs at baseline in GWPCARE1 and GWPCARE2

		Prior AEDs (no longer taking)		
		10 mg/kg/day	20 mg/kg/day	Placebo
	No. AEDs		n=61	n=59
GWPCARE1	0		5 (8.2%)	4 (6.8%)
	1		5 (8.2%)	5 (8.5%)
	≥2		51 (83.6%)	50 (84.7%)
GWPCARE2		n=64	n=69	n=65
	0	4 (6.3%)	2 (2.9%)	2 (3.1%)
	1	7 (10.9%)	7 (10.9%)	8 (12.3%)
	≥2	53 (82.8%)	60 (87.0%)	55 (84.6%)
Source: Clarification response, page 5[12]				

ERG interpretation: The ERG notes that the proportion of participants in the key trials, who had discontinued fewer than two prior AEDs was 16% in GWPCARE1[14] and was 15% in GWPCARE2.[15] The ERG considers that, with respect to prior AED treatments, the data of most (over 80%), but not all, of the trial participants clearly reflect the placement of CBD in the care pathway, as described in the CS. It should be noted that the remaining participants may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled.

We also asked a number of questions regarding the patient characteristics in the main trials given the proposed placement of CBD in the pathway at third-line. These are discussed in more detail in sections 3 and 4 of this report.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale	ERG comment
Population	People with Dravet syndrome whose seizures are inadequately controlled by established clinical management.	People with Dravet syndrome (DS) whose seizures are inadequately controlled by current or prior established clinical management. People with DS where current clinical management is unsuitable or not tolerated. Rationale: This is in line with recommendations in NICE Clinical guideline 137 (CG137)[8]	The population addressed, (people aged two years and over with Dravet syndrome (DS) whose seizures are inadequately controlled by current or prior established clinical management) is consistent with the final scope issued by NICE and with the expected licenced indication for Epidyolex®. The addition of people with DS where current clinical management is unsuitable or not tolerated is consistent with the pathway outlined in NICE CG137.[8] The two main trials in the submission excluded adult (> 18) patients. There are therefore no clinical data relevant to adult patients.
Intervention	Cannabidiol in addition to current clinical management	Cannabidiol in addition to current clinical management	In line with the scope.
Comparator(s)	Established clinical management without cannabidiol, which may include combinations of: • sodium valproate • topiramate • clobazam • stiripentol • levetiracetam • ketogenic diet	Established clinical management without cannabidiol, which may include combinations of: • sodium valproate • topiramate • clobazam • stiripentol • levetiracetam • ketogenic diet	In line with the scope. The comparator used in the submission is CCM, which includes various combinations of different AEDs. Different combinations of AEDs were not considered as separate comparators, as indicated by the NICE scope. It should be noted that the use of a 'mixed' CCM comparator assumes that the effectiveness of CBD does not vary with the combination of drugs to which it is added.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale	ERG comment
	• vagus nerve stimulation	• vagus nerve stimulation	Issues relating to how well the trials in the submission might reflect current clinical management in England and Wales in terms of concurrent treatments are discussed within this report.
Outcomes	The outcome measures to be considered include: • seizure frequency (overall and by seizure type) • response rate (overall and by seizure type) • seizure severity • incidence of status epilepticus • mortality • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • seizure frequency (convulsive seizures and overall) • proportion of people convulsive seizure-free • number of people with episodes of status epilepticus • mortality • adverse effects of treatment • health-related quality of life • CGIC (Caregiver Global Impression of Change) • CGICSD (Caregiver Global Impression of Change in Seizure Duration) Rationale: The primary endpoint of the pivotal clinical trials was change in convulsive seizure frequency. A seizure severity proxy (duration of seizures) was measured through the caregiver surveys as an impression of seizure duration change rather than as a defined metric. The clinical trial patients were a highly refractory group of patients with status epilepticus as part of their disease. In the	The outcomes presented in the CS do not completely match the outcomes identified in the NICE scope. However, this is due to the design of the two main trials. An important point is that although mortality is investigated, the two main trials are of 14 weeks' duration so cannot provide long-term data on SUDEP and other deaths. The exact link between reduction in convulsive seizures and any associated reductions in mortality cannot be determined from the two main randomised trials. The ongoing open label GWPCARE5 trial did not list either SUDEP or overall mortality in the effectiveness outcomes to be assessed.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale	ERG comment
		trials, the number of people with episodes of status epilepticus was reported, not the incidence.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope	Deviations from the NICE reference case included the restricted time horizon of 15 years and the method used to estimate utilities.
Subgroups to be considered	Not applicable	Not applicable	Not applicable
Special considerations including issues related to equity or equality	Not applicable	Not applicable	Not applicable

Source: Table 1, Section B.1.1 of the CS[1]

AED = anti-epileptic drug; CG = clinical guideline; CS = company submission; DS = Dravet syndrome; ERG = Evidence Review Group; SUDEP = Sudden death in epilepsy

3.1 Population

The population defined in the scope is 'people with Dravet syndrome (DS) whose seizures are inadequately controlled by established clinical management'.[16] The company has added to this '*people with DS where current clinical management is unsuitable or not tolerated*'.[1] This addition is consistent with the pathway outlined in NICE CG137.[8]

The submission relied, primarily, on two randomised controlled trials (RCTs) of CBD as an add-on treatment to current clinical management (GWPCARE1[14] and GWPCARE2[15]). Both RCTs (GWPCARE1 and GWPCARE2) were conducted in patients aged two to 18 years with DS, whose seizures were incompletely controlled with previous AEDs and who had had at least four convulsive seizures per week in the past 28 days. Although the decision problem did not specify any age restriction and the expected licenced indication for Epidyolex® is for patients two years of age and older, neither of the key trials used in the submission (GWPCARE1 and GWPCARE2) included adult patients (over the age of 18 years).

The number of previous or current AEDs in relation to CBD was not specified in the NICE scope. However, the treatment pathway proposed by the company (see Figure 2.1 of our report) placed CBD as a third-line treatment (i.e. for patients who have inadequate seizure control with first-line and at least one adjunctive AED). The baseline characteristics for GWPCARE1 and GWPCARE2, reported in the CS (Tables 6 and 7) indicated that some participants included in these studies may have been treatment naïve or have tried only one prior AED.[1]

Of the two main trials, GWPCARE1 included patients from the UK ([redacted] patients from [redacted] centres) but GWPCARE2 did not include patients from the UK.

The CS (Section B.2.7) stated that '*no subgroup analyses were conducted.*' However, the CSRs for both key trials (GWPCARE1[14] and GWPCARE2[15]) reported a number of subgroup analyses, which are further discussed in this report.

ERG comment: The ERG asked a number of questions relating to the population defined in the decision problem and the populations included in the key trials, GWPCARE1 and GWPCARE2. The questions are given below with the company's responses and our interpretation.[12]

ERG question A16: Both of the two main trials (GWPCARE1 and GWPCARE2) excluded adult (>18 years) patients. What are the implications of this, given that the expected licensed indication is for patients two years of age and older with no upper age limit mentioned?

Company response: '*This reflects the demographics of the DS population. Patients are diagnosed at a young age and mortality rates are high. Premature mortality is a major issue in DS, with most deaths occurring before 10 years of age. For these reasons, the number of adults with DS is very low compared with the number of children.*'

ERG interpretation: Around 80% of people with Dravet syndrome can survive into adulthood.[7] Therefore a high proportion of those eligible for cannabidiol are not fully represented in the main trials given the inclusion of patients only up to age 18.

ERG question A3: Under 'Placement of CBD within the care pathway' (page 25 of the company submission) and at other points in the document, it is stated that: '*For patients with Dravet syndrome (DS) considered for treatment with CBD, it will be an add-on treatment for refractory seizures in people*

aged 2 years of age and older once two other appropriate anti-epileptic drugs (AEDs), trialled to a maximally tolerated dose, have failed to achieve seizure freedom.'[12]

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

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

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

ERG interpretation: No references were provided to support the level of polypharmacy in DS. However, the ERG considered the company's response to be reasonable.

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

Company response:

Figure 3.1: Histogram for the number of patients on prior AEDS (no longer taking) at baseline (GWPCARE1)

Figure 3.2: Histogram for the number of patients on prior AEDS (no longer taking) at baseline (GWPCARE2)

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

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

ERG interpretation: The ERG agrees with the company's response.

f. The mean number of concurrent treatments in the trials was approximately three. How does this reflect UK clinical practice? Do the concurrent treatments used in the trials reflect UK practice?

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

ERG interpretation: The ERG notes that the company did not provide any references or statements from clinical experts in support of this response; this may be a point for discussion with clinical experts on the appraisal committee.

ERG question A12: How many UK centres and patients were included in GWPCARE1? How similar does the company consider the trials to be to patients seen in practice in England and Wales? Have you sought any clinical expert input on this issue?

Company response: 'There were 4 UK sites in GWPCARE1, of which 3 recruited, and none in GWPCARE2. Overall there were 16 UK patients in GWPCARE1.

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

GWPCARE1 included patients from the UK, the USA, France and Poland.

GWPCARE2 included patients from the USA, Spain, Poland, Australia, Israel and the Netherlands.

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

ERG interpretation: The ERG notes that the company did not provide any statements from clinical experts, in support of the above response. The applicability of the key trials to the UK population may be a point for discussion with clinical experts on the appraisal committee

We also asked the company to provide full results for all subgroup analyses conducted. The company's response and the results of these analyses are discussed in more detail in section 4 of this report.

3.2 Intervention

The intervention (cannabidiol (Epidyolex®) in addition to current clinical management) is in line with the scope. Orphan designation (EU/3/14/1339) was granted by the European Commission on 15 October 2014 for cannabidiol for the treatment of Dravet syndrome. Regulatory approval by the EMA is anticipated in April 2019.

Epidyolex is indicated for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients two years of age and older. It is described in the CS as '*a highly purified, plant-derived pharmaceutical formulation of cannabidiol, administered as an oral solution*.' [1]

The description of the technology being appraised (Table 2 of the CS) included the following statement about dosage: '*The recommended starting dose of cannabidiol (CBD) is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day). Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 20 mg/kg/day, should be made considering individual benefit and risk.*'[1] However, the majority of the clinical effectiveness evidence presented related to the maximum recommended dose (20 mg/kg/day).

ERG comment: The ERG asked a number of questions relating to the dose of CBD used in the key trials, GWPCARE1 and GWPCARE2, and how this related to the dose that would be expected to be used in UK clinical practice. The questions are given below with the company's responses and our interpretation.[12]

ERG question A1:

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

Company response:

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

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

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

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

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

The decision to escalate would be at the clinician's discretion, in discussion with the patient and/or caregivers. Feedback suggests that specialist clinicians would be comfortable doing this, especially given their experience in managing existing treatments and the complex set of considerations when making dose adjustments. GW therefore considers the assumptions made to model the proportion of patients receiving 20mg/kg/day as reasonable (see answer to A1a).'

ERG interpretation: Given the above response, the ERG considers that only clinical effectiveness data for the 10 mg/kg dose are relevant to the whole population, specified in the decision problem. If only those patients who the physician considers may gain additional seizure reduction by dose escalation will receive the 20 mg/kg dose, and this has been defined as those experiencing ≥75% reduction in convulsive seizures on the 10 mg/kg dose, then data on the clinical effectiveness of the 20 mg/kg dose are only relevant for this specific subgroup; the CS did not provide subgroup data.

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

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

ERG interpretation: The ERG accepts the above response, but notes that this may limit the applicability of any long-term effectiveness data from the open-label extension study, GWPCARE5 to UK clinical practice. The interim report for GWPCARE5,[17] provided by the company in their clarification response, stated that, for [redacted] of participants with DS, the modal dose during the treatment period was [redacted] The overall mean modal dose for DS patients was [redacted] It is not possible to provide a more detailed breakdown of CBD doses received by patients during the open-label extension period, as the relevant tables were missing from the report provided. If, as suggested by the company, the maximum recommended dose of 20 mg/kg/day is most likely to be received only by a small proportion of patients who have responded well to the 10 mg/kg dose and are judged by clinicians to have the potential to achieve further seizure reductions and/or seizure freedom, the ERG is unclear what was the rationale for dose escalation in the context of an open-label extension study (GWPCARE5) when propensity for further response had presumably been established during the blinded phase of studies (GWPCARE1 and GWPCARE2).

ERG question A20: For GWPCARE2, please provide results of comparisons between the 20 mg and 10 mg CBD groups, for all outcomes where these are available.

Company response: '*No formal pre-specified test for significance between the CBD groups was included in the SAPs.*'

ERG interpretation: Equivalent effectiveness and safety cannot be assumed between the two doses. Section 4 of this report gives further detail on results according to dosage.

3.3 Comparators

The description of the comparators is in line with the scope (established clinical management without cannabidiol), which may include combinations of: sodium valproate, topiramate, clobazam, stiripentol, levetiracetam, ketogenic diet and vagus nerve stimulation. The comparator used in the key trials (GWPCARE1 and GWPCARE2) is current clinical management (CCM), which includes various combinations of different AEDs. Different combinations of AEDs were not considered as separate comparators.

The CS (Section B.2.7) states that '*no subgroup analyses were conducted*.' However, the CSRs for both key trials (GWPCARE1[14] and GWPCARE2[15]) reported a number of subgroup analyses, including for concurrent use of a number of individual AEDs . The results of these are included in this report.

ERG comment: It should be noted that the use of a 'mixed' CCM comparator assumes that the effectiveness of CBD does not vary with the combinations of AEDs to which it is added. The ERG questions the validity of this assumption.

In NICE's epilepsy guidance we note that there is some uncertainty on the most appropriate initial and add-on AEDs and that further research is recommended.[8] With this in mind, the ERG was concerned as to how well the trials in the CS might reflect the number and nature of treatments under the umbrella of clinical management in England and Wales. The ERG asked the company to clarify this. Furthermore, we wished to be clear that results in the two main trials reflected the impact of Epidyolex and were not reflective of the particular composition of clinical management. We asked the company to provide full results for all subgroup analyses conducted. The company's response and the results of these analyses are discussed in more detail in section 4 of this report.

3.4 Outcomes

The NICE final scope listed the following outcome measures:

- seizure frequency (overall and by seizure type)
- response rate (overall and by seizure type)
- seizure severity
- incidence of status epilepticus
- mortality
- adverse effects of treatment
- health-related quality of life

The CS focused primarily on convulsive seizures as these were the primary outcome in the two main trials. Data were available on overall frequency of seizures and there was some break down of seizure type in the full clinical study reports (CSRs). The company provided the rationale for differences in relation to seizure severity. '*A seizure severity proxy (duration of seizures) was measured through the caregiver surveys as an impression of seizure duration change rather than as a defined metric*.'[1] The surveys were the CGIC (Caregiver Global Impression of Change) and the CGICSD (Caregiver Global Impression of Change in Seizure Duration). The company also explained the rationale in relation to incidence of status epilepticus. '*The clinical trial patients were a highly refractory group of patients with status epilepticus as part of their disease. In the trials, the number of people with episodes of status epilepticus was reported, not the incidence*.' [1]

ERG comment: The outcomes presented in the CS did not completely match the outcomes identified in the NICE scope. However, this was due to the design of the two main trials. A potentially more important issue is that, although mortality was investigated, the two main trials were of 14 weeks' duration so could not provide long-term data on SUDEP and other deaths. The exact link between reduction in convulsive seizures and any associated reductions in mortality cannot be determined from the two main randomised trials.

The ERG asked a number of questions relating to the outcome measures used in the key trials, GWPCARE1 and GWPCARE2. The questions are given below with the company's responses and our interpretation.[12]

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

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

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

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

Company response: '*The separate document provided (QA9b. Collection of the Seizure Data (Primary Endpoint) on the IVRS) details the training given to the caregivers on recording seizure type and PROs.*'

ERG interpretation: The ERG is satisfied that outcomes were reported appropriately and that those reporting outcomes were suitably qualified to do so.

We also asked the company to provide full results for all outcomes assessed in GWPCARE1 and GWPCARE2, including listed outcomes that were not reported in the CS, incomplete data (e.g. results reported only as relative (%) change, missing baseline and end-point values), and provision of point estimates only (missing inter-quartile range (IQR), standard deviation (SD) or 95% confidence interval (CI)). The company provided a separate document with additional results and missing data.[18] Data from this document and, where necessary, taken directly from the relevant CSRs are included in section 4 of this report.

3.5 Other relevant factors

The company stated that '*The use of cannabidiol is unlikely to raise any equality issues*'. The CS noted that the indication is only for patients aged two years of age and older.

There is no Patient Access Scheme (PAS) application. The list price of cannabidiol is [redacted]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify evidence on the efficacy and safety of drug interventions in Dravet syndrome and Lennox-Gastaut syndrome (to inform a parallel appraisal). Section 4.1 critiques the methods of the review including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis. The systematic review also identified papers relevant to the cost effectiveness of this appraisal which will be discussed in section 5.

4.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical and cost effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[19] The submission was checked against the single technology appraisal (STA) template for company/sponsor submission of evidence.[20]

The company submission reported that a rigorous systematic review was carried out to identify relevant publications for the efficacy, safety and development of economic models for the use of cannabidiol in Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS).[1] The main submission presented one set of searches used to inform both the clinical and cost effectiveness content for both LGS and Dravet syndrome in Appendix D.[1] As the searching for the whole submission was conducted at once, the ERG's appraisal and comments will be presented here for both the clinical and cost effectiveness sections.

The single set of searches was reported in full in D1.1, and strategies were presented in Table 43.[1] The database searches were undertaken on 19 November 2018, and grey literature website searching was carried out between 19 November and 3 December 2018. Search strategies were reported in Table 42 of the CS for the following databases: Embase (ProQuest), PubMed, Heoro.com, and the Cochrane Library (Wiley). Additional searches were provided for ScHARRHUD, EuroQol Database, NHS EED (NHS Economic Evaluation Database), Database of Abstracts of Reviews of Effects (DARE) and HTA (Health Technology Assessment) databases via the Centre for Reviews and Dissemination's website. As part of the clarification process, additional searches were carried out on 6 and 11 February 2019, in order to correct errors and answer the ERG's clarification questions.[21] These strategies were not provided in the clarification response.[12]

All searches contained terms to identify the conditions of interest: Lennox-Gastaut syndrome, Dravet syndrome or alternative terminology for childhood epilepsies, however different terms were included in each strategy. No drug or intervention facets were included in the search, and study design filters were not applied. The searches were not restricted by date or limited by language of publication. A further trials search was presented for NIH Clinicaltrials.gov, and search terms were provided. The ERG noted the NIH trials register records were restricted to 'terminated', 'completed', 'suspended' or 'withdrawn' studies; with further limits to "Interventional studies (clinical trials)" and only those studies with results presented.

The CS documented browsing of the following conference proceedings, together with URLs and conference dates: American Epilepsy Society, International Epilepsy Congress, European Congress on Epileptology and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Additional supplementary web searches were carried out on specific organisational websites, such as NICE, All Wales Medicines Strategy Group (AWMSG) and Scottish Medicines Consortium (SMC).

The CS also reported asking the manufacturer for any additional publications, which yielded two further publications.

ERG comment:

- The search strategies that were reported were logically structured. Inclusion of one facet to search for the conditions of interest was appropriate and sensible, as was the decision not to apply any study design filters or restrictions.
- Each search reported in the CS contained different free-text terms, with little consistency between strategies. The ERG queried this variability during clarification, because comprehensive and methodical searches would be expected to include very similar free-text terms across all databases. Typically, only the database-specific indexing, command language and field tags change between resources. Although the response to clarification reported investigating these issues, corrected strategies were not provided for the ERG's appraisal. Therefore, the ERG was unable to assess how well these changes were made.
- Errors and inconsistencies in the original search strategies impaired the performance of the company's searching. The ERG queried these issues during clarification, however as the company did not provide corrected strategies in their clarification response, the ERG remains concerned about the quality of the company's searches. These errors and inconsistencies may have limited recall of potentially relevant references. The explanation given in the clarification response did not match the numbers retrieved when the ERG corrected the same strategies. Consequently, the ERG is unable to assess how well the searching was designed and conducted.
- The PubMed search presented in the CS contained incorrectly applied truncation within phrase searches e.g. "childhood epilep* encephalopath*". PubMed only permits truncation or phrase searching, the two operations do not work when combined in a single phrase search. The ERG corrected these errors prior to clarification, and re-ran the original and corrected searches to determine how many references were missed by the original strategy (search date 26 march 2019, see Appendix 1 for ERG searches). At the time of searching, the ERG's corrected version of the CS PubMed search retrieved 10,168 records, 6,069 of which were not retrieved by the company's original search. When ERG queried the truncation errors during clarification, the company responded that they found 19 new references after the truncation errors were corrected. As no corrected strategies were provided to the ERG, the ERG was unable to assess how effectively the corrections were made. It is still unclear how the company's corrected CS PubMed search varied so greatly when compared to the ERG version. As a consequence, the ERG remains concerned about the quality of the company's PubMed search.
- The Embase.com strategy in the CS did not include the phrase 'childhood epilepsy encephalopathy' or the abbreviation 'LGS'. The clarification response described incorporating these amendments and re-running the search, resulting in 600 additional records. The company did not provide a corrected search strategy in their clarification response, therefore the ERG was unable to assess how effectively the corrections were incorporated.
- The company's Cochrane Library strategy retrieved 207 records and contained basic phrase searching, without MeSH indexing. Prior to clarification, the ERG amended the CS search by including correct MeSH, truncation, phrase searching and added the abbreviation 'LGS' (see Appendix 1 for ERG searches). The amended ERG strategy retrieved 307 results. During clarification the ERG queried the lack of MeSH and free-text word variants. The company

responded that they had amended their Cochrane strategy to address these omissions, and no additional studies were retrieved. The ERG identified 100 references not picked up by the company's original search. As the company did not provide their corrected strategy, the ERG is unable to assess how well these omissions were addressed, and therefore remains concerned about the quality of the company's Cochrane Library search.

- The search of Heoro.com was considered adequate. The ERG attempted to re-run the search results on 26 March 2019, however significantly different results were retrieved. There appears to be an intermittent error with the Heoro.com resource itself, and the ERG was unable to fully investigate the Heoro.com strategy.

- The CRD databases, DARE, NHS EED and HTA, were searched using 'Lennox-Gastaut or Dravet' in the title only, and lacked relevant MeSH, truncation and other word variants. Prior to clarification, the ERG amended the CS search by including correct MeSH, truncation, phrase searching and added the abbreviations 'LGS' and 'SMEI' (see Appendix 1 for ERG searches). During clarification the ERG queried the lack of MeSH, abbreviations and free-text word variants. The company responded that they had amended their CRD strategy to address these omissions, and six additional studies were retrieved. The ERG search retrieved nine additional records, although as the company did not provide their corrected strategy, the ERG is unable to assess how well these omissions were addressed or why the ERG search retrieved more records. Therefore, the ERG remains concerned about the quality of the company's CRD Library search.

- The NIH Clinicaltrials.gov search reported in the CS did not include which fields were searched. In the clarification response, the company provided sufficient detail for the ERG to re-run their trials register search. The company's original search retrieved 30 results, whereas the ERG search resulted in 14 records. Although the company's search was conducted in November/December 2018 and the ERG re-ran the search in March 2019, it seems unlikely that trial progression would equate to such a difference in search results. The ERG is unable to account for this difference.

- The CS documented the conference proceeding searching and browsing, detailing URLs, years included and results per resource. The ERG considered the conference searching to be well documented.

4.1.2 Inclusion criteria

As stated above, the company conducted a systematic review to identify evidence on the efficacy and safety of drug interventions in Dravet syndrome and Lennox-Gastaut syndrome (to inform a parallel appraisal). The systematic review also identified papers relevant to the cost effectiveness of this appraisal which will be discussed in section 5. The eligibility criteria used to select studies for the review of clinical effectiveness is presented in Table 4.1. No specific exclusion criteria were reported.

Table 4.1: Eligibility criteria for the systematic review of clinical effectiveness

Inclusion Criteria	
Population	• Children and/ or adults with LGS or DS • Include mixed populations with other types of childhood epilepsy
Interventions	• Cannabidiol
Comparators	• Rufinamide, stiripentol: alone or in combination • Other antiepileptic drugs (valproate, topiramate, lamotrigine, clobazam, levetiracetam, felbamate, others); alone or in combination • Placebo/ usual care
Outcomes	• Seizure rate • Seizure severity • % seizure-free • % of participants achieving 50% reduction in seizure rate • % of participants achieving 75% reduction in seizure rate • Number of hospital or ICU admissions • Length of stay • Status epilepticus episodes • Mortality • Adverse events • Adherence to treatment/ study withdrawals
Study design	• Efficacy/safety: randomised controlled trials (RCTs); systematic literature reviews (SLRs) of RCTs for citation chasing
Publication date	• Full text publications: any • Conference abstracts: last 2 years (2016-18) • Most recent update of systematic reviews
Publication language	• Efficacy reviews: any
Source: Appendix D of the CS[1] AE = adverse event; CS = company submission; DS = Dravet syndrome; ICU = intensive care unit; LGS = Lennox-Gastaut syndrome; NICE = National Institute for Health and Clinical Excellence; QoL = quality of life; RCT = randomised controlled trial	

Briefly, the company searched for RCTs of cannabidiol compared to a range of treatments alone or in combination for a range of efficacy and safety outcomes in any language. The company further noted that '*Treatments are always given in combination, however we included RCTs that compare one drug with placebo, where all treatment arms also receive standard therapy. Details of concomitant medication were extracted*'.[1]

ERG comment:

- Two reviewers were involved in the selection of studies for the reviews which helps to minimise bias (confirmed in the response to letter of clarification question A5).[12]
- The ERG was unclear as to why conference abstracts were limited to the past two years and was unsure whether relevant data could have been missed.
- The ERG questioned whether ketogenic diet and vagus nerve stimulation were also valid comparators in the systematic review (as per the NICE scope).[16] The company confirmed that they were considered to be part of CCM of DS.[12]

- It is normally recommended to consider non-randomised evidence in relation to safety. This is particularly relevant as the main trials in the CS were of short duration (14 weeks) so longer term, rarer adverse events might not be identified. However, in response to clarification the company provided interim data on GWPCARE5, an ongoing open label study, designed to assess safety.
- The ERG was unclear on the exact number and nature of studies included in the systematic review. The PRISMA flow chart appeared to indicate that 24 studies were included for clinical effectiveness in the DS population. However there appeared to be eight in the table of included studies (Table 44 of the CS). The ERG also asked '*Table 43, question 9 (screening algorithm) indicates that randomised controlled trials (RCTs) which did not assess an included intervention (defined as CBD) would be excluded. Please explain why RCTs of other AEDs, which do not include a CBD arm and are not used in the submission, are in the list of included efficacy studies.*'[12] The company responded that GWPCARE 1, 2 and 5 were the only trials included for clinical effectiveness in the submission (reported in 10 publications). The remaining trials of treatments other than cannabidiol were included for transparency and completeness only.[12]
- The ERG checked the list of excluded studies. The company did not appear to have excluded relevant studies of cannabidiol.

4.1.3 Critique of data extraction

No information was provided on the number of reviewers who extracted data from included studies.

ERG comment: It is normally recommended that two reviewers are involved in data extraction for a systematic review to avoid bias and error.

4.1.4 Quality assessment

The company assessed the quality of the two main trials GWPCARE 1 and 2 and concluded that both trials were of high quality with a low risk of bias. The ongoing trial, GWPCARE5, was not quality assessed. The particular quality tool used was not referenced. Elements assessed were randomisation, allocation concealment, baseline comparability, researcher blinding, dropout imbalances, selective outcome reporting and use of intention to treat analysis.[1]

No information was provided on the number of reviewers who assessed the quality of included studies.

ERG comment: It is normally recommended that two reviewers are involved in the assessment of study quality to avoid bias and error. Results of the company's quality assessment and the ERG's assessment are presented in section 4.2.

4.1.5 Evidence synthesis

The company stated that no meta-analyses were conducted. Neither were there any indirect comparisons made comparing cannabidiol with other treatments. Both of these sections of the CS also included the following text:

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

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

Therefore, the only viable comparator is established clinical management.'[1]

ERG comment: The ERG agrees that, due to the variation in CCM in DS patients, it is unlikely that data would be available to support indirect treatment comparisons or mixed treatment comparisons of cannabidiol versus individual AEDs or specific combinations of AEDs. However, the ERG feels that the submission could have explored this option more fully. The ERG considers that an indirect comparison/network meta-analysis (NMA) may have been possible, based on the included trials (GWPCARE1 and GWPCARE2) and any RCTs where one of the listed comparator AEDs or non-pharmacological interventions was evaluated as an adjunct to CCM (comparator AED or non-pharmacological intervention + CCM versus CCM). It should also be noted that the use of a 'mixed' CCM comparator assumes that the effectiveness of CBD does not vary with the combinations of AEDs to which it is added. The ERG questions the validity of this assumption.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS identified two RCTs of cannabidiol (GWPCARE 1[14] and GWPCARE2[15]) and an ongoing open-label extension study[17] as relevant to the submission.

ERG comment: The ERG agrees that all relevant RCTs of cannabidiol were included in the submission. The company were asked to provide a protocol and all available results for the ongoing open-label extension study (GWPCARE5) in the CS.

4.2.1 Details of included cannabidiol studies

Both RCTs (GWPCARE1 and GWPCARE2) were conducted in patients aged two to 18 years with DS, whose seizures were incompletely controlled with previous AEDs and who had had at least four convulsive seizures per week in the past 28 days. The intervention was cannabidiol in addition to current clinical management (CCM) and the comparator was CCM without cannabidiol (i.e. CCM plus placebo). GWPCARE2 was a three-arm study, comparing two doses of cannabidiol (10 mg/kg/day and 20 mg/kg/day) in addition to CMM and CCM plus placebo, and GWPCARE1 compared cannabidiol (20 mg/kg/day) in addition to CCM and CCM plus placebo. Both trials had a dose escalation phase (14 days in GWPCARE1 and seven or 11 days in GWPCARE2) followed by a 12-week treatment period. Both trials were international in scope. GWPCARE1 included patients from the UK (four centres of which three recruited and 16 patients overall) but GWPCARE2 did not include patients from the UK.

A summary of study methodology, for GWPCARE1 and GWPCARE1, is provided in Table 4.2.

Table 4.2: Summary of study methodology for included trials

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

	•Use of rescue medication; •Safety, including Columbia Suicide Severity Rating Scale; •Palatability.	• Use of rescue medication; • Safety, including Columbia Suicide Severity Rating Scale; • Palatability.
Pre-planned subgroups	None	None
Source: Table 5 of the CS[1] DS = Dravet syndrome; QOL = quality of life		

ERG comment: The ERG notes that the evidence for CBD is based on international RCTs investigating patient-relevant outcomes. However, neither trial specified that participants should have failed to achieve seizure freedom having trialled at least two other appropriate AEDs to a maximally tolerated dose (as indicated by the company's proposed care pathway shown in Figure 2.1 of this report). The company was asked to provide clarification on how many participants, in the included studies, did not meet this criterion. Information provided confirmed that participants with fewer than two prior (discontinued) AEDs made up 16% in GWPCARE1 and 15% in GWPCARE2.[12] The ERG considers that, with respect to prior AED treatments, the data of most, but not all, of the trial participants clearly reflect the placement of CBD in the care pathway, as described in the CS.[1] (see Section 2.2 of this report). It should be noted that the remaining participants may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled.

The main issue relating to applicability of the trials to UK practice is the age limit of 18 years. Although DS has its onset in childhood the expected licensed indication is for patients two years of age and older with no upper age limit. It is expected that patients will continue taking cannabidiol into adulthood. As stated in section 3.1, adult patients with DS are not represented in the clinical trials in the CS.

It should be noted that both of the key studies included in the CS (GWPCARE1 and GWPCARE2 had a double-blind, treatment maintenance phase of just 12 weeks, which may not be considered adequate, given that the primary outcome measure was change in 28-day convulsive seizure frequency. The ERG, therefore, considers that it is particularly important to establish whether any reductions in seizure frequency, observed in short-term trials of new AEDs such as CBD, are sustained in the longer-term. Evidence is lacking about the long-term effectiveness of CBD. Furthermore, the exact link between reduction in convulsive seizures and any associated reductions in mortality cannot be determined from the two main randomised trials. The interim report for the ongoing open-label extension study, GWPCARE5[17] focusses on safety data; the report does not list either SUDEP or overall mortality in the effectiveness outcomes to be assessed, but does include SUDEP in a table of serious TEAEs reported in >1 patient.

The included studies evaluated different doses of CBD. GWPCARE1 evaluated only 20 mg/kg/day and GWPCARE2 evaluated both 10 mg/kg/day and 20 mg/kg/day. The company were asked to provide clarification on the proportion of patients expected to receive each dose, whether all patients would be expected to start on the lower dose and how eligibility for the higher dose would be established, and whether patients are expected to continue on the maintenance dose in the long-term (see section 3.2 of this report). The company provided a detailed response, summarised by the statement: *'It is anticipated that all patients will start with the lower maintenance dose. Increasing the dose in patients demonstrating good seizure reduction and tolerability to cannabidiol at 10mg/kg/day who the physician considers may gain additional seizure reduction by dose escalation will be at the physician's discretion. Patients not achieving good seizure reduction at 10mg/kg/day are unlikely to achieve efficacy by dose*

escalation.' In the model (scenario analysis), patients achieving good seizure reduction at 10 mg/kg/day and hence receiving dose escalation to 20 mg/kg/day, were defined as those who achieve ≥75% reduction in convulsive seizures. The ERG, therefore, considers that only clinical effectiveness data for the 10 mg/kg/day dose are relevant to the whole population, specified in the decision problem. Under the dose strategy described by the company, data on the clinical effectiveness of the 20 mg/kg/day dose are only relevant for the subgroup of patients who achieve ≥75% reduction in convulsive seizures on the starting dose of 10 mg/kg/day; neither the CS nor the CSRs provided data for this subgroup. The ERG notes that randomised evidence on the effectiveness of the 10 mg/kg dose of CBD is, limited to data from [redacted] patients in the GWPCARE2 study.[1]

The CS stated that there were no pre-planned subgroups in either trial. However, the CSRs for both GWPCARE1[14] and GWPCARE2[15] described a number of potentially relevant subgroup analyses under the heading 'Statistical Methods Planned in the Protocol and Determination of Sample Size.' The company were asked to provide results for all subgroup analyses conducted.

Company response: 'The primary and key secondary endpoints were analysed in the following pre-specified subgroups for GWPCARE2. Very similar subgroups were analysed in GWPCARE1. The sources are shown in the table below.

- *Age group (2-5 years, 6-12 years and 13-18 years)*
- *Sex (Male, Female)*
- *Region (US, Rest of the World)*
- *Clobazam use (Yes, No)*
- *Valproate use (Yes, No)*
- *Stiripentol use (Yes, No)*
- *Clobazam and Stiripentol use (Yes, No)*
- *Levetiracetam use (Yes, No)*
- *Topiramate use (Yes, No)*
- *Baseline average convulsive seizure frequency per 28 days (≤ observed tertile 1, > observed tertile 1 to ≤ observed tertile 2, > observed tertile 2) The observed tertile values were rounded to the nearest 5*
- *Number of current AEDs (<3, ≥3)*
- *Number of prior AEDs (<8, ≥8).*

These outcomes were not included in the Evidence Submission as they are not relevant to clinical prescribing or the cost-utility analysis. They are standard demographic subgroup analyses that are done as part of any SAP. Furthermore, as an orphan indication, these subgroups have small population numbers with low statistical powering.

For the recommended 10 mg/kg/day dose, no clinically relevant trends were seen in these subgroup analyses; the point estimates were similar to that for the ITT population, and CIs between them heavily overlapped.'

The company provided references to the relevant CSRs for the results of these subgroup analyses; these results are described and discussed further in section 4.2.6 of this report.

4.2.2 Statistical analysis of the included cannabidiol studies

The primary outcome for both of the included trials was percentage change in convulsive seizure frequency from baseline to 28 days. A power calculation to ensure adequate sample size for the primary outcome was reported for both of the included trials. For GWPCARE1, a sample of 100 patients would provide 80% power to detect 32% difference in primary outcome with a standard deviation of 56% and a two-sided significance level of 5%. The company reported that 120 patients were randomised and included in the analysis set. For GWPCARE2 the company stated that '*for a Wilcoxon-Mann-Whitney test comparing 2 distributions with a 2-sided significance level of 0.05, a sample size of 62 per group (after pooling the placebo groups) was required to obtain a power of at least 80%. This used data from the GWCARE1 trial.*'[1] The company reported that the calculated sample size of 186 was exceeded and 198 patients were randomised and included in the analysis set in GWPCARE2.

The company reported that all patients in GWPCARE1 received their allocated treatment. The following deviations from protocol were reported for GWPCARE2. Two patients randomised to 10 mg/kg/day and two to placebo were given dosing schedules for 20 mg/kg/ day in error. One patient on 10 mg/kg/day was withdrawn as they were randomised in error and did not receive the treatment.

The company stated that in both trials analysis of the primary outcome was based on intention-to-treat (ITT) analysis. In GWPCARE2 this comprised all randomised patients who received at least one dose of cannabidiol or placebo and who had at least one post-treatment efficacy outcome recorded. In GWPCARE1 ITT analysis was defined as all patients in the safety dataset who had at least one post-treatment efficacy outcome recorded.

The primary outcome in both trials was originally planned to be the percentage change in convulsive seizure frequency from baseline over 28 days. This was compared between treatment groups using a Wilcoxon rank sum test and the median difference was estimated with the Hodges-Lehmann method (described as Holmes-Lehmann in the CS). However, this was changed in GWPCARE2 as part of a protocol amendment. The new analysis of the primary outcome used a negative binomial regression model as it was a better method for over-dispersed count data and accounts for varying lengths of patient follow-up.

The proportions of patients with at least a 25%, 50%, 75% and 100% reduction in seizures were compared between treatment groups using a Cochran-Mantel-Haenszel test. The CGIC score was compared between treatment groups using an ordinal logistic regression model.

ERG comment:

- The statistical analyses appeared to have been conducted appropriately. However, the ERG is concerned about the change of analysis method for the primary outcome in GWPCARE2.
- ITT analysis should be conducted on all patients randomised to a treatment whether or not that treatment was received. In GWPCARE1 the ITT analysis included all 120 randomised patients and in GWPCARE2 it included 198 of the 199 patients.

4.2.3 Trial participant characteristics

Table 4.3 shows the characteristics of the participants in GWPCARE1 and GWPCARE2.

Table 4.3: Baseline characteristics in GWPCARE1 and GWPCARE2

Baseline characteristics*	**GWPCARE1**		**GWPCARE2**		
	Cannabidiol 20 mg/kg/day + CCM	**Placebo + CCM**	**Cannabidiol 10 mg/kg/day + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**
Number in analysis	61	59	[redacted]	[redacted]	[redacted]
Age	Mean 9.7 SD 4.7y Median 9.1y Range 2.5 to 18y	Mean 9.8 SD 4.8y Median 9.2y Range 2.3 to 18.4y	[redacted]	[redacted]	[redacted]
Gender	35 male	27 male	[redacted]	[redacted]	[redacted]
Ethnicity	White: 44 Black/African American: 2 Asian: 1 Not Applicable: 11 Other: 3	White: 50 Black/African American: 2 Asian: 0 Not Applicable: 6 Other: 1	[redacted]	[redacted]	[redacted]
Location	USA: 35 France: 12 Poland: 6 United Kingdom: 8	USA: 37 France: 6 Poland: 8 United Kingdom: 8	[redacted]	[redacted]	[redacted]
Baseline seizure types	Convulsive (tonic, clonic, tonic-clonic or atonic), myoclonic, partial, absence seizures		[redacted]		

Baseline characteristics*	**GWPCARE1**		**GWPCARE2**		
Baseline seizure frequency	All seizures: median 24.0 per 28 days Convulsive seizures: median 12.4/28 days; range 3.9 to 1717	All seizures: median 41.5 per 28 days Convulsive seizures: median 14.9/28 days; range 3.7 to 718	[redacted]	[redacted]	[redacted]
Prior AED use	Mean 4.6 AEDs; SD 4.3	Mean 4.6 AEDs; SD 3.3	[redacted]	[redacted]	[redacted]
Concurrent AED use	Mean AEDs: 3.0; SD 1.0 Clobazam: 40 Valproate: 37 Stiripentol: 30 Levetiracetam: 16 Topiramate: 16 Ketogenic diet: 6 Vagus nerve stimulation: 6	Mean AEDs: 2.9; SD 1.0 Clobazam: 38 Valproate: 34 Stiripentol: 21 Levetiracetam: 17 Topiramate: 15 Ketogenic diet: 4 Vagus nerve stimulation: 9	[redacted]	[redacted]	[redacted]

Source: CS[1] and GWPCARE1 CSR[14]and GWPCARE2 CSR[15]
Footnote: *Missing data were taken from the full CSRs (including separate files containing Tables and Figures), which were provided by the company in their clarification response. Where there were discrepancies between the CS and the CSRs, data were taken from the CSRs.

CCM = current clinical management

GWPCARE1 had a total of 120 patients and GWPCARE2 198. The mean age across both trials was approximately nine. Female and male participants were represented equally in the trials. The overall percentage of women in GWPCARE1 was 48% and in GWPCARE2 was 53%. Both trials had predominantly participants who identified as white (GWPCARE1 78%, GWPCARE 2: 89%). Around half of the participants across the two trials were from the USA. Patients had used on average four or five prior AEDs although as mentioned in Section 3.1 there was a large range of prior treatments (0 to 26). The average number of concurrent treatments was three, although again the range was large.

ERG comment:

- The trials reflect a younger population with Dravet syndrome (mean age of nine and all participants under 18 as per the trials' inclusion criteria)
- The ERG notes that Black and Asian people appear to be underrepresented across the two trials.

The ERG asked a number of questions relating to the population defined in the decision problem[12] and the populations included in the key trials, GWPCARE1 and GWPCARE2. The following have been previously discussed in Section 3.1 so will only be briefly summarised here.

- The company was asked, given the numbers of prior AEDs used by participants, if the trials had more severe populations than might be expected in clinical practice? They stated that polypharmacy on this scale is not uncommon but did not provide any associated references. However, the ERG considered the company's response to be reasonable.
- The company was asked if the number of concurrent treatments in the trials reflected UK practice. They stated that it did but did not provide any accompanying support from clinical experts for this statement. This may benefit from discussion at committee.
- The company was asked how many UK centres and patients were involved in GWPCARE1 (GWPCARE2 did not have any UK patients). They stated that there were four UK sites in GWPCARE1, of which three recruited, and overall there were 16 UK patients in GWPCARE1. The company stated that there were too few UK patients in the trial to provide efficacy outcomes for UK patients specifically. This appears reasonable.
- The ERG asked the company if there was evidence to suggest an association between baseline seizure frequency and the patient's current clinical management. (ERG question A14). The company responded:

'In general, the data support the conclusion that existing prescribing is highly heterogeneous and patients are refractory to existing treatment modalities.

Due to the orphan nature of the disease, no formal pre-specified or post-hoc analysis to assess the association between baseline seizure frequency and CCM treatment was done.

Based on an informal analysis of the patient level data in GWPCARE1 and GWPCARE2 combined, there is a strong correlation between baseline seizure burden and number of concomitant AEDs, as is to be expected (see the figure below). A descriptive analysis of drug proportions amongst patients stratified by seizure frequency at baseline (also in the figure below) for the most commonly used pharmacological agents does not show any obvious trends.' [12]

The ERG is satisfied with this explanation.

4.2.4 Risk of bias assessment for included cannabidiol studies

The quality assessment of the key trials, reported in Appendix D of the CS, recorded judgements alone and did not include any supporting information. It was not clear how many reviewers were involved in the quality assessment process. The particular quality tool used was not referenced. Elements assessed were randomisation, allocation concealment, baseline comparability, researcher blinding, dropout imbalances, selective outcome reporting and use of intention to treat analysis.[1] The company's assessments of GWPCARE1 and GWPCARE2 are in Table 4.4.

Table 4.4: Quality assessment GWPCARE1

	GWPCARE1	GWPCARE2
Randomisation appropriate?	Yes	Yes
Treatment concealment adequate?	Unclear	Unclear
Baseline comparability adequate?	Unclear	Unclear
Researcher blinding adequate?	Yes	Yes
Dropout imbalances?	No	No
Outcome reporting selective?	No	No
Intention to treat?	Yes	Yes
Overall risk of bias?	Low	Low
Source: Table 46, Appendix D of the CS[1]		

ERG comment: Overall the trials were rated by the company as high quality and at low risk of bias. However, the ERG noted that trials would not normally receive a high rating when both treatment concealment and baseline comparability elements have been described as 'unclear'. The ERG re-assessed the two trials against the criteria above. Based on information in the CSRs, treatment concealment appeared to be adequate. Furthermore, the company appeared to have considered baseline comparability in their analyses. The quality assessment did not include an item on the adequacy of participant blinding; but based on information about the matched composition of the intervention and placebo, provided in the CSRs, the ERG considers that participant blinding was adequate. There was some imbalance in dropout (GWPCARE1 CBD 20 mg/kg/day arm: 9/61 [14.8%]; CCM arm: 3/59 [5.1%] and GWPCARE2 CBD 20 mg/kg/day arm: 6/67 [9.0%]; 10 mg/kg/day arm: 3/67 [4.5%]) and CCM arm: 0). However, analysis was conducted based on an intention-to-treat analysis including these patients.

4.2.5 Efficacy results

The efficacy results for GWPCARE1 and GWPCARE2 are shown in Table 4.5. This table includes results for outcomes reported in the CS, with additional data (e.g. baseline and endpoint values, interquartile range (IQR)) as provided in the company's clarification response.[12] and CSRs.[14, 15] Where results differed between sources, the company CSRs were used. The number of convulsive seizure-free days per 28-day period, a key outcome used in the cost effectiveness modelling but not listed in the company's definition of decision problem, is provided; again, results for this outcome were taken from the CSR tables provided in the company's clarification response.

Table 4.5: Efficacy results of GWPCARE1 and GWPCARE2

	GWPCARE1		GWPCARE2		
	Cannabidiol 20 mg/kg/day + CCM	**Placebo + CCM**	**Cannabidiol 10 mg/kg/day + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**
Number randomised	61	59	[redacted]	[redacted]	[redacted]
Study duration	14 weeks		[redacted]		
Primary outcome: Convulsive seizure frequency per 28 days					
Baseline convulsive seizure frequency	Median 12.4 (IQR 6.2 to 28.0	Median 14.9 (IQR 7.0 to 36.0)	[redacted]	[redacted]	[redacted]
Treatment period convulsive seizure frequency	Median 5.9 (IQR 3.2 to 17.3)	Median 14.1 (IQR 4.2 to 31.1)	[redacted]	[redacted]	[redacted]
% change in convulsive seizures during treatment	Median -38.9 (IQR -69.5 to – 4.8)	Median -13.3 (IQR -52.5 to 20.2)	[redacted]	[redacted]	[redacted]
Comparison to placebo	Median difference -22.8 (95% CI: -41.1 to -5.4); p = 0.012)	NA	[redacted]	[redacted]	[redacted]
Secondary outcomes					
Total seizure frequency per 28 days					
Baseline total seizure frequency	Median 24.0 (IQR 10.4 to 141.0)	Median 41.5 (IQR 12.0 to 367.0)	[redacted]	[redacted]	[redacted]

	GWPCARE1		GWPCARE2		
Treatment period total seizure frequency	Median 13.7 (IQR 4.8 to 137.2)	Median 31.1 (IQR 7.7 to 282.6)	[redacted]	[redacted]	[redacted]
% change in total seizures during treatment	Median -28.6 (IQR -70.4 to -4.0)	Median -9.0 (IQR -51.4 to 19.6)	[redacted]	[redacted]	[redacted]
Comparison to placebo	Difference 22.8 (95% CI: 5.4, 41.1)	NA	[redacted]	[redacted]	[redacted]
Response rate					
≥50% reduction in convulsive seizures	26 (42.6%)	16 (27.1%)	[redacted]	[redacted]	[redacted]
Comparison to placebo	OR 2.00 (95% CI: 0.93 to 4.30); p = 0.078	NA	[redacted]	[redacted]	[redacted]
75% reduction in convulsive seizures	14 (23.0%)	7 (11.9%)	[redacted]	[redacted]	[redacted]
Comparison to placebo	OR 2.21 (95% CI: 0.82 to 5.95); p = 0.112	NA	[redacted]	[redacted]	[redacted]
100% reduction in convulsive seizures during treatment period	3 (4.9%)	0 (0%)	[redacted]	[redacted]	[redacted]
Comparison to placebo	Difference 4.9% (95% CI: -0.5 to 10.3); p = 0.083	NA	[redacted]	[redacted]	[redacted]
Use of rescue medication	36 (59.0%)	41 (69.5%)	[redacted]	[redacted]	[redacted]
Global impression of change					
CGIC improvement in overall condition	37 (60.7%)	20 (33.9%)	[redacted]	[redacted]	[redacted]

	GWPCARE1		GWPCARE2		
Status epilepticus					
Convulsive status epilepticus at baseline	0	1 (1.7%)	[redacted]	[redacted]	[redacted]
Convulsive status epilepticus in treatment period	1 (1.6%)	0	[redacted]	[redacted]	[redacted]
Non-convulsive status epilepticus at baseline	2 (3.3%)	3 (5.1%)	[redacted]	[redacted]	[redacted]
Non-convulsive status epilepticus in treatment period	2 (3.3%)	2 (3.4%)	[redacted]	[redacted]	[redacted]
Quality of life					
Overall QOLCE score mean (SD) change from baseline to end of treatment	5.4 (14.60)	3.8 (9.93)	[redacted]	[redacted]	[redacted]
Comparison to placebo	Mean difference 1.5 (95% CI: -3.8 to 6.8); p = 0.577	NA	[redacted]	[redacted]	[redacted]
Convulsive seizure-free days per 28 days					
Baseline period	NR	NR	[redacted]	[redacted]	[redacted]
Treatment period	NR	NR	[redacted]	[redacted]	[redacted]
Change from baseline	NR	NR	[redacted]	[redacted]	[redacted]
Comparison to placebo	NR		[redacted]	[redacted]	[redacted]

Source: CS Tables 10 and 11[1]and CSRs[14, 15]

*[redacted]

CGIC = Caregiver Global Impression of Change; IQR = interquartile range; OR = odds ratio; QOLCE = Quality of Life in Childhood Epilepsy

ERG comment: The ERG notes that only GWPCARE2 provides effectiveness data for the recommended dose of CBD, 10 mg/kg/day, which is specified as the starting dose for all patients in the company's response to clarification.[12] Patients in GWPCARE2, who received 10 mg/kg/day CBD in addition to CCM, achieved better seizure frequency outcomes than those who received CCM + Placebo. For convulsive seizures the company changed the primary outcome analysis method to use negative binomial regression which gave a rate ratio of [redacted] A sensitivity analysis using a Wilcoxon rank sum test and the Hodges-Lehmann estimate of the median difference (the original analysis plan) [redacted] A higher proportion of patients in the 10 mg/kg/day CBD group achieved at least a 50% reduction in convulsive seizures, during the treatment period, than in the placebo group ([redacted]). [redacted] patients in the CBD group of GWPCARE2 and [redacted] in the placebo group achieved freedom from convulsive seizures for the whole 14-week treatment period.

Patients in the 10 mg/kg/day CBD group of GWPCARE2 experienced fewer seizures overall, during the 14-week treatment period, than those in the placebo group ([redacted]).

The ERG does not consider the clinical effectiveness evidence for the 20 mg/kg/day dose of CBD to be directly relevant to this submission. Since the company have stated in their clarification response,[12] that only those patients who the physician considers may gain additional seizure reduction by dose escalation will receive the 20 mg/kg/day dose, and this has been defined as those experiencing ≥75% reduction in convulsive seizures on the 10 mg/kg dose, then data on the clinical effectiveness of the 20 mg/kg/day dose are only relevant for this specific subgroup. Neither the CS nor the CSRs provided data on the effectiveness of 20 mg/kg/day CBD in the subgroup of patients who had responded adequately to the 10 mg/kg/day dose.

The company were asked to provide the results of comparisons between the 20 mg/kg/day and 10 mg/kg/day groups in GWPCARE2, for all outcomes where these were available. The company stated, in their clarification response,[12] that: '*No formal pre-specified test for significance between the CBD groups was included in the SAPs.*' The ERG notes that the CS.[1] Section B.2.6, includes the statement that: '*A higher proportion of patients in the 20 mg CBD group achieved at least a 75% reduction in convulsive seizures (25%) compared with the 10 mg group (11%) and the placebo group (3%).*' The ERG therefore questions the validity of the criteria for dose escalation, described above.

The CS did not include any data on the long-term effectiveness (>14 weeks) of CBD + CCM compared to placebo + CCM. The CS included some interim results from an ongoing open-label extension study (GWPCARE5), see section 4.2.9 of this report. However, the ERG does not consider these results to be directly applicable to this submission, since for [redacted] of participants with DS, the modal dose during the treatment period was >[redacted] The overall mean modal dose for DS patients was [redacted]). The overview of trial design, given in the interim report for this study,[17]states that: [redacted]

[redacted]

We asked the company to comment on the relatively large placebo response observed across the trials included in the CS. The company provided a detailed, referenced response summarised by the following points:

- Large placebo effects are well documented in epilepsy clinical trials. Although no study has formally assessed placebo effects across DS studies, they have been consistently observed in LGS studies.
- A comparison of the size of the placebo effect in GWPCARE1 and GWPCARE2 relative to those seen in other studies in DS is not possible, as there is too much heterogeneity in study design between trials. Nonetheless, numerical comparisons have been published for LGS trials. The primary endpoint (median percent change in convulsive seizure frequency from baseline) in GWPCARE3 (which studied a CBD dose of 10 mg/kg/day in patients with LGS) showed a placebo effect that was at the upper end of, but still in line with, those seen with other agents.
- Even with this placebo effect, a robust treatment effect on the primary and all secondary endpoints was achieved at a CBD dose of 10 mg/kg/day. Assessed across the totality of the clinical development plan, this treatment effect was consistently observed across two studies at a dose of 10 mg/kg/day and four studies at a dose of 20 mg/kg/day. It was further maintained in the open-label extension study.
- The hypothesised sources of placebo effects cited in the literature are either an artefact of the clinical trial environment, or a short-term psychological response to "something new" in patients/caregivers with a high level of clinical need. These effects are unlikely to apply and persist in clinical practice, especially given the highly drug-resistant nature of DS patients.

The ERG agrees with that the placebo effects observed in CBD trials are at the upper end of, but still broadly in line with, those seen with other agents.

4.2.6 Subgroup analysis for included cannabidiol studies

The CS (Section B.2.7) stated that '*no subgroup analyses were conducted*.' However, the CSRs for both key trials (GWPCARE1[14] and GWPCARE2[15]) reported a number of subgroup analyses. The company was asked for further details of the subgroup analyses. They indicated that the primary and key secondary endpoints were analysed for GWPCARE2 and very similar groups for GWPCARE1: Age group (2-5 years, 6-12 years and 13-18 years), Sex (Male, Female), Region (US, Rest of the World), Clobazam use (Yes, No), Valproate use (Yes, No), Stiripentol use (Yes, No), Clobazam and Stiripentol use (Yes, No), Levetiracetam use (Yes, No), Topiramate use (Yes, No), Baseline average convulsive seizure frequency per 28 days (≤ observed tertile 1, > observed tertile 1 to ≤ observed tertile 2, > observed tertile 2), Number of current AEDs (<3, ≥3) and Number of prior AEDs (<8, ≥8). The company further stated that '*These outcomes were not included in the Evidence Submission as they are not relevant to clinical prescribing or the cost-utility analysis. They are standard demographic subgroup analyses that are done as part of any SAP. Furthermore, as an orphan indication, these subgroups have small population numbers with low statistical powering. For the recommended 10 mg/kg/day dose, no clinically relevant trends were seen in these subgroup analyses; the point estimates were similar to that for the ITT population, and CIs between them heavily overlapped.*'[12] Results of the subgroup analysis are presented in Figure 4.1 for the primary endpoint of GWPCARE2 only as this trial compared the proposed dose of CBD (10 mg/kg/day) to placebo.

Figure 4.1:Subgroup analysis of the primary endpoint (10 mg/k/day CBD vs. placebo): negative binomial regression effect modification analysis of convulsive seizure count during baseline and treatment periods (ITT analysis set)

[redacted]

The ERG agrees with the company that the very small numbers of patients in some subgroups mean that the results of these analyses cannot be considered reliable. However, we do not agree that these analyses are '*standard demographic subgroup analyses that are done as part of any statistical analysis plan*' and are '*not relevant to clinical prescribing or the cost-utility analysis.*' The subgroup analyses relating to current and prior AED use and to baseline seizure frequency are specific to this clinical topic area.

[redacted]

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

The CS clinical effectiveness results section did not include any results for health-related quality of life outcomes.[1] Overall results for the Quality of Life in Childhood Epilepsy (QOLCE) score were provided in the company's clarification response and these are reproduced in Table 4.5 of this report.

The innovation section of the CS (Section B.2.12) stated that: '*It is also important to consider that, for some patients with DS, their quality of life may be impaired as much by the side-effects of current treatments and polypharmacy as by the seizures themselves. For those patients who respond to CBD, there may be an opportunity to reduce their concomitant drug burden over time. This may be achieved either through a reduction in dose or through complete elimination of concomitant AEDs, thereby potentially reducing the overall drug-related adverse event burden in these patients.*'[1]

ERG comment: The ERG notes that none of the included trials provided data on reduction or complete elimination of concomitant AEDs. In GWPCARE1 and GWPCARE2, all medications or interventions for epilepsy were required to be stable for four weeks prior to screening and patients had to be willing to maintain a stable regimen throughout the study.

4.2.8 Safety results

This section considers the information about adverse events provided in the CS. A more detailed breakdown of AEs and serious adverse events (SAEs) was provided by the company in their clarification response, along with interim results from the open-label extension study, GWPCARE5.[17] These results are summarised in Table 4.6. Table 4.7 provides details of those individual, treatment-related adverse events which occurred in at least 3% of patients, in any of the included studies. These data appear to indicate a pattern of gastrointestinal and 'tiredness'-related AEs in patients taking CBD, as well as a detrimental effect on markers of liver function. With respect to markers of liver function, the CS[1] reported '*Raised liver aminotransferases were reported with CBD and were seen more often with the higher dose of CBD (20 mg/kg/day), when the patient had elevated transaminases at baseline, or when CBD was taken with concomitant valproate or clobazam. Cases of raised liver transaminases resolved either spontaneously (without dose reduction or interruption of CBD treatment during the studies) or with dose adjustments of CBD or concomitant AEDs'* The rates of individual, treatment-related AEs were generally higher in the 20 mg/kg/day CBD groups than in the 10 mg/kg/day CBD group.

The company's clarification response[12] included the following additional detail on SAEs for the two main included studies:

GWPCARE1

'In total, 10 patients (8.3%) developed at least 1 (all-causalities) TEAE that led to discontinuation and withdrawal from the study: 9 patients in the CBD group (14.8%) (although 1 patient was reported as 'Withdrawn by the Investigator') and 1 patient in the placebo group (1.7%).

Treatment-related TEAEs leading to discontinuation of IMP were reported in 8 CBD patients (13.1%). No treatment-related TEAEs leading to discontinuation of IMP were reported in the placebo group.

Five patients reported at least 1 TEAE leading to withdrawal that was also considered a serious TEAE.

The majority of TEAEs leading to discontinuation were considered treatment-related (25/28 events [89.3%]). The only exceptions were 1 event of moderate convulsion (reported as a serious TEAE) in a CBD patient, 1 event of severe liver function test abnormal in a placebo patient, and 1 event of mild pyrexia in a CBD patient (NB. the latter patient also experienced decreased appetite and fatigue [both moderate] concurrently that were considered treatment-related and were also reported as the reason for withdrawal).

The most common treatment-related TEAE leading to discontinuation was somnolence, which was reported in 5 CBD patients (8.2%). For 4 of these patients, the event was reported as severe and of these, 2 were also considered serious. The remaining patient experienced moderate somnolence. For each patient, the event resolved following cessation of IMP and withdrawal from the trial.

Collectively, 4 CBD patients had liver-related TEAEs that led to withdrawal (PTs: AST increased, GGT [reported term: GGT 115 U/L], transaminases increased, and liver function test abnormal); all events were moderate or severe, considered treatment-related, and most resolved (4/5 events; 80%). Treatment-related decreased appetite leading to discontinuation was reported in 3 CBD patients (4.9%). For 2 of these patients, the event was moderate and for 1 patient it was severe and considered serious. For each patient, the event resolved following cessation of CBD and withdrawal from the trial.

Treatment-related fatigue, AST increased, convulsion, and hypotonia leading to discontinuation of IMP were each reported in 2 CBD patients and led to those patients withdrawing from the trial. One patient

experienced moderate fatigue and severe AST increased concurrently (along with severe GGT and severe platelet count), all of which led to withdrawal, were considered serious TEAEs, and resolved following cessation of CBD. Another patient experienced convulsion and hypotonia concurrently (along with somnolence and aggression), all of which were severe in intensity and resolved following cessation of CBD.

All other TEAEs leading to discontinuation were reported in a single patient only. Only 1 TEAE leading to discontinuation was ongoing following withdrawal of the patient from the trial. This CBD patient experienced moderate transaminases increased; the event was not considered a serious TEAE and the patient experienced no other TEAEs leading to withdrawal.'

GWPCARE2

'[redacted]'

GWPCARE5

No narrative detail was provided for GWPCARE5. The interim report for GWPCARE5[17] included the following information about SAEs for the overall study population (LGS and Dravet syndrome combined):

[redacted]

As can be seen from Table 4.6, the numbers of withdrawals due to adverse events occurring in DS patients during the open-label extension study were not reported. The interim report [redacted][17] [redacted][17] [redacted] The relevant tables, detailing numbers of withdrawals and reasons for withdrawal, were missing from the interim report provided by the company in the clarification response.[12]

ERG comment: The ERG is concerned that the apparently high rate of withdrawals from GWPCARE5, which were not attributable to adverse events, together with the dose escalation in some patients (up to a maximum of 30 mg/kg), may indicate a loss of efficacy over time. No evidence has been provided to support the long-term efficacy (beyond 14 weeks) of the recommended CBD dose (10 mg/kg).

The RCTs included in the CS were too small and of too short duration to provide a full picture of the adverse event profile of CBD and the open-label extension study, GWPCARE5 does not provide data about the recommended CBD dose (10 mg/kg/day).

The safety results for GWPCARE1, GWPCARE2 and GWPCARE5 are shown in Tables 4.7 to 4.8. This Table includes results for outcomes reported in the CS, with additional data taken from the company's clarification response and CSRs.

Table 4.6: Safety results of GWPCARE1, GWPCARE2 and GWPCARE5

	GWPCARE1		GWPCARE2			GWPCARE5
	Cannabidiol 20 mg/kg/day + CCM	**Placebo + CCM**	**Cannabidiol 10 mg/kg/day + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol (variable dose) DS patients**
Number in safety analysis set*	61	59	[redacted]	[redacted]	[redacted]	[redacted]
No (%) with adverse events	57 (93.4%)	44 (74.6%)	[redacted]	[redacted]	[redacted]	[redacted]
No (%) with serious adverse events	10 (16.4%)	3 (5.1%)	[redacted]	[redacted]	[redacted]	[redacted]
No (%) withdrawals due to adverse events	9 (14.8%)	1 (1.7%)	[redacted]	[redacted]	[redacted]	[redacted]
No (%) Treatment-related adverse events	43 (70.5%)	16 (27.1%)	[redacted]	[redacted]	[redacted]	[redacted]
No (%) Treatment-related serious adverse events	5 (8.2%)	0	[redacted]	[redacted]	[redacted]	[redacted]
No (%) withdrawals due to TRAEs	8 (13.1%)	0	[redacted]	[redacted]	[redacted]	[redacted]
No (%) of deaths	0	0	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS [1], Clarification response[12] and CSRs[14, 15, 17]

* All randomised patients who took at least one dose of study medication were included and analysed according to the treatment received; **not considered to be treatment-related

CCM = current clinical management; TRAE = treatment-related adverse event

Table 4.7: Treatment-related adverse events occurring in ≥3% of patients in any study GWPCARE1, GWPCARE2 or GWPCARE5

	GWPCARE1		GWPCARE2			GWPCARE5
	Cannabidiol 20 mg/kg/day + CCM	**Placebo + CCM**	**Cannabidiol 10 mg/kg/day + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol (variable dose) DS patients**
No in safety analysis set*	61	59	[redacted]	[redacted]	[redacted]	[redacted]
No of patients (%) with						
Abdominal pain	2 (3.3%)	1 (1.7%)	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	13 (21.3%)	2 (3.4%)	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	10 (16.4%)	1 (1.7%)	[redacted]	[redacted]	[redacted]	[redacted]
Gait disturbance	3 (4.9%)	0	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
GGT increased	4 (6.6%)	0	[redacted]	[redacted]	[redacted]	[redacted]
LFT abnormal	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Transaminases increased	4 (6.6%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Toxicity to various agents	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	3 (4.9%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	13 (21.3%)	3 (5.1%)	[redacted]	[redacted]	[redacted]	[redacted]
Increased appetite	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Ataxia	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Balance disorder	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Convulsion	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]

	GWPCARE1		GWPCARE2			GWPCARE5
	Cannabidiol 20 mg/kg/day + CCM	**Placebo + CCM**	**Cannabidiol 10 mg/kg/day + CCM**	**Cannabidiol 20 mg/kg/day + CCM**	**Placebo + CCM**	**Cannabidiol (variable dose) DS patients**
Hypotonia	2 (3.3%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Lethargy	7 (11.5%)	2 (3.4%)	[redacted]	[redacted]	[redacted]	[redacted]
Poor quality sleep	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Sedation	1 (1.6%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Psychomotor disorder	1 (1.6%)	2 (3.4%)	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal behaviour	1 (1.6%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Irritability	4 (6.6%)	0	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	19 (31.1%)	4 (6.8%)	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS [1], Clarification response[12] and CSRs[14, 15, 17]
* All randomised patients who took at least one dose of study medication were included and analysed according to the treatment received
CCM = current clinical management

4.2.9 Supporting efficacy evidence from the ongoing GWPCARE5

GWPCARE5 is an ongoing, open-label extension of GWPCARE1 and GWPCARE2 and also of GWPCARE3 and GWPCARE4 (Lennox-Gastaut syndrome). It aims to investigate the safety of cannabidiol in children and adults with inadequately controlled DS or LGS who had previously participated in one of the previous trials. The trial is estimated by the company to complete in June 2019. As yet the trial has published only interim findings in abstract format.

The primary outcome is incidence of adverse events and other measures of safety with patients being followed up for a maximum of three years. These data have been included in the previous section on adverse events. Efficacy outcomes are also being assessed through comparison with baseline values in the randomised study in which the patient participated.

The interim efficacy results were based on 14% of the 278 participants who had completed the study after a median of 50 weeks (range 1 to 99 weeks). There was a median 44% to 57% reduction in convulsive seizures from a baseline of 12 per 28 days and a median 49% to 67% reduction in total seizures from a baseline frequency of 32 per 28 days with cannabidiol. Fifty-two percent of the 278 patients were still undergoing treatment, and 34% had withdrawn from the study.[1]

ERG comment: The ERG does not consider this open-label extension study to be directly applicable to this submission, since it does not include follow-up data from patients continuing on an uninterrupted maintenance dose of 10 mg/kg/day. The overview of trial design, given in the interim report for this study,[22] states that:

[redacted]

4.2.10 Ongoing trials

Apart from GWPCARE5, the company did not list any other relevant ongoing trials.

ERG comment: The company were further asked '*Are there any other ongoing studies that would provide relevant information for this submission (such as longer-term follow-up data relating to changes in mortality including sudden unexpected death in epilepsy (SUDEP))? If so, when will data become available for these studies*?'[12] The company stated that there were not.

There is a lack of long-term data on the effects of CBD on Dravet syndrome. The main randomised trials, as previously stated, are of 14 weeks' duration so cannot provide long-term data on SUDEP and other deaths. The exact link between reduction in convulsive seizures and any associated reductions in mortality cannot be determined from the two randomised trials.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable

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

Not applicable.

4.5 Conclusions of the clinical effectiveness section

The CS included a systematic review of the evidence for CBD for DS. From this review the company identified and presented evidence from two RCTs (GWPCARE1 and GWPCARE2) and an open-label extension study (GWPCARE5). Both RCTs (GWPCARE1 and GWPCARE2) were conducted in patients aged two to 18 years with DS, whose seizures were incompletely controlled with previous AEDs and who had had at least four convulsive seizures per week in the past 28 days. Although the decision problem did not specify any age restriction and the expected licenced indication for Epidyolex® is for patients two years of age and older, neither of the key trials used in the submission (GWPCARE1 and GWPCARE2) included adult patients (over the age of 18 years). Therefore, adults with DS are not represented in the CS.

The company expects to place CBD as an add on treatment for refractory seizures in people aged two years or older once two other appropriate AEDs trialled to a maximum dose have failed to achieve seizure freedom. However, across the two trials approximately 16% of patients had received no or one previous (discontinued) AEDs. It should be noted that these patients may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled.

One of the RCTs had 16 UK patients, the other had none. This is most relevant when considering the nature of background current clinical management, which is the comparator in the trials. Current clinical management is considered to be a 'basket' of choices of AED and although the company conducted a number of subgroup analyses based on the presence or absence of various AEDs, they assumed that there were no treatment interaction effects. The ERG questions this assumption.

A major limitation of the evidence is the small size of the data set relating to the 10 mg/kg/day cannabidiol dose to be used in practice. Just 66 patients in GWPCARE2 and none in GWPCARE1 received the 10 mg/kg/dose. In the open-label extension study, GWPCARE5, the average dose was [redacted] making this study less relevant to the decision problem.

A further limitation is the short-term nature of the RCTs (14 weeks). There is a lack of long-term efficacy and safety data particularly based on the 10 mg/kg/day dose. Any observations of reduction in seizures in the short-term trials, particularly convulsive seizures, may not be sustained in the long-term and the effects on outcomes relating to mortality (especially SUDEP) are unknown.

Patients in GWPCARE2, who received 10 mg/kg/day CBD in addition to CCM, experienced fewer convulsive seizures and fewer seizures overall, during the 14-week treatment period, than those in the placebo group. Alongside this, safety data appear to indicate a pattern of gastrointestinal and 'tiredness'-related AEs in patients taking CBD, as well as a detrimental effect on markers of liver function. The ERG is concerned that the apparently high rate of withdrawals from GWPCARE5, which were not attributable to adverse events, together with the dose escalation in some patients (up to a maximum of 30 mg/kg/day), may indicate a loss of efficacy over time. No evidence has been provided to support the long-term efficacy (beyond 14 weeks) of the recommended CBD dose (10 mg/kg/day).

5. COST EFFECTIVENESS

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

5.1.1 Searches performed for cost effectiveness section

The company submission reported that a rigorous systematic review was carried out to identify relevant publications for the efficacy, safety and development of economic models for the use of cannabidiol in Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS).[1] The main submission presented one set of searches used to inform both the clinical and cost effectiveness content for both LGS and DS in Appendix D.[1] As the searching for the whole submission was conducted at once, the ERG's appraisal and comments are presented in section 4.1.1 of this report.

5.1.2 Inclusion/exclusion criteria used in the study selection

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 5.1.

Table 5.1: Eligibility criteria for the systematic literature reviews

PICOS	Inclusion criteria	Exclusion criteria
Patient population	• Any age • Any gender • Any race • Has DS/SMEI • Or a caregiver of a patient with DS (only applicable to utility and cost searches)	No data reported on relevant population
Intervention	• Any intervention included in the efficacy review • Placebo (only applicable to utility search) • Best supportive care (only applicable to utility and costs searches) • No intervention (only applicable to utility and costs searches)	No data reported on relevant intervention
Comparator	• Any of the included interventions • Placebo (only applicable to cost effectiveness studies search) • Best supportive care (only applicable to cost effectiveness studies search) • No comparator (only applicable to utility and costs searches)	No data reported on relevant comparator

PICOS	Inclusion criteria	Exclusion criteria
Outcomes(s) 1 **(Published economic evaluations)**	• Cost per life-year saved • Cost per QALY gained • Costs saved	No data reported on a relevant outcome
Outcomes(s) 2 **(Utility studies)**	• Utility values • Other quality of life measures using an established questionnaire	No data reported on a relevant outcome; qualitative study reporting views
Outcomes(s) 3 **(Cost/resource use studies)**	• Direct costs • Indirect and informal costs • Resource use	No data reported on a relevant outcome
Study design 1 **(Cost effectiveness analysis studies)**	• Cost-benefit analyses • Cost-effectiveness analyses • Cost-utility analyses • Budget Impact models • Cost minimisation models • Other economic models • Systematic reviews were used for citation chasing only • Studies only available as conference abstracts were included if they reported sufficient relevant data to inform model development or parameterisation	Other study design
Study design 2 **(Utility studies)**	• Randomised controlled trials • Observational studies • Systematic reviews were used for citation chasing only • Studies only available as conference abstracts were included if they reported sufficient relevant data to allow analysis	Other study design
Study design 3 **(Cost/resource use studies)**	• Randomised controlled trials	Other study design

PICOS	Inclusion criteria	Exclusion criteria
	• Observational studies • Database studies • Systematic reviews were used for citation chasing only • Studies only available as conference abstracts were included if they reported sufficient relevant data to inform model development or parameterisation	
Source: Appendix G, I and H of the CS [1].		

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies.

5.1.3 Included/excluded studies in the cost effectiveness review

In total, five unique economic modelling publications met the pre-defined eligibility criteria, including four analyses of HTA submissions of stiripentol[23-26] and an economic evaluation reporting a cost utility Markov model of stiripentol for the treatment of patients with DS who have been unresponsive to concomitant treatment with clobazam and valproate, for the Canadian jurisdiction.[27] No cost effectiveness studies appraising CBD were identified from the search.

The search yielded six utility studies that were relevant to the reference case of patients with DS who were either receiving a drug therapy of interest or were reporting on quality of life (QoL) regardless of treatments.[5, 25, 27-30] However, none of the studies estimated utilities for health states defined by number of convulsive seizures and convulsive seizure-free days, two main parameters in the economic model.

The search for studies reporting cost and resource use identified nine publication that were relevant for the UK.[5, 23, 24, 28, 31-35] However, none of these studies reported costs or resource use for health states defined by number of convulsive seizures and convulsive seizure-free days.

ERG comment: The rationales for excluding CE studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.2: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Cohort state transition model		B.3.2
States and events	• convulsive seizure free, • ≤8 convulsive seizures, • >8 - ≤25 convulsive seizures, • >25 convulsive seizures, • death	Absolute instead of relative reductions were preferred to define health states as they more accurately captures costs and quality of life.	B.3.2
Comparators	Current clinical management	Market research in the UK	B.3.3
Population	People with DS who are aged 2 years or older, whose seizures are inadequately controlled by current clinical management.	Consistent with the therapeutic indication proposed to the European Medicines Agency.	B.3.2
Treatment effectiveness	Treatment effectiveness was estimated based on the frequency of convulsive seizures, number of days without convulsive seizures and discontinuation rates.	The pivotal clinical trials (GWPCARE1 and GWPCARE2) and the open label extension study (GWPCARE5).	B.3.3
Adverse events	Adverse events were based on a pooled analysis considering both the DS and LGS pivotal clinical trials.	GWPCARE1, GWPCARE2, GWPCARE3 and GWPCARE4.	B.3.3
Health related QoL	Utilities were estimated using patient vignettes that were based on the health states included in the cost utility model.	No relevant utility values were identified by the systematic literature review.	B.3.4
Resource utilisation and costs	The cost categories included in the model were treatment costs, health state costs and mortality costs.	Resource utilisation and unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF), Personal Social Services Research Unit (PSSRU), Prescription cost analysis, published research and expert opinion.	B.3.5
Discount rates	Discount of 3.5% for utilities and costs.	As per NICE reference case.	Table 15
Subgroups	No subgroups were explored		B.3.9
Sensitivity analysis	Both DSA and PSA were performed as well as scenario analyses.		B.3.8

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Yes	
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Partly	Different (combinations of) AEDs were not considered as separate comparators.
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	No	Time horizon was restricted to 15 years.
Synthesis of evidence in outcomes	Systematic review (SLR)	Yes	
Measure of health effects	Quality adjusted life years (QALYs)	Yes	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	No	The patient vignette instrument that was used is not considered a standardised and validated instrument by the ERG.
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	No	VAS scores estimated using patient vignettes were used.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic modelling	Partly	Not all parameters have been included in

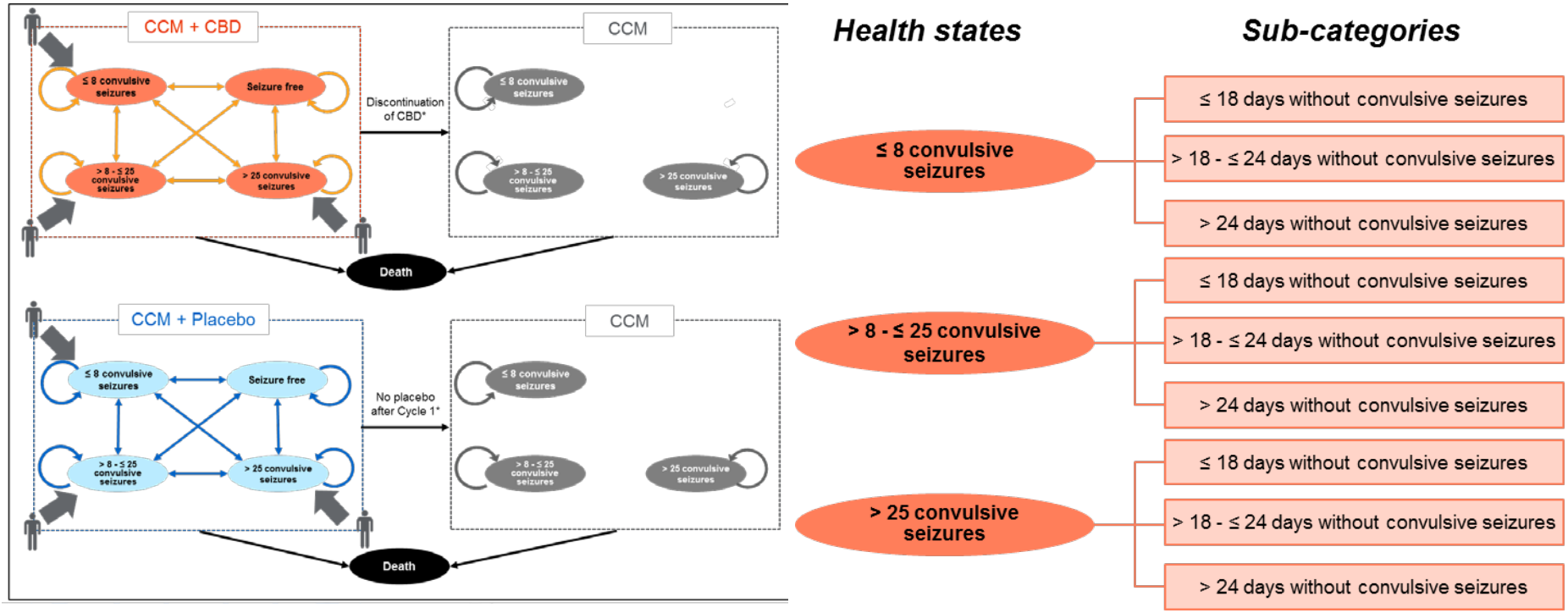
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
			the probabilistic analyses.
NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review			

5.2.2 Model structure

The company developed a cohort state transition model using Microsoft Excel®. The model consisted of five health states, i.e. convulsive seizure free, ≤8 convulsive seizures per 28 days, >8 - ≤25 convulsive seizures per 28 days, >25 convulsive seizures per 28 days, and death (Figure 5.1). Convulsive seizures were defined in the clinical study reports of GWPCARE1 and GWPCARE2 as tonic-clonic, tonic, clonic or atonic seizures.[14, 15] As improvements in patients' quality of life were assumed by the company to relate to the total number of convulsive seizures and number of convulsive seizure-free days, each of the convulsive seizure frequency health states was categorised into three sub-categories based on the number of convulsive seizure-free days experienced in the corresponding health state, i.e. ≤ 18 convulsive seizure-free days, > 18 - ≤ 24 convulsive seizure-free days, and > 24 convulsive seizure-free days (Figure 5.1). Patients receiving CCM plus CBD could transit between the four convulsive seizure frequency health states for the first nine cycles (i.e. 27 months), after which patients stayed in the same health state for the remaining duration of the analysis. Patients receiving CCM without CBD could transit between the convulsive seizure frequency health states during the first cycle only and returned to their baseline convulsive seizure frequency state afterwards (i.e. after three months). The transition probabilities for the first cycle were derived from the GWPCARE1 and GWPCARE2 trials. For the first nine cycles, time-dependent transition probabilities for CBD were estimated using the open-label extension study, GWPCARE5. Patients entered the model via one of the three health states with convulsive seizures (i.e. ≤ 8, > 8 - ≤ 25, > 25 convulsive seizures per month). At each cycle, patients receiving CBD plus CCM either continued to receive CBD, discontinued CBD or died. When patients discontinued CBD treatment, they returned to their baseline convulsive seizure frequency and remained in this state until the end of the time horizon. Patients receiving CCM without CBD could not discontinue treatment.

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

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



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

Source: Based on Figure 3 and 4 of the CS [1]

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

a) The health states defined in the model solely focus on convulsive seizures and convulsive seizure free days. Our concerns relate to the fact that patients with DS who have a reduction in convulsive seizures or who have become convulsive seizure-free, are still likely to suffer from non-convulsive seizures. For example, the health state convulsive seizure-free might include patients who are not free from non-convulsive seizures. When patients are still suffering from non-convulsive seizures, they are at risk of SUDEP and non-SUDEP. In response to clarification question B1a[12] the company clarified that in the GWPCARE studies non-convulsive seizures were an explanatory endpoint only. Nevertheless, it should be noted that overall seizure frequency is listed as a secondary outcome in the GWPCARE studies. Additionally, the company clarified that CBD showed an improvement in non-convulsive seizures. Furthermore, the company provided an overview of the number of non-convulsive seizures across the convulsive seizure frequency-defined health states and clarified that within the treatment period the median number of non-convulsive seizures reduces substantially across convulsive-seizure-based health states. In response to clarification question B1b[12] the company incorporated epilepsy-related SUDEP and non-SUDEP probabilities for the convulsive-seizure free health state that are >0.
b) In the model, patients receiving CCM transfer back to their baseline seizure frequency after the first cycle. In the CS and in response to clarification question B2,[12] the company clarified that this was done as a placebo effect was observed in both the GWPCARE1 and GWPCARE2 studies and argued it was not reasonable to assume that these effects would be sustained in clinical practice. The ERG does not agree with this approach as this effect may also be present in the CBD group (and hence is part of the demonstrated effects) and these patients do not transfer back to their baseline seizure frequency after the first cycle. Removing the presumed placebo effect for CCM while not removing it for CBD would likely result in an overestimated treatment effect for CBD (similar to that which might be expected with pre-post comparisons). Unfortunately, due to the complexity and the lack of transparency of the model, the ERG was not able to explore a scenario in which patients in the CCM group stay in their respective health state after the first cycle instead of transferring back to their baseline health state. The ERG considers that this assumption is most likely to bias the economic model in favour of CBD. The company further argued that patients discontinuing CBD treatment are transferred back to their baseline seizure frequency. However, as the number of days without convulsive seizures (and corresponding utility values) seems to be treatment-dependent favouring CBD, this is not seen as a conservative approach. This last comment is further elaborated upon in sections 5.2.6 and 5.2.8 (and considered in ERG analyses).
c) In response to clarification question B3b,[12] the company clarified that given the cycle length of three months, it was deemed not useful to apply a half-cycle correction. The ERG believes this to be a reasonable assumption which is likely to have minor implications to the results of the model.

5.2.3 Population

In line with its anticipated marketing authorisation, CBD was considered for the treatment of patients with DS who are aged two years or older and in whom the condition is inadequately controlled by the

established current clinical management (CCM) in the UK.[1] This is in line with the final scope issued by NICE. [16]

Baseline demographic characteristics such as mean age, weight and disease severity (i.e. frequency of convulsive seizures and the number of days without convulsive seizures) were obtained from GWPCARE1 and GWPCARE2, and were assumed to be the same for the entire cohort of patients entering the model, i.e. assumed to be treatment independent (Table 5.4).

Table 5.4: Key baseline patient characteristics as applied in the CS base-case model based on patient-level data of phase three GWPCARE1 and GWPCARE2 studies

	<12 years		**≥12 years**	
Demographic characteristics at baseline	[redacted]	[redacted]	[redacted]	[redacted]
% of patients	[redacted]	[redacted]	[redacted]	[redacted]
Mean age	[redacted]	[redacted]	[redacted]	[redacted]
Mean weight	[redacted]	[redacted]	[redacted]	[redacted]
Frequency of convulsive seizures at baseline				
≤ 8 convulsive seizures per 28 days	[redacted]		[redacted]	
> 8 - ≤ 25 convulsive seizures per 28 days	[redacted]		[redacted]	
> 25 convulsive seizures per 28 days	[redacted]		[redacted]	
Number of days without convulsive seizures (per 28 days) at baseline				
≤ 8 convulsive seizures per 28 days				
≤ 18 days	[redacted]		[redacted]	
> 18 - ≤ 24 days	[redacted]		[redacted]	
> 24 days	[redacted]		[redacted]	
> 8 - ≤ 25 convulsive seizures per 28 days				
≤ 18 days	[redacted]		[redacted]	
> 18 - ≤ 24 days	[redacted]		[redacted]	
> 24 days	[redacted]		[redacted]	
> 25 convulsive seizures per 28 days				
≤ 18 days	[redacted]		[redacted]	
> 18 - ≤ 24 days	[redacted]		[redacted]	
> 24 days	[redacted]		[redacted]	
Source: Based on Table 15 of the CS[1]				

ERG comment: The main concern of the ERG relates to the extent to which the population of the trial is representative for the target population of the model. The anticipated marketing authorisation for CBD focuses on the treatment of refractory seizures which are inadequately controlled by established clinical management. As indicated by the response of the company to clarification question A3b,[12] a small proportion (16% in GWPCARE1 and 15% in GWPCARE2) of the patients included in GWPCARE1 and GWPCARE2 do not match this definition (i.e. <2 prior, discontinued AEDs). It is unclear to what extent these patients have influenced the effectiveness parameters included in the model.

However, it should be noted that these patients may still meet the criterion of inadequate seizure control with first-line and at least one adjunctive AED, as AEDs are not always discontinued even when seizures are not controlled. Moreover, due to the limited number of patients aged 18-55 years in GWPCARE1 and GWPCARE2, it is unclear to what extent results of these trials hold true for the adult population.

5.2.4 Interventions and comparators

In the proposed licensed indication (currently awaiting marketing authorisation in the UK) for DS, CBD oral solution is recommended to be administered by means of a starting dose of 2.5 mg/kg twice daily (5 mg/kg/day) increased to a maintenance dose of 10 mg/kg/day [1]. In the CS, the base-case analysis utilises the maintenance dose of 10 mg/kg/day as the company assumes that the majority of patients will receive this dose in clinical practice.

In the GWPCARE2 trial, [14] efficacy of CBD was examined in two different dosages, i.e. CBD 10 mg/kg/day in addition to CCM, and CBD 20 mg/kg/day in addition to current clinical management. In the GWPCARE1 trial, [33] efficacy of CBD was examined based on a dosage of CBD 20 mg/kg/day in addition to CCM. In the open-label extension study (GWPCARE5), mean modal dose during treatment was [redacted]. [17]

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

In the economic model, CCM was established as the following concomitant therapies: valproic acid, clobazam, stiripentol, topiramate and levetiracetam. The company assumed that, although the ketogenic diet and vagus nerve stimulation are issued in the final scope by NICE and clinical guideline 137 as second/third-line treatments alongside AEDs for DS, [8, 16] they were not recommended for all patients due to issues concerning adherence, adverse effects and long term complications such as bone fractures, kidney stones, decreased growth (ketogenic diet) and low efficacy (vagus nerve stimulation). As a result, they were explicitly not incorporated as CCM in the economic model.

ERG comment: The main concerns of the ERG relate to: a) the use of GWPCARE1 and the open label study GWPCARE5 to derive input parameters for the model as the prescribed dose in both studies is higher than the CBD 10 mg/kg/day in the base-case and the anticipated license; b) the combination of all AEDs as CCM.

a) In response to clarification question B7a, [12] the company stated that it is not clinically meaningful to compare patients on 10 mg/kg/day and 20 mg/kg/day doses of CBD. Furthermore, the company stated that the SmPC defines 10 mg/kg/day as the maintenance dose in clinical practice, with a small proportion of patients benefiting from escalation up to 20 mg/kg/day. However, both GWPCARE1 and GWPCARE5 focused on substantially higher dosages of CBD (20 mg/kg/day or more). The company stated (question B12a) that GWPCARE1 was only used to model scenarios in which a minority of patients is escalated to 20 mg/kg/day. In addition, in the CS base-case, transition probabilities for cycles 2-9 in the model were derived from the overall population in GWPCARE5. The company justifies this by stating '*the transition probabilities derived from GWPCARE5 are considered to be a good approximation for those that would have been observed on 10 or 20 mg/kg/day, and are not intended in the model to represent outcomes on doses above 20mg/kg/day.*'[12]

However, the company also stated (response to clarification question B7) '*that a minority of patients may achieve seizure-freedom on the higher dose*', seemingly suggesting that there is a difference in treatment effectiveness between CBD 10 mg/kg/day and CBD 20 mg/kg/day. Hence, it is questionable whether the GWPCARE5 evidence can be used for the maintenance dose of 10 mg/kg/day. To reflect the evidence from GWPCARE5, the ERG has explored the impact of a higher maintenance dose after the first cycle, by examining the results of a scenario in which the maintenance dose was increased to 20 mg/kg/day in accordance with results of the GWPCARE5 study in which [redacted] the mean modal dose was [redacted].[17]

b) Contrary to (the ERG's interpretation of) the final scope issued by NICE, different (combinations of) AEDs were not considered as separate comparators. This implies that the (cost) effectiveness of CBD is assumed to not vary with the combination to which it is added. However, the Clinical Study Reports (CSRs) for the key trials (GWPCARE1 and GWPCARE2) indicate that the company has also conducted a number of subgroup analyses that show an effect on the primary outcome of the presence of a specific AED or number of AEDs in the CCM combination. In response to clarification question B9a,[12] the company stated that given the orphan nature of the condition and the heterogeneous nature of the patients, it is not clinically or statistically meaningful to compare the intervention to individual or specific combinations of AEDs. Consequently, it is unclear to the ERG what the impact is of assuming that the (cost) effectiveness of CBD does not vary with different AED combination.

5.2.5 Perspective, time horizon and discounting

The analysis takes an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits, with a 15-year time horizon.

ERG comment: The main concerns of the ERG relate to the time horizon of the model (15 years). It seems unlikely that all differences in costs and effects are captured in this time frame. For instance, patients with DS are at risk of higher mortality depending on their seizure frequency. In response to clarification question B3,[12] the company clarified that given the lack of long-term data a 15-year time horizon was considered appropriate to provide insight into future costs and benefits. This is inconsistent with the NICE guide to the methods of technology appraisal indicating that a lifetime time horizon is required when alternative technologies lead to differences in survival or benefits that persist for the remainder of a person's life. Given the survival differences in (non-) SUDEP, a lifetime time horizon would have been appropriate. Therefore, the ERG extended the time horizon to 20 years (the maximum allowed in the submitted economic model)

5.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness are the pivotal clinical trials (GWPCARE1 and GWPCARE2) and the open label extension study (GWPCARE5). It should be noted that GWPCARE1 is not used in the base-case analyses, only in the scenario analyses that used CBD 20 mg/kg/day. These studies are used to obtain evidence for the frequency of convulsive seizures, number of days without convulsive seizures, discontinuation rates and adverse events for both CCM plus CBD and CCM. GWPCARE2 was mainly used to inform treatment effectiveness during cycle one, while GWPCARE5 (in combination with assumptions) was used for subsequent cycles. Moreover, treatment effectiveness was estimated separately for patient subgroups <12 years and ≥12 years.

Transition probabilities between convulsive seizure frequency health states

During the first cycle, transition probabilities between convulsive seizure frequency health states (see section 5.2.2 for more details) were based on GWPCARE2 for both CCM plus CBD and CCM. For CCM plus CBD cycles two to nine were informed using the open label extension study (GWPCARE5). After cycle nine, patients receiving CCM plus CBD were assumed to remain in their current convulsive seizure frequency health states. Once CBD was discontinued, patients were assumed to revert back to their baseline convulsive seizure frequency health state.

First cycle for CCM plus CBD and CCM

Transition probabilities between convulsive seizure frequency health states (based on GWPCARE2) are reported in Table 5.5 below for both CCM plus CBD and CCM.

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

		<12 years				≥12 years			
		Seizure	≤8 seizures	8-25 seizures	>25 seizures	Seizure	≤8 seizures	8-25 seizures	>25 seizures
CCM plus CBD 10 mg mg/kg/day	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCM	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]The transition probabilities for CBD 20 mg/kg/day plus CCM (not used in the company base-case) are presented in CS Table 17.

Cycles two to nine for CCM plus CBD

Transition probabilities between convulsive seizure frequency health states (based on the GWPCARE5 trial) are reported in Table 5.6 below for CCM plus CBD.

Table 5.6: Transition probabilities between convulsive seizure frequency health states for CCM plus CBD 10 mg/kg/day (cycles two to nine)a

		<12 years				≥12 years			
		Seizure	≤8 seizures	8-25 seizures	>25 seizures	Seizure	≤8 seizures	8-25 seizures	>25 seizures
Cycle 2	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		<12 years				≥12 years			
		Seizure	≤8 seizures	8-25 seizures	>25 seizures	Seizure	≤8 seizures	8-25 seizures	>25 seizures
Cycle 7	Seizure free	[redacted]							
	≤8 seizures								
	8-25 seizures								
	>25 seizures								
Cycle 8	Seizure free	[redacted]							
	≤8 seizures								
	8-25 seizures								
	>25 seizures								
Cycle 9	Seizure free	[redacted]							
	≤8 seizures								
	8-25 seizures								
	>25 seizures								

[a]The transition probabilities for CBD 20 mg/kg/day plus CCM (not used in the company base-case), are identical as those presented for CBD 10 mg/kg/day plus CCM in this Table (see also CS Table 17).

After cycle nine for CCM plus CBD

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

CBD treatment discontinuation

CBD discontinuation probabilities were dependent on the convulsive seizure frequency health state and were only applied for CCM plus CBD. Treatment discontinuation probabilities for cycle one were based on GWPCARE2, while GWPCARE5 was used for subsequent cycles (Table 5.7). The CBD discontinuation probabilities estimated for subsequent cycles were assumed to remain constant over time for the remaining duration of the time horizon.

Table 5.7: CBD 10 mg/kg/day treatment discontinuation probabilities per health state[a]

	<12 years		≥12 years	
	Cycle 1	Subsequent cycles	Cycle 1	Subsequent cycles
Seizure free	[redacted]	[redacted]	[redacted]	[redacted]
≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]
8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]
>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]

[a]The discontinuation probabilities for CBD 20 mg/kg/day plus CCM (not used in the company base-case) are presented in CS Table 19.

Number of days without convulsive seizures

As described in section 5.2.2, the convulsive seizure frequency health states were subdivided into three groups based on the number of convulsive seizure-free days per 28 days (categories: ≤18 days, >18 - ≤24 days, >24 days, see Table 5.8). This subdivision was incorporated to reflect the impact of number of convulsive seizure-free days on HRQOL and was assumed to be dependent on the treatment received, as well as the convulsive seizure frequency health states.

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

		<12 years			≥12 years		
		≤18 days	>18 - ≤24 days	>24 days	≤18 days	>18 - ≤24 days	>24 days
CCM plus CBD 10 mg/kg/day	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCM	Seizure free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤8 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8-25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>25 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]The probabilities for CBD 20 mg/kg/day plus CCM (not used in the company base-case) are presented in CS Table 18.

Mortality

Patients in the convulsive seizure-free health state were assumed to experience all-cause age-dependent mortality probabilities derived from the national life tables for England.[36] Disease-specific mortality

was incorporated for the other convulsive seizure frequency health states (Table 5.9). DS mortality in terms of SUDEP and non-SUDEP deaths, was retrieved from published literature.[37]

The Dravet-specific SUDEP rate of 9.32/1000-person-years, reported by Cooper et al. (2016),[37] was converted to a 0.23% mortality probability per cycle (i.e. per three months). This mortality probability was assumed for the >8 - ≤25 convulsive seizure frequency health state. To calculate mortality probabilities for the other convulsive seizure frequency health states, risk ratios of [redacted] and [redacted] were assumed for the ≤8 and >25 convulsive seizure frequency health states respectively (relative to the >8 - ≤25 convulsive seizure frequency health state; no evidence was provided for these risk ratios).

To obtain the non-SUDEP mortality probabilities, the Dravet-specific mortality rate (15.84/1000-person-years) was subtracted from the Dravet-specific SUDEP rate (9.32/1000-person-years).[37] Similarly for SUDEP mortality, this mortality rate (6.52/1000-person-years) was converted to a mortality probability per cycle (i.e. 0.16% per three months) and assumed for the >8 - ≤25 convulsive seizure frequency health state. Subsequently, risk ratios of [redacted] and [redacted] were assumed for the ≤8 and >25 convulsive seizure frequency health states respectively (relative to the >8 - ≤25 convulsive seizure frequency health state; no evidence provided for these risk ratios).

Table 5.9: Disease-specific mortality probabilities

	SUDEP	Non-SUDEP
Seizure free	[redacted]	[redacted]
≤8 seizures	[redacted]	[redacted]
8-25 seizures	[redacted]	[redacted]
>25 seizures	[redacted]	[redacted]

ERG comment: The main concerns of the ERG relate to: a) using evidence based on CBD 20 mg/kg/day as a proxy for CBD 10 mg/kg/day for month 3 to month 27 (cycles two to nine) for convulsive seizure frequency and CBD discontinuation; b) assuming constant CBD treatment effectiveness after month 27 (i.e. CBD patients were assumed to remain in the same health state until CBD discontinuation or death while assuming constant CBD discontinuation); c) lack of face validity of the treatment discontinuation probabilities (treatment discontinuation does not always increase with higher convulsive seizure frequencies and is 0% for some health states); d) the number of days without convulsive seizures is assumed to be dependent on both treatment allocation and health state; e) the lack of appropriate explanation and justification regarding the calculation of epilepsy-related mortality rates and; f) using DS evidence that is mainly based on patients aged <18 years for adults.

a) For convulsive seizure frequency and CBD discontinuation, only the first model cycle (month 0 to month 3) was informed by evidence based on CBD 10 mg/kg/day. For month 3 to month 27, the company used evidence from GWPCARE5. In this OLE study, the median (IQR) CBD dose was 21 (15-25) mg/kg/day at 12 weeks and 25 (21-25) mg/kg/d at 96 weeks[38] (mean modal dose during the treatment period for the DS and LGS populations was [redacted] respectively[17]). Hence, the company assumed that evidence from CBD 20 mg/kg/day or higher could be used for CBD 10 mg/kg/day. The company justified this assumption (clarification responses B7 and B12) by stating that there is a lack of a broad dose response on efficacy endpoints between the two doses in GWPCARE2 and GWPCARE3 for DS and LGS respectively. However, no supporting evidence was provided by the company. Moreover, the company stated (response to clarification question B7) 'that a minority of

patients may achieve seizure-freedom on the higher dose', seemingly suggesting that there is a difference in treatment effectiveness between CBD 10 mg/kg/day and CBD 20 mg/kg/day. The company also states (in response to clarification question A15) that 'no formal pre-specified test for significance between the CBD groups was included in the SAPs.' Consequently, the ERG considers the extrapolation beyond month 3 to be potentially biased (as indirect evidence is used). As the company did not explore the impact of this assumption (as requested in clarification question B12c), the ERG performed a scenario analysis.

b) After month 27, CBD evidence is lacking and the company assumed constant treatment effectiveness by assuming that CBD patients remain in the same health state until CBD discontinuation or death while assuming a constant CBD discontinuation probability. The ERG considers this to be uncertain and requested the company (clarification question B4b) to perform a scenario analysis assuming waning of treatment effect over time. Unfortunately, the company did not explore this scenario. Consequently, the ERG performed a scenario analysis to examine the potential impact of this assumption. Additionally, it should be noted that these clinical effectiveness data from GWPCARE5 were only introduced in the cost effectiveness sections of the CS (these were not discussed in the interim CSR nor the clinical effectiveness section of the CS) and thus could not be fully assessed by the ERG.

c) The CBD discontinuation probabilities reported in the original CS as well as those reported in the revised assessment accompanying the company's clarification response seemed to lack face validity. Potentially due to the relatively small sample size, CBD discontinuation does not always increase with higher convulsive seizure frequencies and CBD discontinuation probabilities reported in the original CS also contained 0% probabilities, which the company acknowledged is unlikely to be fully representative of a real-world setting. Given the apparent lack of face validity; the ERG used alternative CBD discontinuation probabilities in its base-case. These alternative CBD discontinuation probabilities were informed by Table 2 of the revised assessment of the company. Except the CBD discontinuation probabilities for the 8-25 convulsive seizures and >25 seizures convulsive seizures health states (for <12 years) reported in Table 2 of the revised assessment, these were averaged (given the reported probabilities do not always increase with higher convulsive seizure frequencies as would be expected). Moreover, the long-term CBD discontinuation probabilities (i.e. beyond cycle 9) reported in Table 2 of the revised assessment were not used by the ERG given these probabilities were not appropriately supported by evidence (see Table 5.10 for the CBD discontinuation probabilities used in the ERG base-case). Moreover, using long-term CBD discontinuation probabilities that are different than for cycles 2-9 is not appropriately supported by evidence, nor was it requested by the ERG.

Table 5.10: CBD 10 mg/kg/day treatment discontinuation probabilities used by the ERG

	<12 years		≥12 years	
	Cycle 1	Subsequent cycles	Cycle 1	Subsequent cycles[a]
Seizure free	[redacted]	[redacted]	[redacted]	[redacted]
≤ 45 seizures	[redacted]	[redacted]	[redacted]	[redacted]
45-110 seizures	[redacted]	[redacted]	[redacted]	[redacted]
> 110 seizures	[redacted]	[redacted]	[redacted]	[redacted]

d) The company assumed that the number of days without convulsive seizures is dependent on both treatment allocation and health state. The company justified this in response to clarification question B15 by stating that CBD impacts both the frequency of convulsive seizures and the number of convulsive seizure-free days per month and that treatment-independent number of convulsive seizure-free days would thus contradict evidence from the pivotal trials. Nevertheless, it would have been informative to explore the impact of this assumption on the results (requested in clarification question B15). Moreover, the number of convulsive seizure-free days per month is only considered as an exploratory outcome in the pivotal trials and is not discussed in the clinical effectiveness sections of the CS. Finally, including treatment dependent number of days without convulsive seizures might overestimate the treatment effect of CBD and is thus adjusted in ERG analyses (see section 5.2.8 for more detail).
e) The lack of justification for the risk ratios used to calculate epilepsy-related mortality probabilities is considered problematic by the ERG. The only justification provided the CS was 'The calculated risk ratios ensured that the annual SUDEP rate for the >25 seizure frequency category was 1.3%; i.e. consistent with the upper limit of published SUDEP death rates'. The ERG considers this justification to be insufficient. Firstly it is unclear why the upper limit of published SUDEP mortality probability is considered applicable to the >25 convulsive seizure frequency health state particularly given this health state is only based on convulsive seizures and does not (directly) capture non-convulsive seizures. Secondly, no evidence has been provided to support the relationship (e.g. type and magnitude) between convulsive seizure frequency and (non-)SUDEP mortality for the population of interest. Thirdly, no justification was provided for the risk ratio of 1.6.

   Given this lack of evidence for the chosen risk ratios, the ERG assumed equal (non-)SUDEP mortality for the convulsive seizure frequency health states as derived from Cooper et al[37] while assuming the risk ratio of 0.42 (=1.4/3.3[39]) for the convulsive seizure-free health state. This resulted in three monthly SUDEP and non-SUDEP probabilities of 0.23% and 0.16% respectively[37] for the convulsive seizure frequency health states while this was 0.10% and 0.07% respectively for the convulsive seizure-free health state. Nevertheless, these (non-)SUDEP probabilities for the convulsive seizure-free health state are potentially underestimated given the seizure-free definition in Trinka et al[39] (used to obtain the risk ratio of 0.42) is presumably not restricted to convulsive seizures only, potentially inducing bias in favour of CBD (given more patients are seizure free after CBD).
f) It is questionable whether the DS evidence can be extrapolated to patients aged over 18 years given the large majority of patients ([redacted] based on GWPCARE1 and GWPCARE2) is aged under 18 (with the remainder only 18 and a few months). The potential impact of this issue on the cost effectiveness is unclear to the ERG.

5.2.7 Adverse events

Adverse events were based on a pooled analysis considering both the DS and LGS phase III trials (GWPCARE1, GWPCARE2, GWPCARE3 and GWPCARE4). The adverse event probabilities were assumed to remain constant for the duration of the time horizon (see CS Table 21).

ERG comment: The main concerns of the ERG relate to: a) the selection of adverse events for the model (based on different thresholds for CBD and CCM); b) combining LGS and DS evidence to obtain

adverse event probabilities and; c) assumptions regarding the occurrence of adverse events in the revised assessment.

a) The company used different thresholds to select the most frequently occurring treatment-emergent adverse events of special interest for CBD and CCM (either events reported in ≥3% or ≥1% of patients respectively). In response to clarification question B17 the company clarified that this selection of adverse events is a priori defined in the statistical analysis plan and is unrelated to observed incidences in the clinical trials. Given the clarification provided by the company, the ERG believes this approach is reasonable.
b) It is unclear to the ERG why the company combined data from both LGS and DS to obtain adverse event probabilities and thus implicitly assumed that the safety profile is identical for both diseases. Moreover, it is unclear to the ERG whether the adverse event probabilities are only based on CBD 10 mg/kg/day evidence (or also based on CBD 20 mg/kg/day). However, the ERG does not believe this is a major issue given that the impact of adverse events in the economic model is minimal (see also response to clarification question B17b).
c) In the revised assessment, the company assumed that adverse events could only occur until cycle 9. In the original CS base-case, adverse events could occur during the entire CBD treatment. This adjustment was not requested by the ERG and no clinical evidence was provided to support this assumption. However, the ERG does not consider this to be particularly problematic given the minimal impact adverse events are expected to have on the estimated cost effectiveness.

5.2.8 Health-related quality of life

Utility values were estimated for every sub-category (i.e. ≤ 18 convulsive seizure-free days, > 18 - ≤ 24 convulsive seizure-free days, and > 24 convulsive seizure-free days; see Figure 5.1) within the four convulsive seizure health states: convulsive seizure free, ≤8 convulsive seizures, >8 - ≤25 convulsive seizures, and >25 convulsive seizures.

Utilities were estimated using patient vignettes that were based on the health states included in the model. In total, 23 vignettes were developed. Patients and/or caregivers of patients with DS or other forms of epilepsy were asked to complete a quality of life questionnaire and to score patient vignettes using a visual analogue scale (VAS). In total, there were 28 respondents; 20 caregivers and eight patients [1]. The average VAS scores obtained in the survey were converted to values between 0 and 1 for the base-case analysis by using the following formula: $U_{HSi} = VAS_{HSi}/100$. In addition, in the sensitivity analyses, the VAS scores were converted using conversions based on time trade-off and standard gamble methods by using formulas taken from Torrance et al.[40] A summary of the utility values used in the base-case model is provided in Table 5.11.

As mentioned in section 5.2.2, patients receiving CCM only revert to baseline convulsive seizure frequency after the first cycle and patients receiving CBD revert to their baseline convulsive seizure frequency after discontinuation of treatment. However, given that the sub-categories of convulsive seizure-free days differ per health state between CBD and CCM, it is important to note that the corresponding baseline utilities also potentially differ between CBD and CCM. The resulting baseline utilities per health state are displayed in Table 5.12.

Health-related quality of life data identified in the review

According to the CS, the SLR identified six studies that were relevant to the NICE reference case of patients with DS who were either receiving a drug therapy of interest or were reporting on quality of

life regardless of treatments. However, none of the studies were used by the company as they stated that the studies did not estimate utilities for health states defined by number of convulsive seizures and convulsive seizure-free days.

Table 5.11: Health state utility values

State	Sub-category	Utility value	Reference	Justification
No convulsive seizures	≤ 18 convulsive seizure-free days	Not estimated	CS[1]	No convulsive seizures
	>18-≤24 convulsive seizure-free days	Not estimated	CS[1]	No convulsive seizures
	> 24 convulsive seizure free days	[redacted]	Vignette study by company	No utilities available in literature
≤8 convulsive seizures	≤ 18 convulsive seizure-free days	Not estimated	CS[1]	No convulsive seizures
	>18-≤24 convulsive seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	> 24 convulsive seizure free days	[redacted]	Vignette study by company	No utilities available in literature
>8 - ≤25 convulsive seizures	≤ 18 convulsive seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	>18-≤24 convulsive seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	> 24 convulsive seizure free days	[redacted]	Vignette study by company	No utilities available in literature
>25 convulsive seizures	≤ 18 convulsive seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	>18-≤24 convulsive seizure-free days	[redacted]	Vignette study by company	No utilities available in literature
	> 24 convulsive seizure free days	[redacted]	Vignette study by company	No utilities available in literature
Source: Based on Table 32 of the CS				

Table 5.12: Health state utility values per treatment

Health state	Utilities for CBD10	Utilities for CBD20[a]	Utilities for CCM
No convulsive seizures	[redacted]	[redacted]	[redacted]

≤8 convulsive seizures	[redacted]	[redacted]	[redacted]
>8 - ≤25 convulsive seizures	[redacted]	[redacted]	[redacted]
>25 convulsive seizures	[redacted]	[redacted]	[redacted]
Source: Based on Table 32 of the CS [a]Only used in a scenario analysis			

Adverse event related disutility values

The company did not incorporate disutilities for any of the adverse events used in the model. The company justified this by claiming that adverse events are unlikely to have a significant impact on the ICERs.

ERG comment: The main concerns of the ERG relate to: a) the methodology used to elicit utility values; b) the inclusion of caregivers QALYs; c) the lack of disutilities for adverse events and; d) the difference in utilities between CBD and CCM.

a) Utility estimates were based on patient vignettes that only presented information on convulsive seizure frequency and convulsive seizure-free days. This approach is condition-oriented and does not appropriately capture other aspects known to influence quality of life and generally incorporated into utility estimates (e.g. mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression) or leaves these aspects to the conceptualization of the respondents. In response to clarification question B19a,[12] the company clarified that for methodological purposes, the vignette study could not formally measure the impact on utilities beyond condition-related factors. The company further argues that "*this is still clinically meaningful, and the use of a "live" population partially overcomes this limitation*". However, it is unclear to what extent the population may be considered to have experience with DS as this was not specifically part of the inclusion criteria ("[redacted]"). Neither the vignette study nor the use of patients to value health states are in line with the NICE reference case, which specifically states that the valuation of health-related quality of life measured in patients (or by their carers) should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method. [41] The use of vignettes and a "live" population is also suggested to be suboptimal in scientific literature compared to multi-attribute utility instruments and public preferences. [42-44] As an alternative, the ERG suggested exploring a scenario in which utilities were based on the Quality of Life in Childhood Epilepsy (QOLCE) instrument which was used in the GWPCARE2 study. In response to this clarification question (B18f [12]), the company clarified that QvOLCE scores were not used to estimate utilities for the base-case for the following reasons: 1) The response rate was low in the trials (~<50%); 2) lack of an appropriate mapping algorithm to convert the QOLCE scores to EQ-5D values; and 3) it was not possible to estimate the QOLCE scores based on both seizure frequency and seizure-free days. The ERG agrees that the low response rate and the lack of an appropriate mapping algorithm are indeed important arguments which makes it hard to obtain valid estimates, but according to the ERG the QOLCE results could have been used to check face validity of the vignette study.
b) In the revised base-case, the company included QALY decrements for caregivers and incorporated these as gains in the total QALY estimates for both CBD and CCM. The decrements per health state are presented in Table 5.13. However, this is not in accordance with the NICE reference case, which

states '*the measurement of changes in health-related quality of life should be reported directly from patients and the utility of these changes should be based on public preferences using a choice-based method*'. Hence, the addition of caregivers QALYs was discarded in the ERG base-case analysis. In addition, the methods of deriving utility estimates for caregivers is questionable given that caregivers were only asked to evaluate three vignette tasks in total, likely not providing the required granularity. Caregivers' vignettes were constructed in the same way as the patients' vignettes but only included only one vignette for every health state. The influence of caregivers' QALYs was examined by the ERG in a scenario analysis.

Table 5.13: Summary of mean caregiver VAS score utility decrements

Health state		Mean decrements (standard error)
No seizures	No seizure	[redacted]
≤8 convulsive seizures	≤18 seizure-free days	[redacted]
	>18-≤24 seizure-free days	[redacted]
	>24 seizure free days	[redacted]
>8 - ≤25 convulsive seizures	≤18 seizure-free days	[redacted]
	>18-≤24 seizure-free days	[redacted]
	>24 seizure free days	[redacted]
>25 convulsive seizures	≤18 seizure-free days	[redacted]
	>18-≤24 seizure-free days	[redacted]
	>24 seizure free days	[redacted]
Source: Based on Table 5 of the revised economic assessment [45]		

c) In the model, the occurrence of adverse events is not accompanied by loss in QALYs. In response to this clarification question (B21[12]), the company argued that 'on this basis, the contribution to disutilities from AEs associated with CBD is likely to be small relative to those from worsening health states. Furthermore, AEs on CBD are happening against a background of those from the drugs in the CCM basket, which may "dilute" their incremental impact'. Not including the impact of adverse events on HRQOL is unlikely to be conservative (given the occurrence of adverse events). However, it was not feasible for the ERG to implement disutilities in the model.

d) As reported in Table 5.8, the number of days without convulsive seizures is treatment-dependent, resulting in treatment-dependent health state utility values (Table 5.12). It should be noted that (as mentioned in 5.2.6), the number of convulsive seizure-free days per month is only considered as an exploratory outcome in the pivotal trials and is not discussed in the clinical effectiveness sections of the CS. Moreover, it is unlcear to the ERG how convulsive seizure-free days are incorporated in the model after CBD discontinuation (i.e. whether the treatment benefits in terms of hight health state utilities are maintained or not). If the treatment benefits are maintained after CBD discontinuation, this might have introduced an upwards bias to the QALY gains for the CBD group. Given the above, the ERG assumed that the number of days without convulsive seizures is treatment independent, averaging these across the treatments at baseline.

5.2.9 Resources and costs

The cost categories included in the model were costs associated with treatment (drug acquisition costs included concomitant therapies and costs associated with treatment-related AEs), health state costs and mortality costs.

Unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and clinical opinion.

Resource use and costs data identified in the review

According to the CS, the SLR identified nine studies[5, 23, 24, 28, 31-35] reporting UK relevant resource use and cost information. None of these were considered to be appropriate for the CEA model, given that costs and resource use for health states in these studies were not defined by the number of convulsive seizures and convulsive seizure-free days.

Treatment costs

The list price of CBD is [redacted]. Costs for AEDs were obtained from the NHS Electronic Drug Tariff 2018[46] and the costs per mg were estimated using a weighted average based on prescribing proportions obtained from the Prescription Cost analysis published by the NHS business services authority[47] (Table 5.14). Treatment administration costs were not considered in the submission, as all included drugs were administered orally. No dose escalation period was assumed in the model. Furthermore, the company stated that monitoring requirements were similar for CBD and CCM, and therefore resource use and costs associated with routine patient monitoring were not incorporated into the cost effectiveness model. AEDs costs were based on the CCM basket that was determined based on market research (Table 16 of the CS). The company referred to this market research as "data on file" and no details were provided. In addition, the company's base-case assumed that a proportion of patients (based on Laux et al.[38]) had a 33% reduction (based on clinical opinion) in the dose of concomitant AEDs (Table 27 of the CS[1]).

As the treatment dosages for CBD and some other AEDs are weight-based, the trial populations were split into four age groups (2-5 years, 6-11 years, 12-17 years and 18-55 years), in order to ensure more precise estimation of the treatment dosages (Table 5.4). The company further amalgamated these groups into two groups for the cost effectiveness analysis to improve statistical power: <12 years and ≥12 years.

Table 5.14: Treatment acquisition costs

Treatment	Average dose (mg/kg/day)		Average cost per mg (£)	Costs per kg per cycle (3 months)		Reference drug dose
	<12 years	≥12 years		<12 years	≥12 years	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clobazam*	0.65	0.45	0.0559	3.32	2.30	Auden McKenzie, 2008[48]
Stiripentol	30.00	50.00	0.0180	49.31	82.18	Biocodex, 2017ref[49]
Valproic acid*	27.50	25.00	0.0002	0.50	0.46	Sanofi, 2006[50]
Topiramate	7.00	5.45	0.0044	2.81	2.19	Janssen-Cilag 2010[51]
Levetiracetam*	40.00	36.36	0.0002	0.73	0.66	UCB Pharma 2015[52]
Source: based on Table 27 and Table 29 of the CS [1].						

*For CBD, a dose reduction of 33% was assumed for this drug (based on clinical opinion).

Health state costs

Health state specific costs and resource use estimates for physician visits, hospitalisations and institutionalisation were obtained from UK clinical experts (Table 5.15). The company stated that these experts indicated that older patients were more likely to be institutionalised, and therefore the probability of being institutionalised and the associated costs were only applied to patients aged 18 years and older. Furthermore, the company did not apply the risk and costs of being institutionalised to patients in the convulsive seizure-free group, based on the suggestion from the literature [53-55] that there is a likely association between decline in cognitive functioning and the symptomatic level of epileptic activity in early age.

Table 5.15: Health state related costs

Resource use		Number of annual visits[1]		Costs per visit		Reference unit prices
		<12 years	≥12 years	<12 years	≥12 years	
Nurse visit	Seizure-Free	2	2	£44	£44	PSSRU 2017[56]
	≤ 8	4	2			
	>8 - ≤ 25	8	4.8			
	> 25	12	12			
Paediatric Epileptologist (<12 years) / Neurologist (≥12 years) Visit	Seizure-Free	1	0.5	£366	£167	NHS Reference Costs 2016-17[57]
	≤ 8	2	0.5			
	>8 - ≤ 25	4	0.5			
	> 25	6	3			
Paediatrician Visit	Seizure-Free	2	0	£196	£0	PSSRU 2017[56]
	≤ 8	4	0			
	>8 - ≤ 25	8	0			
	> 25	12	0			
Emergency department	Seizure-Free	0	0	£237	£237	NHS Reference Costs 2016-17[57]
	≤ 8	6	3			
	>8 - ≤ 25	12	6			
	> 25	24	12			
Phone Call Follow-up	Seizure-Free	0	0	£258	£107	NHS Reference Costs 2016-17[57]
	≤ 8	2	1			
	>8 - ≤ 25	6	2.5			
	> 25	12	6			
Dentist	Seizure-Free	2	2	£127	£127	PSSRU 2017[56]
	≤ 8	2	2			

Resource use		Number of annual visits[1]		Costs per visit		Reference unit prices
		<12 years	≥12 years	<12 years	≥12 years	
	>8 - ≤ 25	2	2			
	> 25	2	2			
Hospitalisation	Seizure-Free	0	0	£597 in general ward £1,583 in ICU	£460 in general ward £1,299 in ICU	NHS Reference Costs 2016-17[57]
	≤ 8	3	1.5			
	>8 - ≤ 25	6	3			
	> 25	12	6			
Institutionalisation[2]	Seizure-Free	0%	0%	£0	£1,337	PSSRU 2017[56]
	≤ 8	0%	10%			
	>8 - ≤ 25	0%	10%			
	> 25	0%	10%			
Cost of Rescue Medication by intake	Seizure-Free	0	0	£34	£34	BNF 2018[58]
	≤ 8	12	6			
	>8 - ≤ 25	24	12			
	> 25	48	24			

Source: Based on Table 29 and Table 30 of the CS

[1]Based on clinical opinion.

[2]The probability and costs of being institutionalised were only applied to patients aged 18 years and older.

Mortality costs

The company stated that due to a lack of evidence on costs associated with death due to DS, costs and resource use associated with SUDEP (£0) and non-SUDEP (£237 for one visit to the emergency department, and £1,583 and £1,299 per day in an intensive care unit for <12 years and ≥12 years respectively) were based on clinical opinion. Costs associated with emergency department visits and intensive care unit were obtained from the NHS reference cost schedule 2016-2017.[57]

Adverse event related costs

Commonly identified treatment emergent adverse events were included in the analysis as one visit to a specialised nurse (£44 per visit, PSSRU 2017[56]), based on clinical experts who indicated that these events were unlikely to be resource intensive.

ERG comment: The concerns of the ERG relate to: a) the dose escalation period in the model is not in line with the escalation period used in the pivotal trials; b) The percentage of patients who are institutionalised in the model in the seizure-free group; c) the costs of ketogenic diet and vagus nerve stimulation are not incorporated into the model; d) the assumption that, in the base-case, CBD leads to a dose reduction of 33% for some AEDs; e) resource use for the seizure-free health state; f) not considering costs associated with routine patient monitoring; g) the justification for the average weight by age group used to calculate treatment costs and; h) mean weight for patients aged 18-55 years.

a) Contrary to the pivotal trials, in which an escalation period (or treatment period) of two weeks is used (i.e., 5 mg/kg/day to start, titrated up to the target dose over two weeks), no escalation period was assumed in the model. Although this may slightly over-estimate the treatment costs (e.g. for the first week in the cycle), the ERG expects no large implications from the simplification.
b) In the initial CS, a zero percentage of the patients in the convulsive seizure-free group was subjected to institutionalisation due to cognitive decline. However, cognitive functioning of these patients could still decline as a result of other aspects of DS, including non-convulsive seizures. Hence, in response to clarification question B22a,[12] the company has included a 2% risk of institutionalisation for patients in the convulsive seizure-free health state. It remains unclear, however, to what extent the patients' risk of institutionalisation is associated with convulsive seizure-freedom and whether this risk is indeed lower compared to the other health states. In accordance with the revised base-case submitted by the company, the ERG used a 2% institutionalisation risk for patients aged above 18 years in the convulsive seizure-free category.
c) In response to clarification question B10, [12] the company stated that the effects of the ketogenic diet and vagus nerve stimulation are included in the effectiveness estimates from the pivotal trials (as some patients received these treatments as part of the CCM). However, although this is a reasonable assumption, however, costs of both the ketogenic diet and the vagus nerve stimulator are not included in the model. This most likely resulted in an underestimation of the CCM costs, which likely favours CBD (as patients with CBD are estimated to live longer and hence the CCM treatment duration is likely longer for CBD).
d) It is stated that patients in both the intervention and comparator group receive the same clinical management, but for some AED, a dose reduction of 33% is applied for CBD plus CCM. In response to clarification question B25a, [12] the company stated that [redacted]. However, this is not consistent with the evidence presented by the company.[1] The poster by Laux et al. indicated that some patients have an increased AED dose, [38, 59] and it is unclear from the evidence what percentage of dose reduction/increase was observed in the patients in whom a dose adjustment was observed. Hence, it is questionable whether it is correct to assume a 33% reduction in a selection of AEDs. The ERG incorporated a 0% dose reduction in their revised base-case.
e) Health state resource utilisation, based on expert opinion, is assumed to be considerably lower for the seizure-free health state. The ERG has explored the impact of this assumption in a scenario in which resource use for the seizure-free group is equal to half of the units reported for the second-best health state for every cost category.
f) The company stated that monitoring requirements were similar for CBD and CCM, and therefore resource use and costs associated with routine patient monitoring were not incorporated into the cost effectiveness model. However, given the survival differences that are estimated to favour CBD in the model, the total routine patient monitoring costs would probably be higher for CBD (given these patients are estimated to live longer) despite monitoring requirements were similar for CBD and CCM. Nevertheless, the ERG does not expect this issue to have a substantial impact on the results.
g) In response to clarification question B5d, [12] the company clarified that it was not possible to definitively conclude whether the mean weights at baseline in the clinical trials (used to calculate treatment costs) were representative of those for the DS population in the UK. No data were identified in the literature and there were too few UK patients in the GWPCARE1 and GWPCARE2 trials (16 overall) to use only this subgroup in the model. In the revised base-case of the model,

however, the company replaced the mean weights across age groups at baseline by the median weights across age groups at baseline, which is likely to be an underestimation of the mean weights. In response to clarification question B5b, [12] the company clarified that this was done to account for the asymmetric weight distribution (likely due to outliers) and that this addresses the face-validity issue in the prior assumptions. According to the ERG this assumption is not reasonable as the weights are used to determine mean dosages over time, and hence, outliers are part of this mean dosage. Hence, the ERG discarded the use of median weights proposed by the company and included mean weights.

h) The mean weights for the age category "18-55 years" in the original submission were deemed implausible as this category was based on a small number of patients (1.89%) and lacked face validity
([redacted]).
Hence, for the category aged 18-55 years, the mean weight in the ERG base-case was based on the LGS submission.

5.2.10 Cost effectiveness results

[redacted]

Table 5.16: Company's base-case results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM	[redacted]	[redacted]	--	--	--
CCM + CBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the base-case results in the economic model

CBD = cannabidiol; CCM = current clinical practice; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year;

ERG comment: The main concerns of the ERG relate to: a) the calculation of QALYs does not match the time horizon; b) relevant results are not presented; c) the additional assumptions in the revised submission and economic model of the company.

a) In the initial base-case submitted by the company the total QALYs for both treatments exceeded the time horizon of the model. Hence these results should be interpreted with extreme caution (see also section 5.2.12). In response to clarification question B30,[12] the company did not elaborate on the origin of this error but provided a revised base-case.
b) Total life years and the duration that patients are in the various health states over time were not presented. This information would help to perform face validity checks on, e.g. the estimated QALYs.
c) The company provided a revision of the original submission and economic model accompanying the clarification letter. [21] It was however, unclear what exactly was changed and why certain input

parameters/assumptions changed (the company made various changes that were not requested by the ERG). The company's revised submission is presented below (Table 5.17). Given the changes to the input parameters and assumptions of the economic model (some of which were not requested by the ERG) as well as some persistent validity issues (see section 5.2.12), the ERG believes these revised results submitted by the company should be interpreted with extreme caution as well. Therefore, the ERG used the revised model submitted by the company (with some of the validity issues resolved), while setting all input parameters as described in the original CS, as a starting point for the ERG analyses.

Table 5.17: Company's revised base-case results

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

Source: Based on the base-case results in the economic model
CBD = cannabidiol; CCM = current clinical practice; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year;

5.2.11 Sensitivity analyses

The company performed and presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) in order to show the uncertainty surrounding the initial CS base-case results.

[redacted]

The company conducted DSAs by varying key model parameters between upper and lower values based on the literature, clinical opinion or a specified range (e.g. +/- 10%). Transition probabilities were not included in the DSA. The initial ICER was most sensitive to discount rates for costs and outcomes and the average dose in subsequent cycles. The ICER exceeded the WTP threshold of £30,000 (Figure 5.2) in these three DSA analyses.

Table 5.18: The company's initial probabilistic base-case results (500 iterations)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM + CBD	[redacted]	[redacted]	--	--	--
CCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the revised PSA results in the economic model.
ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; SoC =standard of care

[redacted]

Scenario analyses

The company conducted several scenario analyses. The initial results showed ICERs ranging between [redacted] and [redacted] per QALY gained. The three most influential scenarios that increased the ICER were varying the CBD dosage ([redacted]), including patients aged between 12 and 55 years only [redacted]), and using algorithm 1 (SG 3) to model utilities [redacted]) The three most influential scenarios that decreased the ICER were including patients aged between two and 11 years only ([redacted]), using algorithm 2 (SG 8) to model utilities [redacted]), and assuming the same long-term discontinuation rate for all convulsive seizure groups ([redacted]).

ERG comment: The main concerns of the ERG relate to: a) the company did not provide all requested scenario analyses; b) not all parameters have been included in the PSA; c) the use of bootstrapping to obtain distributions for transition probabilities in the PSA and; d) the additional assumptions in the revised submission and economic model of the company.

a) The ERG requested the following additional scenario analyses: 1) a scenario analysis using the GWPCARE1 trial only (clarification question B12c); 2) a scenario analysis using the average treatment discontinuation probability across the health states (clarification question B14f); 3) a scenario analysis using equal number of days without seizures across treatment allocation (clarification question B15b); 4) a scenario analysis in which utilities are based on the QOLCE instrument from the phase 3 trials (clarification question B19g); and 5) a scenario assuming a 0% dose reduction of concomitant AEDs (clarification question B25b). Based on these requests the company only added a scenario assuming 0% dose reduction in the revised submission and the company adjusted the discontinuation rates in their revised base-case (though they did not apply the requested discontinuation rates). This hampered the review of the ERG.
b) Based on CS Table 36 some parameters (e.g. non-SUDEP costs) were not included in the PSA. In response to clarification question B28d, [21] the company clarified that the parameters that had a minor impact on the results were not included in the PSA. No further changes were made to the PSA in terms of included parameters. Hence, the ERG believes that the PSA still does not include all relevant parameters (e.g. excluding discontinuation probabilities up to cycle 9, which are potentially influential).
c) Transition probabilities were included in the PSA using a bootstrapping method. However, bootstrapping is not the recommended approach to incorporate interdependent transition probabilities (see for instance Briggs et al.[60]). In response to clarification question B28, [21] the company clarified that the bootstrapping method was preferred to the Dirichlet distribution as the transition probabilities are not only interdependent, but also time dependent. Furthermore, it was argued that the company would have used Dirichlet if only one set of transition probabilities was used. Although the ERG does not necessarily agree with this approach, it is reasonable to assume that this does not have major implications for the results of the model.
d) In response to the clarification letter, [21] the company provided a revision of the original submission and economic model. It was however, unclear what exactly was changed and why certain input parameters/assumptions changed (the company made various changes that were not requested by the ERG). The company's revised sensitivity and scenario analyses are presented below. Given the changes to the input parameters and assumptions of the economic model (that were not requested by the ERG), as well as some persistent validity issues (see section 5.2.12), the ERG believes these revised analyses submitted by the company should be interpreted with extreme caution as well. Consistently, the ERG used the revised model submitted by the company, while setting the

adjusting the input parameters as described in the original CS, as a starting point for the ERG analyses.

Revised sensitivity analyses submitted by the company

The company performed and presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) in order to show the uncertainty surrounding the base-case results.

Compared with the revised deterministic results, the PSA showed slightly lower incremental QALYs and lower incremental costs, which resulted in an increased ICER (£36,046) (Table 5.19). The cost effectiveness acceptability curve in the revised model showed that CCM plus CBD approximately had a [redacted] probability of being cost effective at a willingness to pay (WTP) threshold of [redacted]

The company conducted DSAs by varying key model parameters between upper and lower values based on the literature, clinical opinion or a specified range (e.g. +/- 10%). Transition probabilities were not included in the DSA. The ICER was most sensitive the average dose in all cycles subsequent cycles and the costs of emergency department visits. The ICER exceeded the WTP threshold of £30,000 (Figure 5.3) in these three DSA analyses.

Table 5.19: The company's revised probabilistic base-case results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM + CBD	£226,681	3.98	--	--	--
CCM	£195,578	3.09	£31,103	0.89	£36,046

Source: Based on the revised PSA results in the economic model.
ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; SoC =standard of care

[redacted]

Revised scenario analyses submitted by the company

The company conducted several scenario analyses. The results showed ICERs ranging between [redacted] and [redacted] per QALY gained. The three most influential scenarios that increased the ICER were including patients aged between 12 and 55 years only [redacted]), varying the CBD dosage ([redacted]), and no variation across seizure categories for the number of hospital admissions ([redacted]. The three most influential scenarios that decreased the ICER were all patients 2-5 years at model entry ([redacted], varying the ICU/general ward ratio to 90% in ICU and 10% in general ward ([redacted], and including patients aged between 2 and 11 years only ([redacted]).

5.2.12 Model validation and face validity check

Face validity

The model structure, inputs regarding CCM in the UK and key assumptions regarding health care resource use and long-term efficacy were validated by UK clinical experts.

Internal validity

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

Cross validity

No cross validation was reported.

External validity

Clinical outcomes of the economic model, in terms of proportion of convulsive seizure-free patients (at year 1) and 10-year CCM mortality, were compared against evidence (see CS Appendix J).

ERG comment: The main concerns of the ERG relate to the a) revised assessment submitted by the company; b) internal validity and; c) transparency of the model.

a) After the clarification phase (with delay), the company submitted their clarification responses, a revised assessment and a revised economic model. Besides attempting to resolve validity issues (see clarification question B30), this revised assessment also included adjustment to the structure (duration of adverse events) and input parameters of the economic model. Most of these additional adjustments were not requested by the ERG (e.g. structural adjustments regarding duration of adverse events and adjusting long-term CBD discontinuation probabilities) nor were all adjustments clearly described. Consequently, it is unclear to the ERG what the original CS base-case results would be if the validity issues were resolved. Therefore, the ERG used the revised model submitted by the company, while setting the input parameters to the values as described in the original CS, as a starting point for the ERG analyses.
b) Although the company reported an extensive quality/internal validity check (as summarised above), the model initially submitted by the company had clear internal validity issues given that the estimated QALYs exceeded the model time horizon. This issue was highlighted in clarification question B30. In the clarification phase, the company submitted a model that had QALYs that did not exceed the time horizon, however the company did not highlight the exact changes in the model (code), making it more difficult for the ERG to examine the changes made in response to clarification question B30. Particularly given the updated economic model submitted during the clarification phase included multiple adjustments (which were mostly not requested by the ERG).
c) Additionally, the ERG regarded the VBA coded model to lack transparency, although the company helpfully provided detailed information regarding model implementation in response to clarification question B26, the ERG still believes that an economic model that is not programmed mostly in VBA would be more transparent. Particularly given the relatively simple model structure, an economic model not programmed mostly in VBA would have been preferred. This would allow more extensive validation and implementation of adjustments/analyses by the ERG within the available timeframe.

To internally validate the revised economic model (submitted by the company during the clarification phase), the ERG did the following

- rebuilt the state transition trace in order to recalculate QALYs and costs of CBD. The ERG was able to reproduce the state transition trace and QALY calculation for CBD 10 mg/kg/day to a fair level of accuracy (estimated CBD discounted QALYs, without carer QALYs, [redacted] versus [redacted]). For the costs this was true to a lesser extent (estimated CBD discounted total costs [redacted] versus [redacted]). The difference between the ERG calculations and the company's updated model that was most prominent was the disease management (or health state) costs (estimated CBD discounted management costs [redacted] versus [redacted]) and treatment costs (estimated CBD discounted treatment costs [redacted] versus [redacted]).
- changed the clinical effectiveness input parameters for CBD 10 mg/kg/day to the clinical effectiveness input parameters for CCM. The expected result would be a QALY difference of 0.000. Conversely, the produced results indicated a QALY gain for CBD 10 mg/kg/day of 0.36 (excluding carer QALYs). Even if it is, in addition to the above, assumed that all patients remain in their baseline seizure frequency health state (by setting the diagonal of the transition matrices for cycle 1 on the "# SEIZURES" worksheet to 100%) a QALY gain for CBD 10 mg/kg/day of 0.10 is produced (excluding carer QALYs). This suggests that there are fundamental problems with the economic model (i.e. VBA code) that induce a QALY gain for CBD 10 mg/kg/day. Consequently, the cost effectiveness results, calculated using the economic model submitted by the company, lack credibility. Due to the complexity and limited transparency of the model, the ERG was unable to resolve these validation issues within the available timeframe.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Table 5.20 summarises the main issues highlighted by the ERG in section 5.2, indicates the expected direction of bias introduced by these issues and whether these are examined in any analyses/incorporated in the ERG base-case.

Table 5.20: Main ERG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Model structure (section 5.2.2)			
Ignorance of non-convulsive seizures in the model	+/-	-	-
Assumption that patients in the CCM group transfer back to their baseline seizure frequency after the first cycle	+	-	-
Population, interventions and comparators, perspective and time horizon (sections 5.2.3-5.2.5)			
Extent to which the population of the trial is representative for the target population of the model	+/-	-	-
Weight for patients aged 18 years or older	+	ERG base-case	
The combination of all AEDs as CCM	+/-	-	-
No lifetime time horizon	+/-	Scenario	Scenario
Treatment effectiveness and extrapolation (section 5.2.6)			
Using evidence based on CBD 20 mg/kg/day as a proxy for CBD 10 mg/kg/day for month 3 to month 27	+/-	Scenario	-
Assuming constant treatment effectiveness after month 27	+	Scenario	-
Face validity of the treatment discontinuation probabilities	+/-	ERG base-case	-
Treatment dependent number of days without seizures	+	ERG base-case	-
Lack of appropriate justification regarding the calculation of epilepsy-related mortality rates	+	ERG base-case	-
Health-related quality of life (section 5.2.8)			
The methodology used to elicit utility values	+/-	-	-
Lack of disutilities for adverse events	+	-	-
Resources and costs (section 5.2.9)			

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
The dose escalation period in the model is not in line with the escalation period used in the pivotal trials	-	-	-
The percentage of patients who are institutionalised in the model in the seizure-free group	+	ERG base-case	Scenario
Resource use in the seizure-free group	+	Scenario	-
The costs of ketogenic diet and vagus nerve stimulation are not incorporated into the model	+	-	-
It is assumed that CBD leads to a dose reduction of 33% for some AEDs	+	ERG base-case	Scenario
Not considering costs associated with routine patient monitoring	+	-	-
Cost effectiveness analyses (sections 5.2.10 and 5.2.11)			
Relevant results are not presented	+/-	-	-
Methods used for probabilistic analyses	+/-	-	-
Validation (section 5.2.12)			
Fundamental validity problems with the economic model severely hampering. the credibility of the cost effectiveness results calculated using the economic model submitted by the company	+	-	-

Footnotes: [a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator.
ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; ICER = incremental cost effectiveness ratio; MJ = matters of judgement;

Based on all considerations discussed in section 5.2 (summarised in Table 5.20), the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[61]). The ERG's has major concerns with both the original CS base-case as well as the revised CS base-case (see 5.2). Therefore, as mentioned above, the ERG used the revised model submitted by the company, while setting the input parameters to the values as described in the original CS, as a starting point for the ERG analyses.

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Fixing errors

1. Revised economic model (section 5.2.12).

   The ERG used the revised economic model submitted (by the company) during the clarification phase (using the input parameters as described in the original CS). A word of caution is that this model still has important validity concerns, such as an induced QALY gain for CBD 10 mg/kg/day and the ERG was unable to reproduce costs for CBD 10 mg/kg/day.

Fixing violations

2. Time horizon (section 5.2.5).

   The ERG extended the time horizon to 20 years (maximum time horizon allowed in the submitted model)

Matters of judgment

3. Adjusted weight for adults (section 5.2.3)
   The ERG adjusted the weight for adults (assuming the LGS for patients aged ≥18).
4. Adjusted mortality probabilities (section 5.2.6).
   The ERG adjusted the health state dependent SUDEP and non-SUDEP mortality probabilities.
5. Adjusted discontinuation probabilities (section 5.2.6).
   The ERG adjusted the CBD discontinuation probabilities (see Table 5.10) to improve face validity of this input parameter.
6. Treatment independent number of days without seizures (sections 5.2.6 and 5.2.8).
   The ERG assumed number of days without seizures to be treatment independent to prevent overestimating the utility difference between treatments.
7. Institutionalisation risk in the seizure-free category (section 5.2.9).
   The ERG used a 2% institutionalisation risk in the seizure-free health state for patients aged above 18 years.
8. AED dose reduction for CBD (section 5.2.9).
   The ERG adopted a 0% AED dose reduction for CBD (consistent with CCM)
9. No treatment effect after 27 months (section 5.2.6).

   The ERG assumed that all patients revert to their baseline seizure frequency health state after 27 months (9 cycles) due to lack of evidence regarding long-term effectiveness.

Table 6.1 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the (deterministic) ERG base-case. The 'fixing error' adjustments were combined and the other ERG analyses were performed also incorporating these 'fixing error' adjustments given the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

5.3.1 ERG base-case results

The ERG base-case consisted of an ICER range reflecting the uncertainty surrounding the extrapolation of treatment effectiveness. The probabilistic ERG base-case (Table 6.2) indicated that the ICER, for CBD compared with CCM, would range between £76,013 per QALY gained (assuming a constant treatment effect after 27 months) and £477,476 per QALY gained (assuming no treatment effect after 27 months). For these two assumptions, the probabilities of CBD being cost effective were [redacted] respectively, at a willingness to pay threshold of £20,000 per QALY gained while these probabilities were [redacted] respectively, at a willingness to pay threshold of £30,000 per QALY gained (Figures 5.4 and 5.5). It should however be reiterated that some of the abovementioned potential biases (see for instance the model structure and validity sections) could not be explored by the ERG. Consequently, the ICERs reported might be an underestimation of the true ICERs.

Figure 5.2: Cost effectiveness acceptability curve: ERG base-case assuming a constant treatment effect after 27 months

Figure 5.3: 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) DS. The model structure was focussed on convulsive seizures and did not explicitly capture non-convulsive seizures. Also, assuming that patients treated with CCM revert to their baseline health states after three months (with no possibility to become seizure-free) and remain in this state for the remainder of the time horizon is considered restrictive and potentially biases the cost-effectiveness in favour of CBD. Moreover, the extent to which the trial population (which includes a small proportion of patients that does not match the anticipated marketing authorisation) is representative to the UK setting, is unclear to the ERG. Additionally, the ERG considers that the economic model and base-case analyses described in the CS only partly meets the NICE reference case. Deviations from the NICE reference case included the restricted time horizon of 15 years and the method used to estimate utilities.

Key uncertainties in this cost effectiveness assessment are, according to the ERG, the extrapolation of treatment effectiveness, the estimated health state utility values and the model validity. Firstly, extrapolation of CBD 20 mg/kg/day evidence to CBD 10 mg/kg/day. The CBD effectiveness evidence used beyond three months is based on GWPCARE5, using CBD 20 mg/kg/day as maintenance dose (mean modal dose during treatment was [redacted]). It is debatable whether this evidence is representative for a CBD maintenance dose of 10 mg/kg/day. Secondly, the extrapolation after 27 months is uncertain due to the lack of evidence beyond this time period. After 27 months the company assumed a constant treatment effectiveness, i.e. assuming that CBD patients remain in the same health state until CBD discontinuation or death while assuming a constant CBD discontinuation probability. Thirdly, it is questionable whether the evidence can be extrapolated to patients aged 18 year above given the large majority of patients ([redacted] based on GWPCARE1 and GWPCARE2) is aged below 18 year. This uncertainty related to extrapolation is, in part, reflected in the ERG base-case ICER range. Another source of uncertainty were the estimated health state utility values. The ERG considered the methodology to be not in line the NICE reference case. Finally, the model validity (as well as transparency) can be regarded as a major limitation of the current assessment. Despite the company attempted to resolve validity issues during the clarification phase, the ERG also considered the model validity of the revised model to be problematic. According to the ERG, there are fundamental problems with the economic model that potentially induce a QALY gain for CBD 10 mg/kg/day. Consequently, the cost effectiveness results, calculated using the economic model submitted by the company, lack credibility. Due to the complexity and limited transparency of the model, the ERG was unable to satisfactory resolve these validation issues within the available timeframe.

In the company base-case (probabilistic), the ICER of CBD compared with CCM was estimated to be [redacted] per QALY gained. However, this ICER was based on technically implausible QALY estimates and is, according to the ERG, not informative / seriously flawed. Similarly, the revised base-case ICER submitted by the company (£36,046) should be interpreted with extreme caution given the validity issues and adjustments (model structure and input) made by the company. The ERG has incorporated various adjustments to the CS base-case (using the revised economic model with input parameters from the original CS as starting point). The ERG base-case consisted of an ICER range, reflecting the uncertainty surrounding the long-term extrapolation of treatment effectiveness. The ERG base-case (probabilistic) indicated that the probabilistic ICER, for CBD compared with CCM, would range between £76,013 per QALY gained and £477,476 per QALY per QALY gained. However, it should be reiterated that some of the abovementioned potential biases (model structure, validity) could not be explored by the ERG. Consequently, the ICERs reported are likely to be underestimations of the true ICERs.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Analyses undertaken by the ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. It should be noted that the ERG used the revised model submitted by the company (with some of the validity issues resolved), while setting all input parameters as described in the original CS, as a starting point for the ERG analyses (fixing errors analysis). The changes to the input parameters and assumptions of the revised economic model (some of which were not requested by the ERG) are discussed in Chapter 5. Table 6.1 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The probabilistic CS and ERG base-cases are presented in Table 6.2. These are all conditional on the ERG base-case. Finally, Table 6.3 provides the results of the exploratory scenario analyses (described in Section 5.3.2), all conditional on the ERG base-case assuming a constant treatment effect after 27 months. The submitted model file contains technical details on the analyses performed by the ERG.

Table 6.1: Deterministic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) vs BSC
Company base-case (original CS)					
CCM	£190,322	18.585			
CCM + CBD	£300,687	21.819	£110,364	3.234	£34,126
Fixing errors (company's revised model, setting the input parameters as in the original CS)					
CCM	£191,458	4.585			
CCM + CBD	£302,148	5.501	£110,689	0.916	£120,838
Fixing errors + time horizon of 20 year					
CCM	£229,820	5.509			
CCM + CBD	£367,006	6.654	£137,186	1.145	£119,785
Fixing errors + adjusted weight for adults					
CCM	£199,915	4.585			
CCM + CBD	£327,882	5.501	£127,966	0.916	£139,698
Fixing errors + adjusted mortality probabilities					
CCM	£192,052	4.525			
CCM + CBD	£299,326	5.375	£107,274	0.850	£126,275
Fixing errors + adjusted discontinuation probabilities					
CCM	£191,458	4.585			
CCM + CBD	£239,437	5.239	£47,979	0.654	£73,379
Fixing errors + treatment independent number of days without seizures					
CCM	£191,458	4.585			
CCM + CBD	£302,148	5.478	£110,689	0.892	£124,037
Fixing errors + institutionalisation risk in the seizure-free category					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) vs BSC
CCM	£191,458	4.585			
CCM + CBD	£302,913	5.501	£111,455	0.916	£121,673
Fixing errors + AED dose reduction for CBD					
CCM	£191,458	4.585			
CCM + CBD	£302,917	5.501	£111,459	0.916	£121,677
ERG base-case (assuming a constant treatment effect after 27 months)					
CCM	£243,272	5.414			
CCM + CBD	£299,780	6.126	£56,508	0.712	£79,401
ERG base-case (assuming no treatment effect after 27 months)					
CCM	£243,272	5.414			
CCM + CBD	£301,873	5.533	£58,601	0.119	£493,726

Table 6.2: Probabilistic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) vs BSC
Company base-case (original CS)					
CCM	£190,208	18.625			
CCM + CBD	£300,984	21.772	£110,776	3.147	£37,422
ERG base-case (assuming constant treatment effect after 27 months)					
CCM	£244,040	5.416			
CCM + CBD	£297,062	6.114	£53,023	0.698	£76,013
ERG base-case (assuming no treatment effect after 27 months)					
CCM	£243,325	5.425			
CCM + CBD	£297,789	5.539	£54,464	0.114	£477,476

Table 6.3: Probabilistic scenario analyses (conditional on ERG base-case assuming a constant treatment effect after 27 months)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) vs BSC
ERG base-case (assuming constant treatment effect after 27 months)					
CCM	£244,040	5.416			
CCM + CBD	£297,062	6.114	£53,023	0.698	£76,013
ERG base-case (assuming constant treatment effect after 27 months) + increase treatment dose of CBD to 20 mg/kg/day after the 1st cycle					
CCM	£243,651	5.411			
CCM + CBD	£364,835	6.108	£121,184	0.697	£173,781
ERG base-case (assuming constant treatment effect after 27 months) + include caregivers QALY					
CCM	£243,497	3.608			

CCM + CBD	£296,125	4.625	£52,629	1.017	£51,734
ERG base-case (assuming constant treatment effect after 27 months) + resource use for the seizure-free group assumed equal to half of the units reported for the second-best health state					
CCM	£244,039	5.412			
CCM + CBD	£298,769	6.100	£54,730	0.687	£79,617
ERG base-case (assuming constant treatment effect after 27 months) + only use evidence based on the 10 mg/kg/day CBD dose					
CCM	£243,436	5.409			
CCM + CBD	£296,520	6.094	£53,084	0.684	£77,574

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Appendix 1: ERG version of CS searches including corrections

PubMed search

The ERG noted that the following search terms failed to work properly, due to incorrectly applied truncation within the phrase search:

"Dravet* syndrome"

"childhood epilep* encephalopath*"

The ERG re-ran the company's search (#1), as well as running a corrected version of the company's search (#4). The company's original search including errors was removed from the corrected search results using the Boolean operator 'NOT' (#5), which resulted in 6069 references missed by the company's search.

ERG's PubMed (NLM) search testing the company's strategy with and without errors

Search	Add to builder	Query	Items found
#5	Add	Search **(#4 NOT #1)**	6069
#4	Add	Search **(#2 OR #3)**	10168
#3	Add	Search **("Lennox Gastaut Syndrome"[Mesh] OR ("Epilepsies, Myoclonic"[Mesh] AND (child* or infan*)) OR "Dravet syndrome" OR "Lennox Gastaut" OR "childhood epilepsy encephalopathies" OR "severe myoclonic epilepsy" OR SMEI OR LGS)**	10111
#2	Add	Search **("Lennox Gastaut Syndrome"[Mesh] OR ("Epilepsies, Myoclonic"[Mesh] AND (child* or infan*)) OR "Dravets syndrome" OR "Lennox Gastaut" OR "childhood epilepsy encephalopathy" OR "severe myoclonic epilepsy" OR SMEI OR LGS)**	9889
#1	Add	Search **("Lennox Gastaut Syndrome"[Mesh] OR ("Epilepsies, Myoclonic"[Mesh] AND (child* or infan*)) OR "Dravet* syndrome" OR "Lennox Gastaut" OR "childhood epilep* encephalopath*" OR "severe myoclonic epilepsy" OR SMEI)**	4164

PubMed (NLM): up to 2019/03/26

Cochrane Library search

The company's Cochrane Library search contained very basic phrase searching without inclusion of MeSH Indexing. The ERG amended the CS search by including correct MeSH, truncation, phrase searching and added the abbreviation 'LGS'. The ERG's corrected Cochrane Library search retrieved 307 results, whereas the company's reported strategy retrieved only 207.

Cochrane Library: up to 2018/01/24
Searched 24.1.19

ID	Search	Hits
#1	MeSH descriptor: [Epilepsies, Myoclonic] explode all trees	51
#2	MeSH descriptor: [Lennox Gastaut Syndrome] explode all trees	24
#3	#1 and (child* or infan*)	47
#4	#3 or #2	74
#5	"Dravet syndrome" OR "Lennox Gastaut" OR "Dravets syndrome"	237
#6	"childhood epilepsy encephalopathy" OR "severe myoclonic epilepsy" OR SMEI	36
#7	LGS	129
#8	**#4 or #5 or #6 or #7**	**307***

* with Cochrane Library publication date from Jan 1890 to Dec 2018

The original company submission search of the Cochrane Library retrieved 207 references.

CRD search: NHS EED, DARE & HTA databases

The company's search of the CRD databases was restricted to 'Lennox-Gastaut or Dravet' in the title only. The ERG amended the CS search by including correct MeSH, truncation, phrase searching and added the abbreviations 'LGS' and 'SMEI'. The ERG's corrected CRD search retrieved, 17 results, whereas the company's reported strategy retrieved only 9.

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

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

The original company submission search of the CRD databases retrieved 9 results.